JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

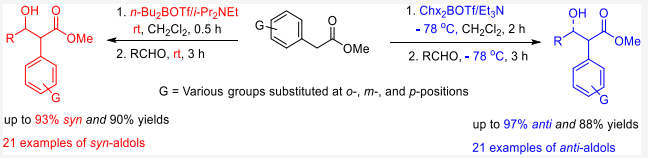
Temperature- and Reagent-Controlled Complementary *Syn*- and *Anti*-Selective Enolboration–Aldolization of Substituted Phenylacetates

Angela Y. Thomas,[†] Tommy L. Walls III,[†] Brionna N. Nelson, Stafford W. Primeaux, and Prem B. Chanda*

Cite This: *J. Org. Chem.* 2021, 86, 6184–6194 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: In contrast to methyl phenylacetates, methyl arylacetates do not provide *syn*-aldols in the dicyclohexylboron triflate/triethylamine (Chx_2BOTf/Et_3N)-mediated enolboration–aldolization reaction. However, a combination of a less bulky boron reagent (dibutylboron triflate, n-Bu_2BOTf), a bulky amine (i-Pr_2NEt), and ambient temperature is required to obtain *syn*-aldols from methyl arylacetates. The corresponding *anti*-aldol products have been synthesized by the enolboration–aldolization of methyl arylacetates in the presence of Chx_2BOTf/Et_3N at a lower temperature. We report the first example of a complementary *syn*- and *anti*-selective enolboration–aldolization of arylacetates.



INTRODUCTION

Boron-mediated aldol reactions are invaluable synthetic tools for the stereo-controlled preparation of β-hydroxy carbonyl compounds.[1] Enolboration–aldolization of ketones,[2] thioesters,[3] propanoates,[4] 3,3,3-trifluoropropanoates,[5] vinylogous esters,[6] and phenylacetates[7] have been well studied. However, a systematic study of the enolboration–aldolization of various arylacetates remains unexplored. Aldols derived from arylacetates, such as 2,3-diaryl-3-hydroxypropanoates, are privileged motifs and commonly found in many bioactive compounds.[8] 1,2,3-Triazole analogs of 2,3-diaryl-3-hydroxypropanoates, which are prepared from *p*-bromophenylacetates, exhibit higher enzyme inhibition activity and selectivity than the corresponding compounds derived from unsubstituted phenylacetates (Figure 1).[9] In the synthesis of 1,2,3-triazole analogs, an approximately equal mixture of *syn*- and *anti*-diastereomers was prepared using lithium bis(trimethylsilyl)amide (LiHMDS)-mediated aldol reactions of arylacetates. However, only one isomer, either *syn*- or *anti*-aldol, was found to be useful in preparing a potent inhibitor of the aromatase enzyme complex (CYP 450 19A1). This requires a convenient synthetic method to obtain either the pure *syn*- or *anti*-2,3-diaryl-3-hydroxypropanoates from arylacetates. Additionally, Davies and co-workers also prepared these aldols in a two-step reaction sequence from diazo acetates to synthesize highly functionalized 2,3-dihydrobenzofurans (Scheme 1).[10] These structural units are commonly present in various natural products and pharmaceuticals.[11] An aldol reaction of arylacetates could be a convenient synthetic methodology to prepare such synthons (Scheme 2). The importance of the stereoselective synthesis of such aldols motivated us to investigate enolboration–aldolization reactions of substituted phenylacetates for the development of diastereoselective synthesis of β-hydroxy-α-substituted phenyl carboxylic acid ester aldols.

The synthesis of *syn*- and *anti*-β-hydroxy-α-methyl- or trifluoromethyl carboxylates has been achieved with the appropriate selection of the alkoxy group, boron reagent, amine base, and reaction temperature (Scheme 3, reactions A and B).[4,5] Unlike propanoates and 3,3,3-trifluoropropanoates, a methyl phenylacetate provides either *anti*- or *syn*-aldols by simply altering the temperature and amines (Scheme 3, reaction C).[7a] Similar to methyl phenylacetate, other arylacetates provided *anti*-aldol products at a low reaction temperature (−78 °C). However, at room temperature, methyl

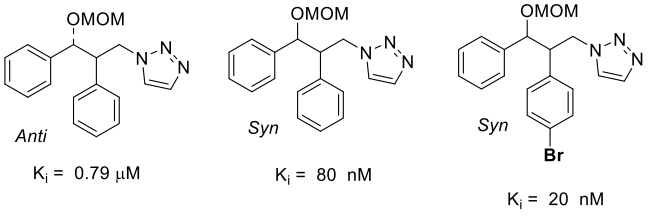


Figure 1. Aromatase (CYP 450 19A1) inhibitors.

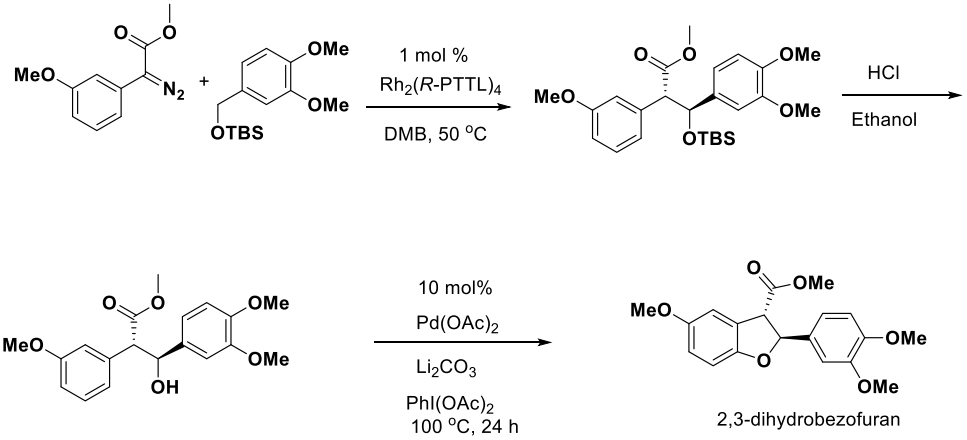
Received: December 24, 2020
Published: April 9, 2021

Downloaded via UNIV OF CONNECTICUT on May 15, 2021 at 07:31:24 (UTC).
See https://pubs.acs.org/sharingguidelines for options on how to legitimately share published articles.

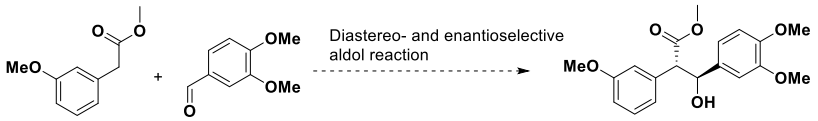
© 2021 American Chemical Society

https://doi.org/10.1021/acs.joc.0c03024
J. Org. Chem. 2021, 86, 6184–6194

Scheme 1. Sequential C−H Functionalizatlon Reactions for the Enantioselective Synthesis of Highly Functionalized 2,3-Dihydrobenzofurans by Davies Research Group[10]



Scheme 2. Possible Route for the Synthesis of Highly Functionalized Aldols via Diastereo- and Enantioselective Aldol Reactions of Substituted Phenylacetates



phenylacetate yielded *syn*-aldols as the major products while other arylacetates yielded *anti*-aldols as the major products. This led us to investigate *syn*-selective enolboration−aldolization of arylacetates. Our finding reveals that the combination of a less bulky boron reagent, a bulky amine, and ambient temperature is required for the synthesis of *syn*-*β*-hydroxy-*α*-substituted phenyl carboxylates via the boron-mediated aldol reaction of arylacetates. Herein, we discuss the development of temperature- and reagent-controlled complementary *syn*- and *anti*-selective enolboration−aldolization reactions of substituted phenylacetates.

RESULTS AND DISCUSSION

To optimize the reaction conditions for the diastereoselective enolboration−aldolization of substituted phenylacetates, methyl 2-*p*-tolylacetate (**1**) was enolized, in dichloromethane with dicyclohexylboron triflate (Chx_2BOTf, **4**) in the presence of triethylamine at −78 °C, followed by aldolization with benzaldehyde (**6a**) at the same temperature. The oxidative workup of the resultant boron aldolate intermediate provided methyl 3-hydroxy-3-phenyl-2-*p*-tolylpropanoate (**7a**) with excellent *anti*-selectivity (97% *anti*, 73% yield, Table 1, entry 1). This result was found to be consistent with the enolboration−aldolization of methyl phenylacetate at low temperature,[7a] but the enolboration−aldolization of **1**, at room temperature, provided the *anti*-isomer as a major product (70% *anti*, Table 1, entry 2). Interestingly, an unsubstituted phenylacetate, methyl phenylacetate, has been reported to provide 88% of the *syn*-isomer under identical conditions.[7a] Thus, it demonstrates that a minor variation of a substrate can drastically change the diastereoselectivity.

The poor *syn*-selectivity of the enolboration−aldolization of **1** led us to examine the impact of other factors on diastereoselectivity.[4−6] As expected, a more bulky ester, isopropyl 2-*p*-tolylacetate (**2**), marginally improved the *anti*-selectivity at room temperature (76% *anti*, Table 1, entry 3). However, the enolization of **2** with a less bulky boron reagent, dibutylboron triflate ($n\text{-}Bu_2BOTf$, **5**), in the presence of a bulky amine, *N*,*N*-diisopropylethylamine ($i\text{-}Pr_2NEt$), remarkably altered the diastereoselectivity of this transformation (72% *syn*, 81% yield, Table 1, entry 4).

We then focused our attention toward evaluating the effect of the ester on the *syn*-favoring boron reagent, **5**. To our expectation, the reaction of ethyl 2-*p*-tolylacetate (**3**) with **5**, under the same conditions, improved the *syn*-selectivity (85% *syn*, 79% yield, Table 1, entry 5). Moreover, the least bulky ester, **1**, displayed even superior *syn*-selectivity under these conditions (90% *syn*, 81% yield, Table 1, entry 6). To probe the impact of high temperature, the enolboration−aldolization of **1** with **5** was carried out at reflux. However, this increase in temperature resulted in an adverse effect on both the selectivity and yield (86% *syn*, 66% yield, Table 1, entry 7). Replacing dichloromethane with toluene had no impact on selectivity or yield (90% *syn*, 72% yield, Table 1, entry 8). We were also interested in examining whether the reaction time could be reduced without a negative impact on the diastereoselectivity and yield. Gratifyingly, we found that the enolization time for the *syn*-selective conditions could be brought from 2 h to 30 min.

To demonstrate the generality of this reaction under the standardized conditions for both *syn*-($n\text{-}Bu_2BOTf$, **5**/$i\text{-}Pr_2NEt$, rt) and *anti*-aldol formation (Chx_2BOTf, **4**/Et_3N, −78 °C), a series of aldehydes with variable steric and electronic features (hindered and unhindered, aliphatic, and aromatic with electron-donating and electron-withdrawing groups) were converted to their corresponding *β*-hydroxy-*α*-substituted phenylacetates. Therefore, methyl 2-*p*-tolylacetate (**1**) was treated with a reagent **4** in the presence of Et_3N at −78 °C, followed by aldolization with aromatic aldehydes bearing electron-donating, 4-methyl and 4-methoxy (**6b**, **6c**), and electron-withdrawing, 4-fluoro and 4-nitro (**6d**, **6e**), at the same temperature. This provided excellent *anti*-selectivity (95−96%) and in an overall yield of 67−78% (Table 2,

https://doi.org/10.1021/acs.joc.0c03024
J. Org. Chem. 2021, 86, 6184−6194

Scheme 3. Diastereoselective Enolboration–Aldolization of Carboxylic Acid Esters

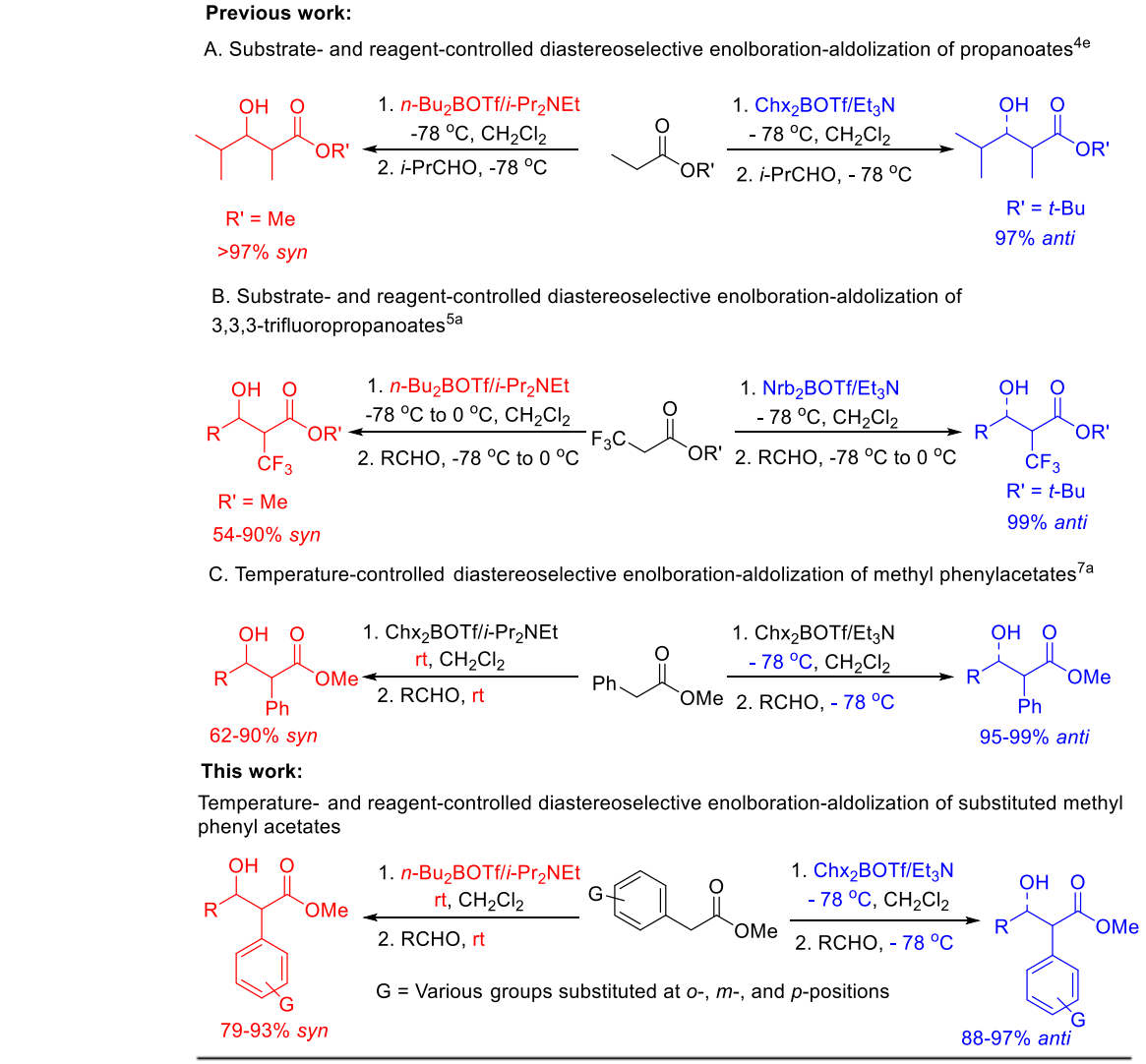
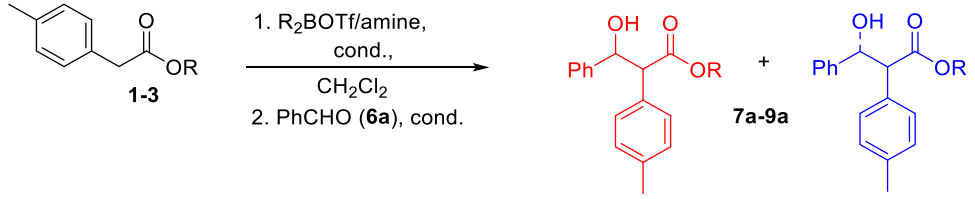


Table 1. Optimization of *Syn*- and *Anti*-Selectivity

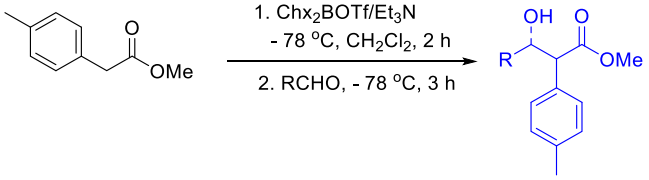


	ester		reaction conditions[a]			aldol products		
entry	#	R	amine	R_2BOTf	temp.	#	yield (%)[b]	*syn*:*anti*[c]
1	**1**	**Me**	**Et_3N**	**Chx_2BOTf**	**−78 °C**	**7a**	**73**	**3:97**
2	**1**	Me	Et_3N	Chx_2BOTf	rt	**7a**	64	30:70
3	**2**	*i*-Pr	Et_3N	Chx_2BOTf	rt	**8a**	70	24:76
4	**2**	*i*-Pr	*i*-Pr_2NEt	*n*-Bu_2BOTf	rt	**8a**	81	72:28
5	**3**	Et	*i*-Pr_2NEt	*n*-Bu_2BOTf	rt	**9a**	79	85:15
6	**1**	**Me**	***i*-Pr_2NEt**	***n*-Bu_2BOTf**	**rt**	**7a**	**81**	**90:10**
7	**1**	Me	*i*-Pr_2NEt	*n*-Bu_2BOTf	reflux	**7a**	66	86:14
8	**1**	Me	*i*-Pr_2NEt	*n*-Bu_2BOTf	rt	**7a**	72	90:10[d]

[a]Enolization and aldolization times were 2 and 3 h, respectively. [b]Combined yield of *syn* and *anti*-isomers. [c]*syn* and *anti*-ratios were determined by ^1H NMR spectroscopy. [d]Toluene was used as a solvent.

https://doi.org/10.1021/acs.joc.0c03024
J. Org. Chem. 2021, 86, 6184−6194

Table 2. Examination of Aldehydes for the *Anti*-Selective Aldol Reaction of Methyl 2-*p*-tolylacetate (1)



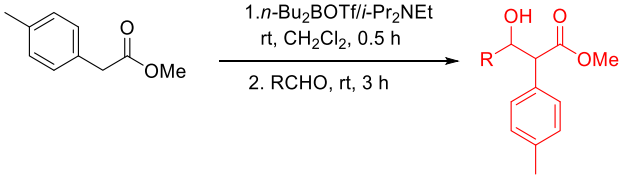
	RCHO		aldol		
entry	6	R	7	yield (%)[a]	*syn*:*anti*[b]
1	**6a**	C_6H_5	**7a**	73	3:97
2	**6b**	4-MeC_6H_4	**7b**	72	4:96
3	**6c**	4-$MeOC_6H_4$	**7c**	77	5:95
4	**6d**	4-FC_6H_4	**7d**	78	4:96
5	**6e**	4-$NO_2C_6H_4$	**7e**	67	5:95
6	**6f**	*E*-PhCH=CH	**7f**	76	4:96
7	**6g**	2-thienyl	**7g**	79	5:95
8	**6h**	*t*-Bu	**7h**	62	4:96
9	**6i**	*i*-Pr	**7i**	83	4:96
10	**6j**	*n*-Pr	**7j**	81	5:95

[a]Combined yields of *syn* and *anti*-isomers. [b]*syn* and *anti*-ratios were determined by ^{1}H NMR spectroscopy of a crude reaction mixture except in the case of entry 10 (^{13}C NMR was used).

entries 2–5). Similarly, cinnamaldehyde (*α,β*-unsaturated aldehyde, **6f**), heteroaromatic thiophene 2-carbaldehyde (**6g**), and sterically hindered as well as unhindered aliphatic aldehydes (**6h–j**) provided the similar selectivity (95–96% *anti*) and yields (76–83%) (Table 2, entries 6–10), but sterically hindered pivaldehyde (**6h**) provided a relatively lower yield of 62% (Table 1, entry 8).

Likewise, the same series of aldehydes under *syn*-selective conditions provided significantly good *syn*-selectivity (87–91%) in 69–83% yield (Table 3). The lone exception was once again pivaldehyde (79% *syn*, 54% yield).

Table 3. Examination of Aldehydes for the *Syn*-Selective Aldol Reaction of Methyl 2-*p*-tolylacetate (1)



	RCHO		aldol		
entry	6	R	7	yield (%)[a]	*syn*:*anti*[b]
1	**6a**	C_6H_5	**7a**	81	90:10
2	**6b**	4-MeC_6H_4	**7b**	76	87:13
3	**6c**	4-$MeOC_6H_4$	**7c**	77	90:10
4	**6d**	4-FC_6H_4	**7d**	83	89:11
5	**6e**	4-$NO_2C_6H_4$	**7e**	76	88:12
6	**6f**	*E*-PhCH=CH	**7f**	74	90:10
7	**6g**	2-thienyl	**7g**	69	90:10
8	**6h**	*t*-Bu	**7h**	54	79:21
9	**6i**	*i*-Pr	**7i**	73	89:11
10	**6j**	*n*-Pr	**7j**	76	91:9

[a]Combined yields of *syn* and *anti*-isomers. [b]*syn* and *anti*-ratios were determined by ^{1}H NMR spectroscopy of a crude reaction mixture except in the case of entry 10 (^{13}C NMR was used).

To expand the scope of this methodology, substituted methyl phenylacetates (ortho, meta, and para) with differing electronics and sterics were prepared via a Fischer esterification reaction. We chose various substituents in the phenyl ring based on two criteria: (1) availability of the corresponding substituted phenylacetic acid and (2) their electronic and steric properties to further evaluate the scope of our new *syn*- and *anti*-selective aldol chemistry.

All esters were examined under *anti*-selective conditions (Table 4). Phenylacetates with an electron-donating methyl group at the ortho- and meta positions provided 93% *anti*-selectivity in 75–90% yield. The methoxy group, which behaves as an electron-donating group due to resonance effects, was also examined. A *p*-methoxy-substituted ester provided 94% *anti*-selectivity in 77% yield, whereas an *o*-methoxy-substituted ester provided slightly lower selectivity (90% *anti*) but in good yield (82%). Since the introduction of a fluorine atom is known to alter the physical and biological properties of a molecule, we decided to synthesize *o*- and *m*-fluorine-substituted aldol products. *m*-Fluorine-substituted ester provided 96% *anti*-selectivity in a 76% yield. Like the *o*-methoxy group, an *o*-fluoro group also provided slightly lower selectivity (88% *anti*) but in good yield (86%). As discussed earlier, 1,2,3-triazole analogs of aldol products derived from bromine-substituted esters exhibit high inhibition potency against the aromatase enzyme complex (CYP 450 19A1) (Figure 1).[9] Therefore, we prepared *o*- and *p*-bromine-substituted aldols. Bromine-substituted esters provided 93–96% *anti*-selectivity in 70–87% yield. A trifluoromethyl-substituted ester provided similar results (93% *anti*, 88% yield) to fluoro-substituted esters (88–96% *anti*, 76–86% yield). The introduction of a bulky *t*-Bu group at the para position did not alter selectivity (91% *anti*), although a slightly lower yield (67%) was obtained. Additionally, aryl-substituted esters provided 93% *anti*-aldols in 80% yield. The same series of esters were also examined under *syn*-selective conditions and provided 87–93% *syn*-selectivity in yields ranging from 59 to 90% (Table 5).

CONCLUSIONS

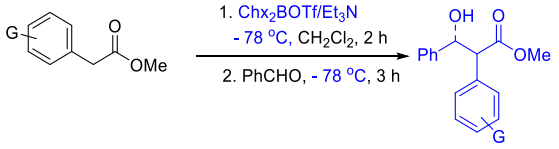
Complementary boron-mediated *syn*- and *anti*-selective aldol reactions of *o*-, *m*-, and *p*-substituted phenylacetates have been developed for the first time. The diastereoselectivity of this transformation was found to be dependent on temperature and the selection of a boron reagent. Throughout the course of our studies, we were successful in the synthesis of a series of diastereomerically pure *syn*- and *anti*-2,3-diarylpropanoates with various substituents on both aromatic rings. Thus, this methodology will provide easy access to molecules of high pharmaceutical importance and will enable their structure–activity relationships to be further explored.

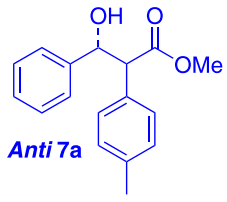
EXPERIMENTAL SECTION

General Information. All reactions were performed under an argon atmosphere. Dichloromethane was freshly distilled from anhydrous magnesium sulfate, and anhydrous toluene was purchased from Fisher Scientific. The oil bath was used as a heat source. All other chemicals were purchased from either Fisher Scientific Company or VWR and used without further purification. Reaction flasks, glass syringes, and needles were dried in an oven at 150 °C for 12 h. All compounds were purified by column chromatography using silica gel (100–200 mesh, Sorbent Technologies, Inc.) with hexane–ethyl acetate mixture as eluent. Pure fractions of the compound were collected after thin-layer chromatography (TLC) analysis, and it was

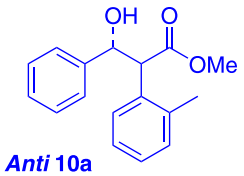
https://doi.org/10.1021/acs.joc.0c03024
J. Org. Chem. 2021, 86, 6184–6194

Table 4. *Anti*-Selective Aldol Reactions of Various *o*, *m*-, and *p*-Substituted Methyl Phenylacetates[a]

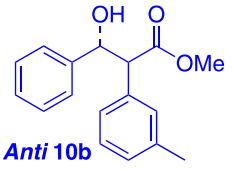




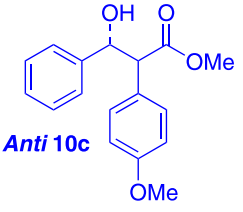
Anti:syn - 97:3
Yield - 73%



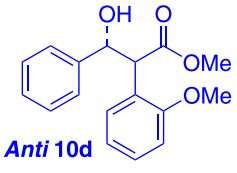
Anti:syn - 93:7
Yield - 90%



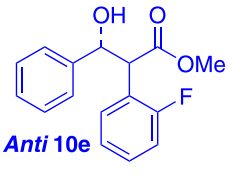
Anti:syn - 93:7
Yield - 75%



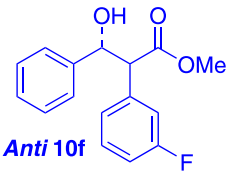
Anti:syn - 94:6
Yield - 77%



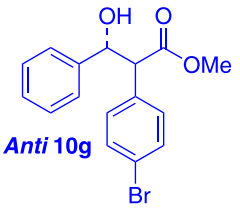
Anti:syn - 90:10
Yield - 82%



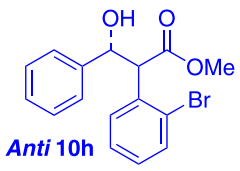
Anti:syn - 88:12
Yield - 86%



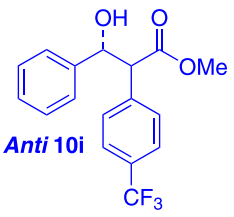
Anti:syn - 96:4
Yield - 76%



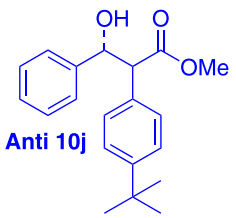
Anti:syn - 96:4
Yield - 70%



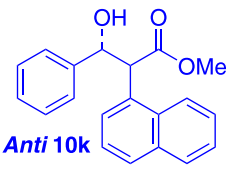
Anti:syn - 93:7
Yield - 87%



Anti:syn - 93:7
Yield - 88%



Anti:syn - 91:9
Yield - 67%



Anti:syn - 93:7
Yield - 80%

[a]All reported yields are combined yields of *syn* and *anti*-isomers. *syn* and *anti*-ratios were determined by ^{1}H NMR spectroscopy of a crude reaction mixture.

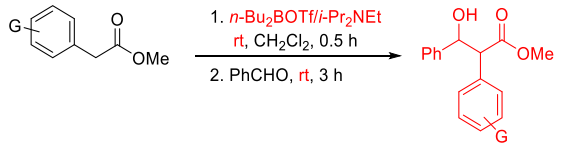
performed using glass-backed, thin-layer silica gel chromatography plates (Sorbent Technologies, Inc., 200 μm thickness, F-254 Indicator). ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature on a Bruker 400 MHz spectrometer. Chemical shift (δ) values are reported in parts per million (ppm), and they are referenced to tetramethylsilane. These data are reported as: δ value (multiplicity, *J*-value, integration, where s = singlet, d = doublet, t = triplet, dd = doublet of doublets, td = triplet of doublets, q = quartet, m = multiplet, brs = broad singlet). High-performance liquid chromatography (HPLC) coupled to accurate mass electrospray ionization (ESI) mass spectrometry was utilized in obtaining high-resolution mass spectra (HRMS). Specifically, an Agilent 1260 Infinity II quaternary liquid chromatograph coupled to an Agilent 6230 electrospray time-of-flight mass spectrometer was used for the detection of analytes. The samples were run in positive mode ionization with a capillary voltage of 4000v. No LC column was used for sample delivery; only flow through injection was utilized (direct injection from LC to a mass spectrometer). Mobile phases used were A: 30% liquid chromatography-mass spectrometry (LCMS) grade water with 0.1% formic acid and B: 70% LCMS grade acetonitrile with 0.1% formic acid with a flow rate of 0.4 mL/min.

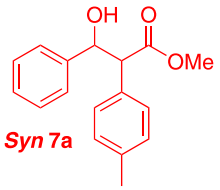
All substituted phenylacetates were prepared by the Fischer esterification reaction. Diastereomeric ratios (*syn*:*anti*-ratios) were determined by either ^{1}H NMR or ^{13}C NMR analysis of a crude reaction mixture.

General Procedure for the *anti*-Selective Aldol Reaction (A).[7a] Dicyclohexylborane was prepared by a reported procedure.[4e,7a,12] Thus, prepared dicyclohexylborane (Chx_2BH) (0.267 g, 1.5 mmol, 1.5 equiv) was transferred to a 50 mL round-bottom flask and suspended in 3 mL of dichloromethane. Then, trifluoromethanesulfonic acid (TfOH) (0.15 mL, 1.69 mmol, 1.69 equiv) was added dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h followed by cooling to −78 °C. Substituted methyl phenylacetate (1 mmol, 1.0 equiv), dissolved in 1 mL of dichloromethane, was slowly added to the cooled reaction mixture. Then, triethylamine (Et_3N) (0.30 mL, 2.2 mmol, 2.2 equiv) was added dropwise to the reaction mixture and stirred for 2 h at the same temperature (−78 °C). Desired aldehyde (1.5 mmol, 1.5 equiv) was added dropwise to the solution of enolate and stirred for 3 h at

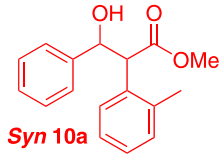
https://doi.org/10.1021/acs.joc.0c03024
J. Org. Chem. 2021, 86, 6184−6194

Table 5. *Syn*-Selective Aldol Reactions of Various *o*, *m*-, and *p*-Substituted Methyl Phenylacetates[a]

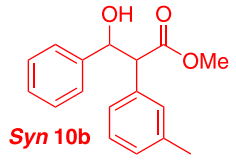




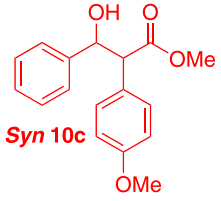
Syn:anti - 90:10
Yield - 73%



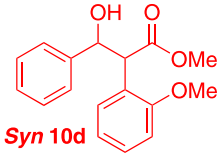
Syn:anti - 91:9
Yield - 84%



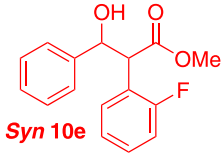
Syn:anti - 90:10
Yield - 84%



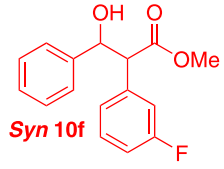
Syn:anti - 88:12
Yield - 72%



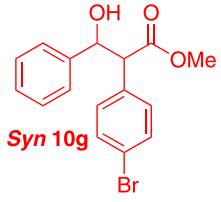
Syn:anti - 89:11
Yield - 76%



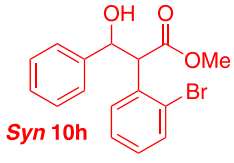
Syn:anti - 90:10
Yield - 59%



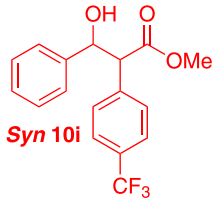
Syn:anti - 88:12
Yield - 82%



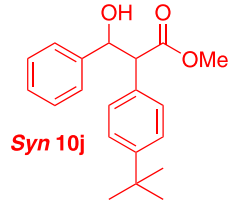
Syn:anti - 90:10
Yield - 63%



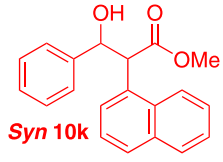
Syn:anti - 93:7
Yield - 73%



Syn:anti - 90:10
Yield - 76%



Syn:anti - 87:13
Yield - 90%



Syn:anti - 92:8
Yield - 79%

[a]All reported yields are combined yields of *syn* and *anti*-isomers. *syn* and *anti*-ratios were determined by ^{1}H NMR spectroscopy of a crude reaction mixture.

the same temperature (−78 °C). The reaction mixture containing boron aldolate was quenched by the addition of pH 7 buffer solution (2 mL) and mixed with MeOH (2 mL) followed by slow addition of 30% hydrogen peroxide (2 mL) and stirred for 4 h at room temperature. The organic layer containing the aldol product was separated and an aqueous layer was washed with dichloromethane (3 × 10 mL). The combined organic layers were then washed with saturated sodium chloride solution (5 mL) and dried over anhydrous Na_2SO_4. It was then filtered, concentrated *in vacuo*, and purified by silica gel column chromatography to obtain a pure *anti*-aldol product.

General Procedure for the *syn*-Selective Aldol Reaction (B). Dibutylboron triflate, *n*-Bu_2BOTf (1.0 M, 1.5 mL, 1.5 mmol, 1.5 equiv) was transferred to a 50 mL round-bottom flask and substituted phenylacetate (1 mmol, 1.0 equiv), dissolved in 1 mL of dichloromethane, was added to this solution. Typically, 1.5 mL of dichloromethane was added to the mixture. *N*,*N*-Diisopropylethylamine (*i*-Pr_2NEt) (0.38 mL, 2.2 mmol, 2.2 equiv) was then added dropwise to the reaction mixture and stirred for 0.5 h at room temperature. The desired aldehyde (1.5 mmol, 1.5 equiv) was added dropwise to the solution of enolate and stirred for 3 h at the same temperature (rt). The reaction mixture containing boron aldolate was cooled to 0 °C and quenched by the addition of pH 7 buffer solution (2 mL) and mixed with MeOH (2 mL) followed by slow addition of 30% hydrogen peroxide (2 mL) and stirred for 4 h at room temperature. The organic layer containing the aldol product was separated and an aqueous layer was washed with dichloromethane (3 × 10 mL). The combined organic layers were then washed with saturated sodium chloride solution (5 mL) and dried over anhydrous Na_2SO_4. It was then filtered, concentrated *in vacuo*, and purified by silica gel column chromatography to obtain a pure *syn*-aldol product.

Methyl 3-Hydroxy-3-phenyl-2-*p*-tolylpropanoate (7a). ***syn* 7a.** Compound *syn* **7a** was prepared by general procedure B. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1, v/v) was used to obtain pure *syn* **7a** as a white solid, yield: 199 mg, 73%, mp 106.1−107.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32−7.22 (m, 7H), 7.13 (d, J = 7.9 Hz, 2H), 5.25 (d, J = 7.7 Hz, 1H), 3.84 (d, J = 7.7 Hz, 1H), 3.50 (s, 3H), and 2.33 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.0, 141.1, 137.8, 131.8, 129.5, 129.1, 128.4, 128.1, 126.8, 75.2, 59.4, 52.1, and 21.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{17}H_{18}O_3Na$, 293.1148, found, 293.1148; $[M - H_2O + H]^+$ calcd for $C_{17}H_{17}O_2$, 253.1223; found, 253.1229.

https://doi.org/10.1021/acs.joc.0c03024
J. Org. Chem. 2021, 86, 6184−6194

anti 7a. Compound *anti* **7a** was prepared by general procedure A. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1 to 8:2, v/v) was used to obtain pure *anti* **7a** as a white solid, yield: 192 mg, 71%, mp 98.7−99.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18−7.16 (m, 3H), 7.11−7.09 (m, 2H), 6.99−6.95 (m, 4H), 5.15 (d, J = 9.3 Hz, 1H), 3.85 (d, J = 9.3 Hz, 1H), 3.70 (s, 3H), and 2.24 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 174.2, 141.0, 137.3, 132.3, 129.3, 128.5, 128.2, 127.9, 126.8, 76.7, 59.5, 52.4, and 21.1. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{17}H_{18}O_3Na$, 293.1148, found, 293.1129; $[M - H_2O + H]^+$ calcd for $C_{17}H_{17}O_2$, 253.1223; found, 253.1230.

Methyl 3-Hydroxy-2,3-dip-tolylpropanoate (7b). *syn 7b*. Compound *syn* **7b** was prepared by general procedure B. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1, v/v) was used to obtain pure *syn* **7b** as a white solid, yield: 188 mg, 66%, 90.8−92.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26−7.20 (m, 4H), 7.15−7.10 (m, 4H), 5.21 (d, J = 8.0 Hz, 1H), 3.83 (d, J = 8.0 Hz, 1H), 3.50 (s, 3H), 2.33 (s, 3H), 2.32 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.9, 138.2, 137.8, 137.7, 132.1, 129.5, 129.1, 126.7, 75.1, 59.5, 52.0, 21.3, and 21.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{20}O_3Na$, 307.1305, found, 307.1287; $[M - H_2O + H]^+$ calcd for $C_{18}H_{19}O_2$, 267.1380; found, 267.1379.

anti 7b. Compound *anti* **7b** was prepared by general procedure A. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1 to 8:2, v/v) was used to obtain pure *anti* **7b** as a white solid, yield: 196 mg, 69%, mp 96.2−98.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02−6.98 (m, 8H), 5.12 (d, J = 9.3 Hz, 1H), 3.85 (d, J = 9.3 Hz, 1H), 3.70 (s, 3H), 2.25 (s, 3H), and 2.24 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 174.2, 138.0, 137.5, 137.3, 132.4, 129.3, 128.9, 128.5, 126.7, 76.5, 59.4, 52.3, 21.2, and 21.1. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{20}O_3Na$, 307.1305, found, 307.1299; $[M - H_2O + H]^+$ calcd for $C_{18}H_{19}O_2$, 267.1380; found, 267.1373.

Methyl 3-Hydroxy-3-(4-methoxyphenyl)-2-*p*-tolylpropanoate (7c). *syn 7c*. Compound *syn* **7c** was prepared by general procedure B. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1, v/v) was used to obtain pure *syn* **7c** as a white solid, yield: 204 mg, 68%, mp 106.6−108.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27−7.24 (m, 4H), 7.15 (d, J = 7.9 Hz, 2H), 6.85−6.82 (m, 2H), 5.20 (d, J = 8.1 Hz, 1H), 3.82 (d, J = 8.0 Hz, 1H), 3.78 (s, 3H), 3.50 (s, 3H), and 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.9, 159.4, 137.8, 133.3, 132.1, 129.5, 129.0, 128.0, 113.8, 74.9, 59.6, 55.3, 52.0, and 21.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{20}O_4Na$, 323.1254, found, 323.1237; $[M - H_2O + H]^+$ calcd for $C_{18}H_{19}O_3$, 283.1329; found, 283.1322.

anti 7c. Compound *anti* **7c** was prepared by general procedure A. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1 to 8:2, v/v) was used to obtain pure *anti* **7c** as a white solid, yield: 219 mg, 73%, mp 116.8−118.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (d, J = 8.6 Hz, 2H), 7.00−6.95 (m, 4H), 6.71 (d, J = 8.7 Hz, 1H); 5.12 (d, J = 9.4 Hz, 1H), 3.83 (d, J = 9.4 Hz, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 3.03 (brs, 1H), and 2.25 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 174.3, 159.2, 137.2, 133.2, 132.4, 129.3, 128.5, 128.0, 113.6, 76.2, 59.6, 55.3, 52.3, and 21.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{20}O_4Na$, 323.1254, found, 323.1245; $[M - H_2O + H]^+$ calcd for $C_{18}H_{19}O_3$, 283.1329; found, 283.1319.

Methyl 3-(4-Fluorophenyl)-3-hydroxy-2-*p*-tolylpropanoate (7d). *syn 7d*. Compound *syn* **7d** was prepared by general procedure B. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1, v/v) was used to obtain pure *syn* **7d** as a white solid, yield: 214 mg, 74%, mp 111.5−113.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29−7.25 (m, 2H), 7.21−7.13 (m, 4H), 7.00−6.96 (m, 2H), 5.24 (d, J = 7.5 Hz, 1H), 3.78 (d, J = 7.5 Hz, 1H), 3.53 (s, 3H), 2.61 (brs, 1H), and 2.33 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.0, 162.5 (d, J_{C-F} = 244.6 Hz), 138.0, 136.8 (d, J_{C-F} = 3.0 Hz), 131.5, 129.6, 129.1, 128.5 (d, J_{C-F} = 8.1 Hz), 115.2 (d, J_{C-F} = 21.2 Hz), 74.5, 59.4, 52.2, and 21.2. HRMS (ESI-TOF) m/z: $[M - H_2O + H]^+$ calcd for $C_{17}H_{16}FO_2$, 271.1129; found, 271.1129.

anti 7d. Compound *anti* **7d** was prepared by general procedure A. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1 to 8:2, v/v) was used to obtain pure *anti* **7d** as a white solid, yield: 216 mg, 75%, mp 62.8−64.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07−7.03 (m, 2H), 7.00−6.92 (m, 4H), 6.88−6.84 (m, 2H), 5.14 (d, J = 9.4 Hz, 1H), 3.78 (d, J = 9.5 Hz, 1H), 3.71 (s, 3H), and 2.25 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 174.2, 162.3 (d, J_{C-F} = 244.4 Hz), 137.5, 136.7 (d, J_{C-F} = 3.3 Hz), 132.1, 129.4, 128.5, 128.4 (d, J_{C-F} = 8.0 Hz), 115.1 (d, J_{C-F} = 21.2 Hz), 76.0, 59.8, 52.4, and 21.2. HRMS (ESI-TOF) m/z: $[M - H_2O + H]^+$ calcd for $C_{17}H_{16}FO_2$, 271.1129; found, 271.1130.

Methyl 3-Hydroxy-3-(4-nitrophenyl)-2-*p*-tolylpropanoate (7e). *syn 7e*. Compound *syn* **7e** was prepared by general procedure B. The product was purified by silica gel column chromatography and hexane/ethyl acetate (8.5:1.5, v/v) was used to obtain pure *syn* **7e** as a yellow solid, yield: 211 mg, 67%, mp 157.4−158.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.13−7.08 (m, 4H), 5.40 (d, J = 6.3 Hz, 1H), 3.80 (d, J = 6.4 Hz, 1H), 3.60 (s, 3H), 3.11 (brs, 1H), and 2.32 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.2, 148.2, 147.6, 138.3, 130.4, 129.6, 129.2, 127.6, 123.5, 73.9, 58.5, 52.4, and 21.2. HRMS (ESI-TOF) m/z: $[M - H_2O + H]^+$ calcd for $C_{17}H_{16}NO_4$, 298.1074; found, 298.1079.

anti 7e. Compound *anti* **7e** was prepared by general procedure A. The product was purified by silica gel column chromatography and hexane/ethyl acetate (8.5:1.5, v/v) was used to obtain pure *anti* **7e** as a yellow solid, yield: 201 mg, 64%, mp 74.5−77.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J = 8.7 Hz, 2H), 7.22 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 7.9 Hz, 2H), 6.91 (d, J = 8.0 Hz, 2H), 5.27 (d, J = 9.4 Hz, 1H), 3.77 (d, J = 9.4 Hz, 1H), 3.72 (s, 3H), 3.57 (brs, 1H), and 2.27 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.8, 148.2, 147.5, 138.0, 129.7, 128.4, 127.7, 123.3, 75.7, 59.6, 52.6, and 21.2. HRMS (ESI-TOF) m/z: $[M - H_2O + H]^+$ calcd for $C_{17}H_{16}NO_4$, 298.1074; found 298.1078.

(*E*)-Methyl 3-Hydroxy-5-phenyl-2-*p*-tolylpent-4-enoate (7f). *syn 7f*. Compound *syn* **7f** was prepared by general procedure B. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1, v/v) was used to obtain pure *syn* **7f** as a white solid, yield: 197 mg, 67%, mp 77−79 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.23 (m, 7H), 7.17 (d, J = 7.9 Hz, 2H), 6.65 (d, J = 15.9 Hz, 1H), 6.19 (dd, J = 6.8, 15.9 Hz, 1H), 4.83 (t, J = 6.9 Hz, 1H), 3.73 (d, J = 7.3 Hz, 1H), 3.64 (s, 3H), 2.37 (brs, 1H), and 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.1, 137.9, 136.7, 132.4, 131.8, 129.6, 129.1, 128.7, 128.6, 127.9, 126.8, 73.8, 57.9, 52.2, and 21.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{19}H_{20}O_3Na$, 319.1305, found, 319.1296; $[M - H_2O + H]^+$ calcd for $C_{19}H_{19}O_2$, 279.1380; found, 279.1380.

anti 7f. Compound *anti* **7f** was prepared by general procedure A. The product was purified by silica gel column chromatography and hexane/ethyl acetate (8.5:1.5, v/v) was used to obtain pure *anti* **7f** as a white solid, yield: 215 mg, 73%, mp 96.7−98.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25−7.18 (m, 7H), 7.11 (d, J = 8.0 Hz, 2H), 6.53 (dd, J = 1.2, 15.9 Hz, 1H), 6.01 (dd, J = 5.9, 15.9 Hz, 1H), 4.83 (t, J = 7.5 Hz, 1H), 3.70 (d, J = 7.0 Hz, 1H), 3.69 (s, 3H), 3.04 (brs, 1H), and 2.30 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.9, 137.6, 136.7, 132.4, 131.6, 129.6, 128.8, 128.6, 127.7, 126.6, 74.1, 58.2, 52.3, and 21.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{19}H_{20}O_3Na$, 319.1305, found, 319.1298; $[M - H_2O + H]^+$ calcd for $C_{19}H_{19}O_2$, 279.1380; found, 279.1384.

Methyl 3-Hydroxy-3-(thiophen-2-yl)-2-*p*-tolylpropanoate (7g). *syn 7g*. Compound *syn* **7g** was prepared by general procedure B. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1 to 8.5:1.5, v/v) was used to obtain pure *syn* **7g** as a yellow semisolid, yield: 172 mg, 62%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, J = 8.1 Hz, 2H), 7.25−7.22 (m, 1H), 7.16 (d, J = 7.9 Hz, 2H), 7.00−6.99 (m, 1H), 6.95−6.93 (m, 1H), 5.54 (d, J = 8.2 Hz, 1H), 3.90 (d, J = 8.2 Hz, 1H), 3.57 (s, 3H), and 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.7, 144.7, 138.1, 131.7, 129.7, 129.0, 126.6, 125.2, 125.0, 71.4, 60.0, 52.2, and 21.2. HRMS

https://doi.org/10.1021/acs.joc.0c03024
J. Org. Chem. 2021, 86, 6184−6194

(ESI-TOF) m/z: $[M - H_2O + H]^+$ calcd for $C_{15}H_{15}O_2S$, 259.0787; found, 259.0790.

anti **7g**. Compound *anti* **7g** was prepared by general procedure A. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1 to 8.5:1.5, v/v) was used to obtain pure *anti* **7g** as an off-white solid, yield: 208 mg, 75%, mp 119.8−121.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16−7.14 (m, 1H), 7.08−7.03 (m, 4H), 6.79−6.77 (m, 1H), 6.61−6.60 (m, 1H), 5.44 (d, J = 9.1 Hz, 1H), 3.91 (d, J = 9.1 Hz, 1H), 3.71 (s, 3H), 3.36 (brs, 1H), and 2.28 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.8, 144.8, 137.5, 132.1, 129.4, 128.5, 126.5, 125.0, 124.9, 72.6, 59.6, 52.4, and 21.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{15}H_{16}O_3SNa$, 299.0712, found, 299.0701; $[M - H_2O + H]^+$ calcd for $C_{15}H_{15}O_2S$, 259.0787; found, 259.0789.

Methyl 3-Hydroxy-4,4-dimethyl-2-*p*-tolylpentanoate (7h). *syn* ***7h***. Compound *syn* **7h** was prepared by general procedure B. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9.2:0.8, v/v) was used to obtain pure *syn* **7h** as a colorless liquid, yield: 107 mg, 43%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 7.8 Hz, 2H), 4.00 (d, J = 7.6 Hz, 1H), 3.71 (d, J = 7.6 Hz, 1H), 3.62 (s, 3H), 2.32 (s, 3H), 1.89 (brs, 1H), and 0.91 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 174.4, 137.7, 133.1, 129.7, 129.5, 78.6, 53.5, 52.2, 35.6, 26.3, and 21.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{15}H_{22}O_3Na$, 273.1461, found, 273.1461; $[M - H_2O + H]^+$ calcd for $C_{15}H_{21}O_2$, 233.1536; found, 233.1532.

anti ***7h***. Compound *anti* **7h** was prepared by general procedure A. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9.2:0.8, v/v) was used to obtain pure *anti* **7h** as a white solid, yield: 148 mg, 59%, mp 83.1−84.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 7.9 Hz, 2H), 3.83−3.81 (m, 2H), 3.66−3.62 (m, 4H), 2.32 (s, 3H), and 0.89 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 175.2, 137.3, 135.1, 129.5, 128.3, 82.2, 52.3, 51.1, 36.3, 26.5, and 21.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{15}H_{22}O_3Na$, 273.1461, found, 273.1449; $[M - H_2O + H]^+$ calcd for $C_{15}H_{21}O_2$, 233.1536; found, 233.1528.

Methyl 3-Hydroxy-4-methyl-2-*p*-tolylpentanoate (7i). *syn* ***7i***. Compound *syn* **7i** was prepared by general procedure B. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9.2:0.8, v/v) was used to obtain pure ***syn* 7i** as a colorless liquid, yield: 151 mg, 64%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 7.9 Hz, 2H), 3.94 (dd, J = 5.9 Hz, 6.6 Hz, 1H), 3.70 (d, J = 6.8 Hz, 1H), 3.64 (s, 3H), 2.32 (s, 3H), 2.32 (brs, 1H), 1.66−1.58 (m, 1H), 0.98 (d, J = 6.0 Hz, 3H), and 0.96 (d, J = 6.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 174.0, 137.5, 132.4, 129.5, 129.2, 76.9, 54.5, 52.1, 30.8, 21.1, 19.8, and 16.8. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{14}H_{20}O_3Na$, 259.1305, found, 259.1296; $[M - H_2O + H]^+$ calcd for $C_{14}H_{19}O_2$, 219.1380; found, 219.1377.

anti ***7i***. Compound *anti* **7i** was prepared by general procedure A. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9.2:0.8, v/v) was used to obtain pure *anti* **7i** as a white solid, yield: 186 mg, 79%, mp 83.5−84.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, J = 8.1 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 4.05 (dd, J = 2.8 Hz, 9.4 Hz, 1H), 3.69 (d, J = 9.4 Hz, 1H), 3.67 (s, 3H), 2.33 (s, 3H), 1.48−1.44 (m, 1H), 0.93 (d, J = 6.9 Hz, 3H), and 0.86 (d, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 174.6, 137.4, 133.3, 129.6, 128.3, 77.3, 55.6, 52.2, 29.1, 21.2, 20.4, and 14.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{14}H_{20}O_3Na$, 259.1305, found, 259.1299; $[M - H_2O + H]^+$ calcd for $C_{14}H_{19}O_2$, 219.1380; found, 219.1379.

Methyl 3-Hydroxy-2-*p*-tolylhexanoate (7j). *syn* ***7j***. Compound *syn* **7j** was prepared by general procedure B. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9.2:0.8, v/v) was used to obtain pure *syn* **7j** as a white solid, yield: 155 mg, 66%, mp 46.7−48.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 7.9 Hz, 2H), 4.17 (q, J = 6.6 Hz, 1H), 3.66 (s, 3H), 3.54 (d, J = 6.4 Hz, 1H), 2.33 (s, 3H), 2.33 (brs, 1H), 1.57−1.49 (m, 1H), 1.40−1.36 (m, 3H), and 0.91 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 174.0, 137.6, 132.2, 129.5, 129.2, 72.0, 57.0, 52.1, 36.7, 21.2, 19.1, and 14.1. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{14}H_{20}O_3Na$, 259.1305, found, 259.1278; $[M - H_2O + H]^+$ calcd for $C_{14}H_{19}O_2$, 219.1380; found, 219.1375.

anti ***7j***. Compound *anti* **7j** was prepared by general procedure A. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9.2:0.8, v/v) was used to obtain pure *anti* **7j** as a white solid, yield: 190 mg, 80%, mp 87.1−89.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17−7.12 (m, 4H), 4.17−4.12 (m, 1H), 3.66 (s, 3H), 3.54 (d, J = 9.1 Hz, 1H), 2.33 (s, 3H), 1.60−1.45 (m, 1H), 1.32−1.22 (m, 3H), and 0.82 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 174.5, 137.5, 133.3, 129.6, 128.3, 73.2, 58.4, 52.2, 36.1, 21.2, 18.7, and 13.9. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{14}H_{20}O_3Na$, 259.1305, found, 259.1282; $[M - H_2O + H]^+$ calcd for $C_{14}H_{19}O_2$, 219.1380; found, 219.1373.

Methyl 3-Hydroxy-3-phenyl-2-*o*-tolylpropanoate (10a). *syn* ***10a***. Compound *syn* **10a** was prepared by general procedure B. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1, v/v) was used to obtain pure *syn* **10a** as a white solid, yield: 209 mg, 77%, mp 61.4−63.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (dd, J = 1.4 Hz, 7.6 Hz, 1H), 7.29−7.14 (m, 8H), 5.33 (d, J = 7.5 Hz, 1H), 4.21 (d, J = 7.5 Hz, 1H), 3.51 (s, 3H), 2.56 (brs, 1H), and 2.16 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.3, 141.3, 138.0, 133.4, 130.7, 128.4, 128.1, 127.8, 127.7, 126.9, 126.5, 75.3, 54.3, 52.1, and 19.9. HRMS (ESI-TOF) m/z: $[M - H_2O + H]^+$ calcd for $C_{17}H_{17}O_2$, 253.1223; found, 253.1223.

anti ***10a***. Compound *anti* **10a** was prepared by general procedure A. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9.2:0.8, v/v) was used to obtain pure *anti* **10a** as a white solid, yield: 226 mg, 84%, mp 107.8−109.8 °C. 1H NMR (400 MHz, $CDCl_3$): δ 7.40 (dd, J = 1.3 Hz, 7.7 Hz, 1H), 7.17−7.12 (m, 4H), 7.10−7.04 (m, 3H), 6.94 (d, J = 7.4 Hz, 1H), 5.20 (d, J = 9.4 Hz, 1H), 4.15 (d, J = 9.5 Hz, 1H), 3.69 (s, 3H), and 1.86 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 174.6, 140.6, 136.9, 133.9, 130.6, 128.0, 127.8, 127.6, 126.6 126.2, 76.5, 55.1, 52.4, and 19.5. HRMS (ESI-TOF) m/z: $[M - H_2O + H]^+$ calcd for $C_{17}H_{17}O_2$, 253.1223; found, 253.1220.

Methyl 3-Hydroxy-3-phenyl-2-*m*-tolylpropanoate (10b). *syn* ***10b***. Compound *syn* **10b** was prepared by general procedure B. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1, v/v) was used to obtain pure *syn* **10b** as a white solid, yield: 205 mg, 76%. mp 83.3−85.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.11 (m, 9H), 5.26 (d, J = 8.0 Hz, 1H), 3.84 (d, J = 8.0 Hz, 1H), 3.50 (s, 3H), 2.34 (brs, 1H), and 2.34 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.8, 141.1, 138.5, 134.8, 129.9, 128.9, 128.7, 128.4, 128.1, 126.8, 126.2, 75.2, 59.9, 52.1, and 21.6. HRMS (ESI-TOF) m/z: $[M - H_2O + H]^+$ calcd for $C_{17}H_{17}O_2$, 253.1223; found, 253.1218.

anti ***10b***. Compound *anti* **10b** was prepared by general procedure A. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1, v/v) was used to obtain pure *anti* **10b** as a white solid, yield: 190 mg, 70%, mp 92.5−94.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18−7.15 (m, 3H), 7.10−7.07 (m, 2H), 7.04 (d, J = 7.6 Hz, 1H), 6.97 (d, J = 7.5 Hz, 1H), 6.89 (s, 1H), 6.86 (d, J = 7.6 Hz, 1H), 5.15 (d, J = 9.2 Hz, 1H), 3.84 (d, J = 9.2 Hz, 1H), 3.70 (s, 3H), 3.23 (brs, 1H), and 2.22 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 174.1, 140.9, 138.2, 135.2, 129.3, 128.4, 128.4, 128.2, 127.8, 126.7, 125.7, 76.6, 59.8, 52.4, and 21.4. HRMS (ESI-TOF) m/z: $[M - H_2O + H]^+$ calcd for $C_{17}H_{17}O_2$, 253.1223; found, 253.1228.

Methyl 3-Hydroxy-2-(4-methoxyphenyl)-3-phenylpropanoate (10c). *syn* ***10c***. Compound *syn* **10c** was prepared by general procedure B. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1, v/v) was used to obtain pure *syn* **10c** as a white solid, yield: 183 mg, 64%, mp 101.8−103.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30−7.24 (m, 7H), 6.85 (dd, J = 2.2 Hz, 6.7 Hz, 2H), 5.24 (d, J = 7.5 Hz, 1H), 3.81 (d, J = 7.5 Hz, 1H), 3.78 (s, 3H), 3.51 (s, 3H), and 2.56 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.2, 159.5, 141.1, 130.3, 128.3, 128.0, 126.8, 114.2, 75.1, 58.9, 55.4, and 52.1. HRMS (ESI-TOF) m/z: $[M - H_2O + H]^+$ calcd for $C_{17}H_{17}O_3$, 269.1172; found, 269.1156.

https://doi.org/10.1021/acs.joc.0c03024
J. Org. Chem. 2021, 86, 6184−6194

anti ***10c.*** Compound *anti* **10c** was prepared by general procedure A. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1−8.5:1.5, v/v) was used to obtain pure *anti* **10c** as a white solid, yield: 206 mg, 72%, mp 68.9−72.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19−7.17 (m, 3H), 7.11−7.08 (m, 2H), 7.00−6.98 (m, 2H), 6.71−6.69 (m, 2H), 5.13(d, J = 9.4 Hz, 1H), 3.82 (d, J = 9.4 Hz, 1H), 3.72 (s, 3H), and 3.71 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 174.3, 159.0, 141.0, 129.7, 128.2, 127.9, 127.4, 126.8, 114.0, 76.8, 59.1, 55.3, and 52.4. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{17}H_{18}O_4Na$, 309.1097, found, 309.1068; [M − H_2O + H]$^+$ calcd for $C_{17}H_{17}O_3$, 269.1172; found, 269.1173.

Methyl 3-Hydroxy-2-(2-methoxyphenyl)-3-phenylpropanoate (10d). *syn* ***10d.*** Compound *syn* **10d** was prepared by general procedure B. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1, v/v) was used to obtain pure *syn* **10d** as a white solid, yield: 195 mg, 68%, mp 81.2−83.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (dd, J = 1.5 Hz, 7.6 Hz, 1H), 7.26−7.19 (m, 6H), 6.92 (td, J = 0.6 Hz, 7.5 Hz, 1H), 6.79 (d, J = 8.2 Hz, 1H), 5.37 (dd, J = 2.7 Hz, 5.9 Hz, 1H), 4.47 (d, J = 5.9 Hz, 1H), 3.58 (s, 3H), 3.57 (s, 3H), and 3.08 (d, J = 2.9 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.8, 157.6, 141.4, 130.0, 129.0, 127.9, 127.6, 126.7, 123.6, 120.7, 111.1, 74.6, 55.7, 52.1, and 51.2. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{17}H_{18}O_4Na$, 309.1097, found, 309.1084; [M − H_2O + H]$^+$ calcd for $C_{17}H_{17}O_3$, 269.1172; found, 269.1173.

anti ***10d.*** Compound *anti* **10d** was prepared by general procedure A. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1 to 8.5:1.5, v/v) was used to obtain pure *anti* **10d** as a white solid, yield: 212 mg, 74%, mp 110.4−112.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16−7.09 (m, 6H), 7.04 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 6.79 (td, J = 0.8 Hz, 7.5 Hz, 1H), 6.70 (d, J = 8.2 Hz, 1H), 5.17 (dd, J = 3.5 Hz, 8.6 Hz, 1H), 4.28 (d, J = 8.6 Hz, 1H), 3.86 (d, J = 4.0 Hz), 3.68 (s, 3H), and 3.58 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 175.0, 156.8, 141.1, 129.6, 128.8, 127.8, 127.5, 126.7, 124.6, 120.7, 111.0, 75.4, 55.5, 52.9, and 52.3. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{17}H_{18}O_4Na$, 309.1097, found, 309.1093; [M − H_2O + H]$^+$ calcd for $C_{17}H_{17}O_3$, 269.1172; found, 269.1171.

Methyl 2-(2-Fluorophenyl)-3-hydroxy-3-phenylpropanoate (10e). *syn* ***10e.*** Compound *syn* **10e** was prepared by general procedure B. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1, v/v) was used to obtain pure *syn* **10e** as a white solid, yield: 145 mg, 53%, mp 82.3−85.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (td, J = 1.6 Hz, 7.6 Hz, 1H), 7.26−7.20 (m, 6H), 7.10 (td, J = 1.0 Hz, 7.6 Hz, 1H), 6.98−6.93 (m, 1H), 5.40 (d, J = 6.0 Hz, 1H), 4.3 (d, J = 6.0 Hz, 1H), 3.60 (s, 3H), and 2.91 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.9, 161.2 (d, J_{C-F} = 245.4 Hz), 140.8, 130.5 (d, J_{C-F} = 3.2 Hz), 129.4 (d, J_{C-F} = 8.5 Hz), 128.3, 128.0, 126.5, 124.1 (d, J_{C-F} = 3.6 Hz), 121.9 (d, J_{C-F} = 14.5 Hz), 115.4 (d, J_{C-F} = 22.7 Hz), 74.3, 52.4, and 51.0. HRMS (ESI-TOF) m/z: [M − H_2O + H]$^+$ calcd for $C_{16}H_{14}FO_2$, 257.0972; found, 257.0961.

anti ***10e.*** Compound *anti* **10e** was prepared by general procedure A. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1−8.5:1.5, v/v) was used to obtain pure *anti* **10e** as a white solid, yield: 209 mg, 76%, mp 74.6−76.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20−7.13 (m, 7H), 7.01−6.97 (m, 1H), 6.89−6.85 (m, 1H), 5.21 (d, J = 8.8 Hz, 1H), 4.23 (d, J = 9.0 Hz, 1H), and 3.72 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.7, 160.4 (d, J_{C-F} = 245.1 Hz), 140.5, 130.0 (d, J_{C-F} = 3.6 Hz), 129.4 (d, J_{C-F} = 8.4 Hz), 128.2, 128.0, 126.7, 124.2 (d, J_{C-F} = 3.6 Hz), 123.0 (d, J_{C-F} = 14.6 Hz), 115.6 (d, J_{C-F} = 22.1 Hz), 75.6 (d, J_{C-F} = 1.0 Hz), 52.6, 52.2. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{16}H_{15}FO_3Na$, 297.0897, found, 297.0898; [M − H_2O + H]$^+$ calcd for $C_{16}H_{14}FO_2$, 257.0972; found for [M − H_2O + H]$^+$, 257.0981.

Methyl 2-(3-Fluorophenyl)-3-hydroxy-3-phenylpropanoate (10f). *syn* ***10f.*** Compound *syn* **10f** was prepared by general procedure B. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1, v/v) was used to obtain pure *syn* **10f** as a white solid, yield: 196 mg, 72%, mp 71−73 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29−7.25 (m, 6H), 7.10−7.00 (m, 2H), 6.98−6.96 (m, 1H), 5.28 (d, J = 7.2 Hz, 1H), 3.87 (d, J = 7.2 Hz, 1H), 3.54 (s, 3H), and 2.57 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.6, 162.8 (d, J_{C-F} = 244.7 Hz), 140.7, 137.2 (d, J_{C-F} = 7.4 Hz), 130.0 (d, J_{C-F} = 8.3 Hz), 128.4, 128.2, 126.6, 125.2 (d, J_{C-F} = 2.9 Hz), 116.3 (d, J_{C-F} = 22.0 Hz), 115.0 (d, J_{C-F} = 21.0 Hz), 75.0, 59.2 (d, J_{C-F} = 1.4 Hz), and 52.3. HRMS (ESI-TOF) m/z: [M − H_2O + H]$^+$ calcd for $C_{16}H_{14}FO_2$, 257.0972; found, 257.0978.

anti ***10f.*** Compound *anti* **10f** was prepared by general procedure A. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1 to 8.5:1.5, v/v) was used to obtain pure *anti* **10f** as a white solid, yield: 201 mg, 73%, mp 75.5−77.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22−7.11 (m, 6H), 7.00−6.97 (m, 1H), 6.89−6.84 (m, 1H), 5.20 (d, J = 9.0 Hz, 1H), 4.23 (d, J = 9.0 Hz, 1H), and 3.72 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.7, 160.4 (d, J_{C-F} = 245.2 Hz), 140.5, 130.0 (d, J_{C-F} = 3.6 Hz), 129.4 (d, J_{C-F} = 8.4 Hz), 128.2, 128.0, 126.7, 124.2 (d, J_{C-F} = 3.6 Hz), 123.0 (d, J_{C-F} = 14.6 Hz), 115.5 (d, J_{C-F} = 22.1 Hz), 75.6, 52.6, and 52.2. HRMS (ESI-TOF) m/z: [M − H_2O + H]$^+$ calcd for $C_{16}H_{14}FO_2$, 257.0972; found, 257.0983.

Methyl 2-(4-Bromophenyl)-3-hydroxy-3-phenylpropanoate (10g). *syn* ***10g.*** Compound *syn* **10g** was prepared by general procedure B. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1, v/v) was used to obtain pure *syn* **10g** as a white solid, yield: 190 mg, 57%, mp 117.7−119.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (dd, J = 1.9 Hz, 6.6 Hz, 2H), 7.29−7.23 (m, 5H), 7.16 (dd, J = 1.8 Hz, 6.6 Hz, 2H), 5.28 (d, J = 6.8 Hz, 1H), 3.83 (d, J = 6.8 Hz, 1H), 3.55 (s, 3H), and 2.71 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.8, 140.7, 133.7, 131.7, 131.1, 128.4, 128.2, 126.6, 122.1, 74.8, 58.9, and 52.3. HRMS (ESI-TOF) m/z: [M − H_2O + H]$^+$ calcd for $C_{16}H_{14}BrO_2$, 317.0172; found, 317.0165.

anti ***10g.*** Compound *anti* **10g** was prepared by general procedure A. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1−8.5:1.5, v/v) was used to obtain pure *anti* **10g** as a white solid, yield: 223 mg, 66%, mp 134.8−137.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (dd, J = 1.9 Hz, 6.6 Hz, 2H), 7.20−7.18 (m, 3H), 7.10−7.07 (m, 2H), 6.95 (dd, J = 1.8 Hz, 6.6 Hz, 2H), 5.12 (d, J = 9.4 Hz, 1H), 3.84 (d, J = 9.4 Hz, 1H), 3.72 (s, 3H), and 3.11 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.5, 140.5, 134.3, 131.7, 130.4, 128.4, 128.1, 126.7, 121.8, 76.6, 59.4, and 52.5. HRMS (ESI-TOF) m/z: [M − H_2O + H]$^+$ calcd for $C_{16}H_{14}BrO_2$, 317.0172; found, 317.0182.

Methyl 2-(2-Bromophenyl)-3-hydroxy-3-phenylpropanoate (10h). *syn* ***10h.*** Compound *syn* **10h** was prepared by general procedure B. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1, v/v) was used to obtain pure *syn* **10h** as a white colorless semisolid, yield: 227 mg, 68%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (dd, J = 1.4 Hz, 7.8 Hz, 1H), 7.51 (dd, J = 0.7 Hz, 8.0 Hz, 1H), 7.30 (td, J = 0.7 Hz, 7.8 Hz, 1H), 7.25 (s, 5H), 7.12 (td, J = 1.5 Hz, 7.9 Hz, 1H), 5.36 (dd, J = 2.7 Hz, J = 6.7 Hz, 1H), 4.67 (d, J = 6.8 Hz, 1H), 3.55 (s, 3H), and 2.75 (d, J = 2.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.7, 140.7, 134.6, 133.0, 130.0, 129.3, 128.3, 128.1, 127.6, 126.8, 126.6, 75.1, 56.6, and 52.3. HRMS (ESI-TOF) m/z: [M − H_2O + H]$^+$ calcd for $C_{16}H_{14}BrO_2$, 317.0172; found, 317.0181.

anti ***10h.*** Compound *anti* **10h** was prepared by general procedure A. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1 to 8.5:1.5, v/v) was used to obtain pure *anti* **10h** as a white solid, yield: 270 mg, 81%, mp 121.3−123.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (dd, J = 1.3 Hz, 8.0 Hz, 1H), 7.36 (dd, J = 1.6 Hz, 7.8 Hz, 1H), 7.24−7.19 (m, 6H), 7.07−7.03 (m, 1H), 5.23 (d, J = 8.0 Hz, 1H), 4.55 (d, J = 8.0 Hz, 1H), 3.70 (s, 3H), and 3.70 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.9, 140.4, 135.3, 133.3, 130.0, 129.2, 128.2, 127.9, 127.6, 126.6, 125.1, 75.7, 57.4, and 52.6. HRMS (ESI-TOF) m/z: [M − H_2O + H]$^+$ calcd for $C_{16}H_{14}BrO_2$, 317.0172; found, 317.0180.

Methyl 3-Hydroxy-3-phenyl-2-(4-trifluoromethyl)-phenylpropanoate (10i). *syn* ***10i.*** Compound *syn* **10i** was prepared by general procedure B. The product was purified by silica gel column

https://doi.org/10.1021/acs.joc.0c03024
J. Org. Chem. 2021, 86, 6184−6194

chromatography and hexane/ethyl acetate (9:1, v/v) was used to obtain pure *syn* **10i** as a white solid, yield: 220 mg, 68%, mp 130.5−132.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.30−7.23 (m, 5H), 5.35 (d, J = 6.8 Hz, 1H), 3.95 (d, J = 6.7 Hz, 1H), 3.57 (s, 3H), and 2.71 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.6, 140.6, 138.8, 130.2 (q, J_{C-F} = 32.3, 64.8 Hz), 129.8, 128.5, 128.3, 126.5, 125.4 (q, J_{C-F} = 3.8, 7.5 Hz), 124.2 (q, J_{C-F} = 270.5, 540.9 Hz), 74.8, 59.2, and 52.4. HRMS (ESI-TOF) m/z: $[M - H_2O + H]^+$ calcd for $C_{17}H_{14}F_3O_2$, 307.0940; found, 307.0943.

anti ***10i***. Compound *anti* **10i** was prepared by general procedure A. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1 to 8.5:1.5, v/v) was used to obtain pure *anti* **10i** as a white solid, yield: 267 mg, 82%, mp 78.8−80.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J = 8.1 Hz, 2H), 7.22−7.19 (m, 5H), 7.10−7.08 (m, 2H), 5.18 (d, J = 9.3 Hz, 1H), 3.96 (d, J = 9.3 Hz, 1H), 3.74 (s, 3H), and 3.11 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.5, 140.5, 139.5, 130.2 (q, J_{C-F} = 32.3, 64.5 Hz), 129.3, 128.7, 128.5, 126.9, 125.7 (q, J_{C-F} = 3.7, 7.5 Hz), 124.3 (q, J_{C-F} = 270.5, 540.9 Hz), 76.7, 60.0, and 52.8. HRMS (ESI-TOF) m/z: $[M - H_2O + H]^+$ calcd for $C_{17}H_{14}F_3O_2$, 307.0940; found, 307.0950.

Methyl 2-(4-*tert*-butylphenyl)-3-hydroxy-3-phenylpropanoate (10j). ***syn 10j***. Compound *syn* **10j** was prepared by general procedure B. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1, v/v) was used to obtain pure *syn* **10j** as a white solid, yield: 245 mg, 78%, mp 96.2−98.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.24 (m, 9H), 5.24 (d, J = 8.2 Hz, 1H), 3.85 (d, J = 8.2 Hz, 1H), 3.48 (s, 3H), 2.37 (brs, 1H), and 1.31 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.8, 151.1, 141.2, 131.9, 128.8, 128.4, 128.1, 126.9, 125.8, 75.4, 59.6, 52.0, 34.6, and 31.4. HRMS (ESI-TOF) m/z: $[M - H_2O + H]^+$ calcd for $C_{20}H_{23}O_2$, 295.1693; found, 295.1689.

anti ***10j***. Compound *anti* **10j** was prepared by general procedure A. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9:1 to 8.5:1.5, v/v) was used to obtain pure *anti* **10j** as a white solid, yield: 189 mg, 61%, mp 125−126.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20−7.17 (m, 5H), 7.11−7.09 (m, 2H), 7.03−7.00 (m, 2H), 5.14 (d, J = 8.9 Hz, 1H), 3.87 (d, J = 8.8 Hz, 1H), 3.70 (s, 3H), and 1.24 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 174.2, 150.6, 141.1, 132.2, 128.3, 128.2, 127.8, 126.7, 125.5, 76.7, 59.3, 52.3, 34.5, and 31.4. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{20}H_{24}O_3Na$, 335.1618, found, 335.1620; $[M - H_2O + H]^+$ calcd for $C_{20}H_{23}O_2$, 295.1693; found for $[M - H_2O + H]^+$, 295.1693.

Methyl 3-Hydroxy-2-(naphthalen-1-yl)-3-phenylpropanoate (10k). ***syn 10k***. Compound *syn* **10k** was prepared by general procedure B. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9.7:0.3 to 9.5:0.5, v/v) was used to obtain pure *syn* **10k** as a yellow solid, yield: 224 mg, 73%, mp 143.8−145.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82−7.79 (m, 4H), 7.49−7.45 (m, 3H), 7.35−7.23 (m, 5H), 5.38 (d, J = 7.6 Hz, 1H), 4.05 (d, J = 7.6 Hz, 1H), 3.52 (s, 3H), and 2.59 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.9, 141.0, 133.4, 133.1, 132.4, 128.6, 128.5, 128.4, 128.2, 128.1, 127.8, 126.4, 126.3, 75.2, 59.9, and 52.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{20}H_{18}O_3Na$, 329.1148, found, 329.1143; $[M - H_2O + H]^+$ calcd for $C_{20}H_{17}O_2$, 289.1223; found, 289.1227.

anti ***10k***. Compound *anti* **10k** was prepared by general procedure A. The product was purified by silica gel column chromatography and hexane/ethyl acetate (9.5:0.5 to 9:1, v/v) was used to obtain pure *anti* **10k** as a yellow solid, yield: 226 mg, 74%, mp 119.2−121.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74−7.69 (m, 2H), 7.65 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 1.2 Hz, 1H), 7.42−7.40 (m, 2H), 7.18 (dd, J = 1.8, 8.5 Hz, 1H), 7.14−7.10 (m, 5H), 5.30 (d, J = 9.4 Hz, 1H), 4.06 (d, J = 9.3 Hz, 1H), and 3.72 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 174.0, 140.8, 133.3, 132.8, 128.3, 128.3, 128.0, 127.9, 127.8, 127.7, 126.5, 126.2, 126.1, 76.7, 60.0, and 52.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{20}H_{18}O_3Na$, 329.1148, found, 329.1133; $[M - H_2O + H]^+$ calcd for $C_{20}H_{17}O_2$, 289.1223; found, 289.1220.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c03024.

Spectroscopic data from ^{1}H and ^{13}C NMR (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Prem B. Chanda − *Department of Chemistry and Physics, Southeastern Louisiana University, Hammond, Louisiana 70402, United States;* orcid.org/0000-0003-1735-3649; Email: prem.chanda@selu.edu

Authors

Angela Y. Thomas − *Department of Chemistry and Physics, Southeastern Louisiana University, Hammond, Louisiana 70402, United States*

Tommy L. Walls III − *Department of Chemistry and Physics, Southeastern Louisiana University, Hammond, Louisiana 70402, United States*

Brionna N. Nelson − *Department of Chemistry and Physics, Southeastern Louisiana University, Hammond, Louisiana 70402, United States*

Stafford W. Primeaux − *Department of Chemistry and Physics, Southeastern Louisiana University, Hammond, Louisiana 70402, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c03024

Author Contributions

†A.Y.T. and T.L.W. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge funding from the Southeastern Louisiana University and Louisiana Biomedical Research Network (LBRN). Mass Spectrometry Facility of the Louisiana State University is acknowledged for acquisition of high-resolution mass spectrometry data.

■ REFERENCES

(1) (a) Cowden, C. J.; Paterson, I. *Organic Reactions*; John Wiley & Sons: New York, 1997; Vol. *51*, pp 1−200. (b) Mahrwald, R. *Boron and Silicon Enolates in Crossed Aldol Reactions*; Modern Aldol Reactions; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2004; Vol. *1*, pp 127−160. (c) Mahrwald, R. *Boron Enolates*; Aldol Reactions; Springer: Heidelberg, London, New York, 2009; pp 23−38. (d) Abiko, A. Boron Enolate Chemistry. *ACS Symp. Ser.* **2016**, *1236*, 123−171.

(2) (a) Mukaiyama, T.; Inoue, T. New Cross-aldol Reactions via Vinyloxyboranes. *Chem. Lett.* **1976**, *5*, 559−562. (b) Van Horn, D. E.; Masamune, S. Stereoselective Synthesis of β-hydroxy-α-methylketones via *Z*- and *E*-vinyloxyboranes Generated Directly from Cyclohexyl Ethyl Ketone. *Tetrahedron Lett.* **1979**, *20*, 2229−2232. (c) Inoue, T.; Mukaiyama, T. Regio- and Stereoselective Cross-aldol Reactions via Dialkylboryl Triflates. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174−178. (d) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. Major Effect of the Leaving Group in Dialkylboron Chlorides and Triflates in Controlling the Stereospecific Conversion of Ketones into either (*E*)- or (*Z*)-Enol Borinates. *J. Am. Chem. Soc.* **1989**, *111*, 3441−3442.

(3) Hirama, M.; Masamune, S. Stereoselective Synthesis of β-hydroxy-α-methylcarboxylic Acid Thiol Esters via Vinyloxyboranes. *Tetrahedron Lett.* **1979**, *20*, 2225−2228.
(4) (a) Corey, E. J.; Kim, S. S. Versatile Chiral Reagent for the Highly Enantioselective Synthesis of either *Anti* or *Syn* Ester Aldols. *J. Am. Chem. Soc.* **1990**, *112*, 4976−4977. (b) Brown, H. C.; Ganesan, K. Dicyclohexyliodoborane/Triethylamine - a New Reagent which Achieves the Facile Enolboration of Esters and Tertiary Amides. *Tetrahedron Lett.* **1992**, *33*, 3421−3424. (c) Brown, H. C.; Ganesan, K. Enolboration. 6. Dicyclohexyliodoborane, A Versatile Reagent for the Stereoselective Synthesis of Either *Z*- or *E*-Enolates from Representative Esters. *J. Org. Chem.* **1994**, *59*, 2336−2340. (d) Masamune, S.; Abiko, A.; Liu, J.-F. Concerning the Boron-Mediated Aldol Reaction of Carboxylic Esters. *J. Org. Chem.* **1996**, *61*, 2590−2591. (e) Inoue, T.; Liu, J.-F.; Buske, D. C.; Abiko, A. Boron-Mediated Aldol Reaction of Carboxylic Esters: Complementary *Anti*- and *Syn*-Selective Asymmetric Aldol Reactions. *J. Org. Chem.* **2002**, *67*, 5250−5256. (f) Ramachandran, P. V.; Pratihar, D. Asymmetric Aldol Reaction with Diisopinocampheyl Enolborinates of Propionates. *Org. Lett.* **2009**, *11*, 1467−1470.
(5) (a) Veeraraghavan Ramachandran, P.; Parthasarathy, G.; Gagare, P. D. Bis-*exo*-2-norbornylboron Triflate for Stereospecific Enolization of 3,3,3-trifluoropropionates. *Org. Lett.* **2010**, *12*, 4474−4477. (b) Veeraraghavan Ramachandran, P.; Parthasarathy, G.; Gagare, P. D. Preparation and Application of 2-(arylmethoxy)isopinocampheols for the Asymmetric Aldol Reaction of 3,3,3-trifluoropropionates. *Tetrahedron Lett.* **2011**, *52*, 5359−5362. (c) Veeraraghavan Ramachandran, P.; Parthasarathy, G.; Gagare, P. D. B-Chlorodialkylboranes for the Enolboration of 3,3,3-trifluoropropionates. *Tetrahedron Lett.* **2011**, *52*, 6055−6057.
(6) Veeraraghavan Ramachandran, P.; Nicponski, D.; Kim, B. Total Regio- and Diastereocontrol in the Aldol Reactions of Dienolborinates. *Org. Lett.* **2013**, *15*, 1398−1401.
(7) (a) Veeraraghavan Ramachandran, P.; Chanda, P. B. Solvent- or Temperature-Controlled Diastereoselective Aldol Reaction of Methyl Phenylacetate. *Org. Lett.* **2012**, *14*, 4346−4349. (b) Veeraraghavan Ramachandran, P.; Chanda, P. B. Enantioselective Synthesis of *Anti*- and *Syn*-β-hydroxy-α-phenyl Carboxylates via Boron-Mediated Asymmetric Aldol Reaction. *Chem. Commun.* **2013**, *49*, 3152. (c) Veeraraghavan Ramachandran, P.; Chanda, P. B. Overriding effect of Temperature over Reagent and Substrate Size for Boron-mediated Aldol Reaction of Methyl Phenylacetate. *Tetrahedron Lett.* **2013**, *54*, 5886−5888.
(8) (a) van Aardt, T. G.; van Heerden, P. S.; Ferreira, D. The First Direct Synthesis of Pterocarpans via Aldol Condensation of Phenylacetates with Benzaldehydes. *Tetrahedron Lett.* **1998**, *39*, 3881−3884. (b) van Aardt, T. G.; van Rensburg, H.; Ferreira, D. Synthesis of Isoflavonoids. Enantiopure *cis*- and *trans*-6a-hydroxypterocarpans and a Racemic *trans*-pterocarpan. *Tetrahedron* **2001**, *57*, 7113−7126. (c) McNulty, J.; Nair, J. J.; Griffin, C.; Pandey, S. Synthesis and Biological Evaluation of Fully Functionalized *seco*-Pancratistatin Analogues. *J. Nat. Prod.* **2008**, *71*, 357−363. (d) McNulty, J.; Nair, J. J.; Singh, M.; Crankshaw, D. J.; Holloway, A. C. Potent and Selective Inhibition of Human Cytochrome P450 3A4 by *seco*-pancratistatin Structural Analogs. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2335−2339.
(9) (a) McNulty, J.; Nair, J. J.; Vurgun, N.; DiFrancesco, B. R.; Brown, C. E.; Tsoi, B.; Crankshaw, D. J.; Holloway, A. C. Discovery of a Novel Class of Aldol-derived 1,2,3-triazoles: Potent and Selective Inhibitors of Human Cytochrome P450 19A1 (Aromatase). *Bioorg. Med. Chem. Lett.* **2012**, *22*, 718−722. (b) McNulty, J.; Nielsen, A. J.; Brown, C. E.; DiFrancesco, B. R.; Vurgun, N.; Nair, J. J.; Crankshaw, D. J.; Holloway, A. C. Investigation of Aryl Halides as Ketone Bioisosteres: Refinement of Potent and Selective Inhibitors of Human Cytochrome P450 19A1 (Aromatase). *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6060−6063.
(10) Wang, H.; Li, G.; Engle, K. M.; Yu, J.-Q.; Davies, H. M. L. Sequential C−H Functionalization Reactions for the Enantioselective Synthesis of Highly Functionalized 2,3-Dihydrobenzofurans. *J. Am. Chem. Soc.* **2013**, *135*, 6774−6777.
(11) (a) Shen, T.; Wang, X.-N.; Lou, H.-X. Natural Stilbenes: an Overview. *Nat. Prod. Rep.* **2009**, *26*, 916−935. (b) Veitch, N. C. Isoflavonoids of the Leguminosae. *Nat. Prod. Rep.* **2007**, *24*, 417−464. (c) Watzke, A.; O'Malley, S. J.; Bergman, R. G.; Ellman, J. A. Reassignment of the Configuration of Salvianolic Acid B and Establishment of Its Identity with Lithospermic Acid B. *J. Nat. Prod.* **2006**, *69*, 1231−1233. (d) Tsui, G. C.; Tsoung, J.; Dougan, P.; Lautens, M. One-Pot Synthesis of Chiral Dihydrobenzofuran Framework via Rh/Pd Catalysis. *Org. Lett.* **2012**, *14*, 5542−5545.
(12) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Syntheses via Boranes*; Wiley-Interscience: New York, 1975; pp 28−29.

https://doi.org/10.1021/acs.joc.0c03024
J. Org. Chem. 2021, 86, 6184−6194