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Enantioselective synthesis of *anti*- and *syn*-β-hydroxy-α-phenyl carboxylates *via* boron-mediated asymmetric aldol reaction†

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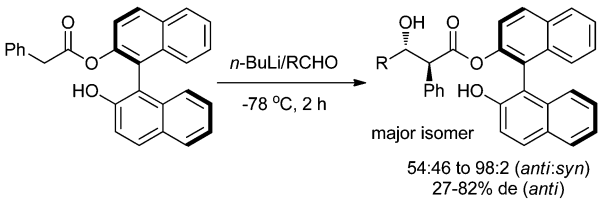
A reagent-controlled, diastereo- and enantioselective synthesis of *anti*- and *syn*-β-hydroxy-α-phenyl carboxylates has been achieved by the proper choice of solvent, temperature, alkoxy group, and amine for the diisopinocampheylboron-mediated asymmetric enolization–aldolization of phenylacetates. The pure diastereomers can be readily separated by column chromatography.

The utility of diastereo- and enantioselective aldol reactions is almost unparalleled in the art of organic synthesis of simple and complex organic molecules.[1] A comparison of the several promoters available for this transformation discloses the advantages offered by borane-derived reagents.[2] Among the carbonyl partners, ketones, thioesters, and imides have been well explored.[1,2] Nevertheless, the enolboration–aldolization of carboxylate esters, a ubiquitous class of carbonyls, has remained relatively unexplored.[3,4] The potential synthetic utility of aldol adducts derived from arylacetates, especially when used for the synthesis of aryl analogs of bio-active molecules,[5] prompted our recent study that revealed an extraordinary effect of solvent and temperature on the diastereoselectivity of racemic β-hydroxy-α-phenyl esters.[6] To the best of our knowledge, there is only one report on the preparation of chiral β-hydroxy-α-phenyl esters, which entails a substrate-controlled aldol reaction of lithium enolates of 2′-hydroxy-1,1′-binaphthyl phenylacetate (Scheme 1).[7] This reaction provided 54 : 46 to 98 : 2 selectivity for *anti*-aldols in 27–82% de, and lacks a protocol for the complementary *syn*-aldols.

The expensive chiral auxiliary and moderate selectivity described therein, as well as the demonstrated success of diisopinocampheylboron-mediated aldol reaction[4f,8] encouraged the examination of a reagent-controlled asymmetric aldol reaction of phenylacetates. The details of the study and the successful preparation of *anti*- and *syn*-aldols in high enantiomeric purities are described herein.

To optimize the conditions for the selective formation of either *syn* or *anti* chiral β-hydroxy-α-phenyl esters, a project was designed to examine the enolate formation–aldolization of methyl- (**2**), ethyl- (**3**), isopropyl- (**4**), and *tert*-butyl- (**5**) phenylacetates using (−)-diisopinocampheylboron triflate [(−)-Ipc$_2$BOTf, (−)-**1**]. The literature suggested that the enolization–aldolization of *tert*-butyl phenylacetate (**5**), bearing a bulky alkoxy group, should provide high *anti*-selectivity for the aldol reaction.[4f] However, we were apprehensive due to our past difficulty in enolizing this ester with dicyclohexylboron triflate.[6] Indeed, an attempted reaction of **5** with (−)-**1** in the presence of Et$_3$N at −30 °C, followed by aldolization of benzaldehyde (**6a**) at the same temperature showed insignificant product formation. On the basis of the preparation of racemic *anti*-aldols from methyl phenylacetate by the appropriate choice of the solvent and temperature, the effect of the reaction parameters on the diastereomeric ratio (dr) and enantiomeric ratio (er) using esters bearing less bulky than the *t*-butoxy group was examined. Thus, phenylacetates **2–4** were enolized in "*anti*-favoring solvent",[6] carbon tetrachloride, with (−)-**1** in the presence of Et$_3$N at −30 °C,[9] followed by aldolization with benzaldehyde (**6a**) at the same temperature. Hydrogen peroxide oxidation, in the presence of pH 7 buffer, provided a crude mixture of diastereomers of the β-hydroxy-α,β-diphenyl esters (**7a–9a**). Analysis of the carbinolic proton using ^{1}H NMR spectroscopy disclosed the diastereoselectivity of the reaction. The pure diastereomers were readily separated by silica gel column chromatography and their combined yields are presented in Table 1.[10] The er was determined by ^{1}H NMR analysis of the menthyl carbonate derivative of the diols derived from the major diastereomer.[11]



Scheme 1 Diastereoselective aldol reaction of 2′-hydroxy-1,1′-binaphthyl ester enolates with aldehydes.

Esters **2** and **3** provided 85% and 83% *anti*-isomer of 3-hydroxy-2,3-diphenylpropanoates (**7a**, **8a**, respectively) in 80% and 81%

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† Electronic supplementary information (ESI) available: Synthesis and characterization of compounds, ^{1}H and ^{13}C NMR spectra and detailed experimental procedure. See DOI: 10.1039/c3cc40860d

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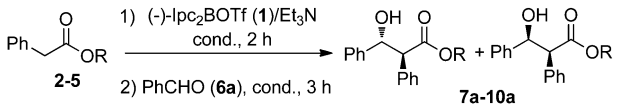
Table 1 Optimization of *anti*- and *syn*-selective asymmetric aldol reaction of phenylacetates with (−)-**1**



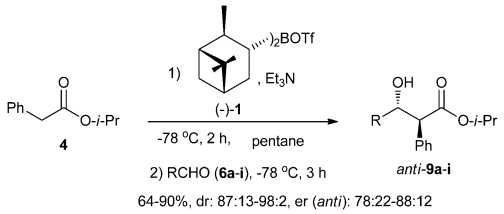
		Cond.[a]		Aldol			
Entry	Ester	Enol–aldol.	Solvent	#	Yield[b] (%)	*syn* : *anti*[c]	er[d]
1	**2**	A	CCl_4	**7a**	80	15 : 85	78 :22
2	**3**	A	CCl_4	**8a**	81	17 : 83	79 : 21
3	**4**	A	CCl_4	**9a**	78	8 : 92	79 : 21
4	**5**	A	CCl_4	**10a**	—[e]	—	—
5	***4***	*B*	*Pentane*	***9a***	*83*	*8 : 92*	*87 : 13*
6	**4**	B	Et_2O	**9a**	88	8 : 92	80 : 20
7	**4**	B	Toluene	**9a**	89	7 : 93	78 : 22
8	**4**	B	CH_2Cl_2	**9a**	83	68 : 32	—[f]
9[g]	**4**	B	Pentane	**9a**	79	21 : 79	—[f]
10[h]	**4**	B	Pentane	**9a**	86	12 : 88	79 : 21
11[i]	**4**	B	Pentane	**9a**	84	8 : 92	86 : 14
12	**2**	C	CH_2Cl_2	**7a**	75	78 : 22	—[f]
13	***3***	*C*	CH_2Cl_2	***8a***	*75*	*83 : 17*	*>99 : <1*
14	**4**	C	CH_2Cl_2	**9a**	75	72 : 28	—[f]
15	**3**	D	CH_2Cl_2	**8a**	67	81 : 19	—[f]
16	**3**	—[j]	CH_2Cl_2	**8a**	77	82 : 18	>99 : <1
17[g]	**3**	C	CH_2Cl_2	**8a**	60	82 : 18	—[f]

[a] A = enolization: (−)-**1**/Et_3N, −30 °C; aldolization: **6a**, −30 °C. B = enolization: (−)-**1**/Et_3N, −78 °C; aldolization: **6a**, −78 °C. C = enolization: (−)-**1**/Et_3N, 0 °C; aldolization: **6a**, −78 °C. D = enolization: (−)-**1**/Et_3N, 25 °C; aldolization: **6a**, −78 °C. [b] Combined yields of pure *syn* and *anti* isomers. [c] *Syn* and *anti* ratios were determined using ^{1}H NMR spectroscopy of the crude product. [d] er was determined by the ^{1}H NMR analysis of menthyl carbonate derivatives of diols derived from aldol products. [e] Insignificant product formation. [f] Not determined. [g] i-Pr_2NEt was used as amine. [h] Concentration of reaction was decreased to half. [i] Concentration of reaction was doubled. [j] The antipode of the reagent, (+)-**1** was used under condition C.

combined yields, respectively, with similar er (78 : 22 and 79 : 21 respectively; Table 1, entries 1 and 2). The *anti*-selectivity improved to 92% with **4** (Table 1, entry 3), although the er of isopropyl 3-hydroxy-2,3-diphenylpropanoates (**9a**) remained the same.

Despite the high *anti*-selectivity with **4**, the unsatisfactory er prompted a full examination of the effects of solvent, amines, and the mode of addition[12] at low temperature. High *anti*-selectivity was expected on the basis of our earlier observation that lower temperatures favor the formation of *anti*-isomers during the aldol reaction of **2**, irrespective of the solvent.[6] Indeed, the reaction of **4** conducted in pentane, ethers, toluene, and CH_2Cl_2 at −78 °C (Table 1, entries 5–8) revealed similar diastereoselectivity (92–93% *anti*-) in all of the solvents except in CH_2Cl_2. Unexpectedly, the reaction provided only a moderate 68 : 32 diastereoselectivity favoring the *syn*-isomer in CH_2Cl_2 (Table 1, entry 8). Pentane was chosen as the optimal solvent for *anti*-aldols due to the higher er (87 : 13) (Table 1, entry 5). The effect of the amine was determined by replacing with i-Pr_2NEt, whereafter the *anti*-selectivity dropped from 92% to 79% (Table 1, entry 9). Altering the concentration of the reaction from 0.2 M to either 0.1 M or 0.4 M did not drastically change the *anti*-selectivity or er of the *anti*-isomer (Table 1, entries 10 and 11).

With the optimal conditions for the selective formation of *anti*-aldols in hand (Scheme 2), a series of aldehydes of varying



Scheme 2 Optimum conditions for *anti*-selective asymmetric aldol reaction of **4** with (−)-**1**.

steric and electronic requirements (hindered and unhindered, aliphatic, and arylic with electron-donating and electron-withdrawing groups) was treated with the enolate derived from **4** to furnish the corresponding *anti*-β-hydroxy-α-phenyl esters in moderate to high yields, very good dr, and moderate to high er. As summarized in Table 2, electron-donating (**6b** and **6c**) and withdrawing (**6d** and **6e**) groups on the phenyl ring did not affect the yields or er of the pure *anti*-isomers. A representative heteroaromatic aldehyde, thiophene-2-carbaldehyde (**6f**), provided the highest diastereoselectivity (98 : 2) of all the aldehydes tested. Both unbranched aliphatic, *n*-propyl (**6g**), and branched aliphatic aldehydes, isobutyraldehyde (**6h**) and pivalaldehyde (**6i**) also gave similar results. The diastereoselectivity was extremely high for the hindered aldehyde **6i**.

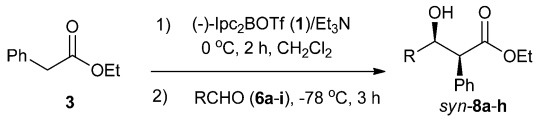
Attention was then turned to standardizing the conditions to prepare the *syn*-aldols with high er. Fortuitously, the initial screening of solvents for the enolization–aldolization of **4** with (−)-**1** had revealed 68% *syn*-selectivity in CH_2Cl_2, at −78 °C (Table 1, entry 8). On the basis of the improved *syn*-selectivity at higher temperature, presumably due to the thermodynamic *Z*-enolate,[6] the enolization temperature was increased to 0 °C, while maintaining the aldolization temperature at −78 °C,[13] whereat the diastereoselectivity of *syn*-**9a** showed minor improvement (72% *syn*, Table 1, entry 14). On the basis of the effect of the sterics on *syn*-selectivity, we examined esters **2** and **3** under the same conditions.

The ethyl ester (**3**) gave the best results: 83% *syn*-selectivity with an excellent enantiomeric ratio of >99 : <1 (Table 1, entry 13). While increasing the enolization temperature to 25 °C did not improve the *syn*-selectivity, the yield decreased to 67% (Table 1, entry 15). Replacing Et_3N with i-Pr_2NEt further decreased the yield to 60% without any improvement in the dr (Table 1, entry 17).

Table 2 Examination of aldehydes for *anti*-selection

	RCHO		Aldol			
Entry	**6**	**R**	#	Yield[a] (%)	dr[b]	er[c] (*anti*)
1	**6a**	C_6H_5	2*S*,3*R*-**9a**	83	92 : 8	87 : 13
2	**6b**	4-MeC_6H_4	2*S*,3*R*-**9b**	90	89 : 11	81 : 19
3	**6c**	4-$MeOC_6H_4$	2*S*,3*R*-**9c**	76	94 : 6	81 : 19
4	**6d**	4-FC_6H_4	2*S*,3*R*-**9d**	80	90 : 10	80 : 20
5	**6e**	4-$CF_3C_6H_4$	2*S*,3*R*-**9e**	70	87 : 13	80 : 20
6	**6f**	2-Thioph	2*S*,3*R*-**9f**	64	98 : 2	88 : 12
7[d]	**6g**	*n*-Pr	2*S*,3*S*-**9g**	68	88 : 12	88 : 12
8[d]	**6h**	i-Pr	2*S*,3*S*-**9h**	68	88 : 12	81 : 19
9	**6i**	*t*-Bu	2*S*,3*R*-**9i**	70	97 : 3	78 : 22

[a] Combined yields of pure *syn*- and *anti*-isomers. [b] dr was determined by ^{1}H NMR analysis of the crude reaction mixture. [c] er was determined by the ^{1}H NMR analysis of mono- or dimenthyl carbonate derivatives of diols derived from aldol products. [d] dr was determined by ^{13}C NMR analysis of the crude reaction mixture.



66-82%, dr: 82:18-86:14, er (*syn*): 93:7- >99:<1

Scheme 3 Optimum conditions for *syn*-selective asymmetric aldol reaction of **3** with (−)-**1**.

Table 3 Examination of aldehydes for *syn*-selection

	RCHO		Aldol			
Entry	**6**	**R**	#	Yield[a] (%)	dr[b]	er[c] (*syn*)
1	**6a**	C_6H_5	2*S*,3*S*-**8a**	75	83 : 17	>99 : <1
2	**6b**	4-MeC_6H_4	2*S*,3*S*-**8b**	73	82 : 18	93 : 7
3	**6c**	4-$MeOC_6H_4$	2*S*,3*S*-**8c**	66	86 : 14	93 : 7
4	**6d**	4-FC_6H_4	2*S*,3*S*-**8d**	67	84 : 16	96 : 4
5	**6e**	4-$CF_3C_6H_4$	2*S*,3*S*-**8e**	82	84 : 16	>99 : <1
6	**6f**	2-Thioph	2*S*,3*S*-**8f**	81	83 : 17	96 : 4
7[d]	**6g**	*n*-Pr	2*S*,3*R*-**8g**	72	85 : 15	>99 : <1
8[d]	**6h**	i-Pr	2*S*,3*R*-**8h**	75	85 : 15	>99 : <1
9	**6i**	*t*-Bu	2*S*,3*S*-**8i**	—[e]	—	—

[a] Combined yields of pure *syn*- and *anti*-isomers. [b] dr was determined by ^{1}H NMR analysis of the crude reaction mixture. [c] er was determined by the ^{1}H NMR analysis of mono- or dimenthyl carbonate derivatives of diols derived from aldol products. [d] dr was determined by ^{13}C NMR analysis of crude reaction mixture. [e] This reaction afforded a 3 : 2 ratio of *syn* : *anti* aldol product.

The dr of the reaction was determined by analyzing the ^{1}H NMR of the crude mixture; pure *syn*-isomers were readily separated by column chromatography. As earlier, reduction and conversion to the menthyl carbonate derivative allowed for er determination.

The generality of the reaction (Scheme 3) was validated under the optimum conditions for the *syn*-selection with the same series of aldehydes, wherein moderate to high yields and good *syn*-selectivities were achieved. Unlike the *anti*-isomer, the *syn*-isomer was obtained in excellent er. Thus, enolization of **3** with (−)-**1** in the presence of Et_3N at 0 °C, followed by aldolization with the selected aldehydes at −78 °C in CH_2Cl_2 provided *syn*-**8a–8h** in 82 : 18–86 : 14 dr with 93 : 7 to >99 : <1 er of the *syn*-isomer in 66–82% yields. The results are summarized in Table 3.

The absolute stereochemistry of *anti*-**9** was determined to be 2*S*,3*R* by comparing the optical rotation of methyl (2*S*,3*R*)-3-hydroxy-2,3-diphenylpropanoate (**7a**) with that reported in the literature.[14] Similarly, the absolute stereochemistry of *syn*-**8** was determined to be 2*S*,3*S* by comparing the optical rotation of the diol derived from ethyl *syn*-3-hydroxy-2,3-diphenylpropanoate (**8a**) with that of the known (1*S*,2*R*)-1,2-diphenylpropane-1,3-diol.[15] On the basis of analogy, the 2*S*,3*R* configuration has been assigned for all of the *anti*-aldols and the 2*S*,3*S* configuration for the *syn*-aldols.[16]

In conclusion, we have developed the first boron-mediated asymmetric aldol reaction of phenylacetates. An appropriate matching of the alkoxy group of the ester, solvent, temperature, and amines is key for achieving the aldol products bearing *anti*- and *syn*-β-hydroxy-α-phenyl moieties in high dr and er. Pure *anti*- and *syn*-diastereomers can be readily separated by silica gel column chromatography. Both antipodes of α-pinene are naturally available in abundance, making this stoichiometric asymmetric process economical and very attractive.

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12 The solution of ester **4** was cooled to 0 °C and the cold solution was transferred dropwise to the mixture of the reagent (−)-**1** and Et_3N at −78 °C. After enolization for 2 h at the same temperature, aldehyde **6a** was also cooled to −78 °C and added dropwise to a mixture of enolate for aldolization.
13 While optimizing enantioselectivity of the *anti*-isomer, −78 °C was found to be optimal.
14 Reported $[\alpha]_D^{18} = -122.6$ (*c* 1.22, MeOH), 77% ee for methyl (2*S*,3*R*)-3-hydroxy-2,3-diphenylpropanoate (**7a**) (ref. 7). Observed $[\alpha]_D^{22} = -75.0$ (*c* 1.22, MeOH), 56% ee for the same compound, **7a**.
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16 The 2*S*,3*S* configuration has been assigned for *anti*-**9g** and **9h** and the 2*S*,3*R* configuration has been assigned for *syn*-**8g** and **8h** on the basis of Cahn–Ingold–Prelog priority rules.

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