ORGANIC LETTERS

2012
Vol. 14, No. 17
4346–4349

Solvent- or Temperature-Controlled Diastereoselective Aldol Reaction of Methyl Phenylacetate

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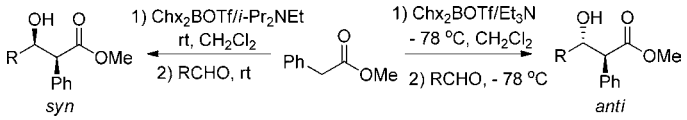
Received June 28, 2012

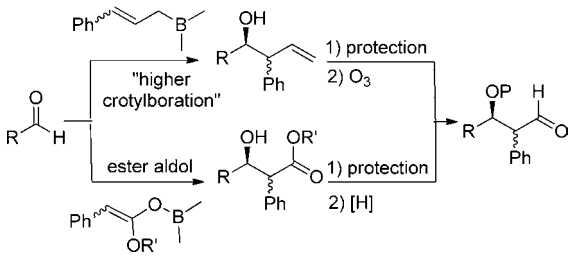
ABSTRACT



Unlike the enolboration–aldolization of methyl propanoate, the choice of either the solvent or temperature determines the diastereoselectivity during the enolboration–aldolization of methyl phenylacetate. In CH_2Cl_2, the reaction favors the *anti*-pathway at −78 °C and the *syn*-pathway at rt. Conversely, the reaction produces the *anti*-isomer up to rt and the *syn*-isomer at refluxing temperatures in nonpolar solvents.

The yield and selectivity in chemical reactions depend on the reaction conditions. It is particularly critical in diastereoselective C–C bond forming reactions. During the synthesis of phenyl analogs of certain bioactive natural products,[1] we were faced with the diastereoselective synthesis of β-hydroxyl α-phenyl formyl moieties. Our interest in organoborane reagents and reactions[2] led to two possible approaches to achieve the necessary synthon: (i) Brown's[3] "higher crotylboration"–ozonolysis using (*E*)-dicyclohexyl(3-phenylallyl)borane (cinnamyldicyclohexylborane) derived from 1-phenyl-1,2-propadiene (phenylallene) or (ii) enolization–aldolization–reduction of phenylacetate (Scheme 1).[4] The former procedure is limited to the preparation of the *E*-isomer of the reagent and *anti*-isomer of the product.

Scheme 1. Synthesis of β-Hydroxyl α-Phenyl Formyl Moiety via Higher Crotylboration or Enolboration–Aldolization



Although the boron-mediated cross-aldol reaction of carbonyls ranks high among important C–C bond forming reactions[5] and the enolboration–aldolization of ketones,[6] thioesters,[7] and imides[8] has been thoroughly examined and well-exploited for organic syntheses,[5] a similar application of the carboxylic acid ester enolates remained relatively unexplored[9] until reports by the Corey[10] and Brown[11]

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10.1021/ol301782s © 2012 American Chemical Society
Published on Web 08/10/2012

groups involving a dialkylbromo- and iodoborane, respectively. Subsequently, Masamune and Abiko described[12] the successful diastereoselective enolization−aldolization of alkyl propanoates with dialkylboron triflates to the corresponding *syn*- or *anti*-aldols, through the appropriate choice of the enolizing agent, alkyl propanoates, and amines. All of the above studies revealed the effects of the sterics of the ester moiety, the reagent, and the amine on diastereoselectivity to establish the optimal conditions in which the bulky *tert*-butyl propanoates yielded the *anti*-aldol (> 97%) with dicyclohexylboron triflate (Chx_2BOTf, **1**) in the presence of Et_3N and methyl propanoates, affording the *syn*-aldols (> 97%) with di-*n*-butylboron triflate (*n*-Bu_2BOTf, **2**) in the presence of *i*-Pr_2NEt. However, benzyl propanoates provided predominantly *syn*- or *anti*-aldols with **1** at different reaction temperatures.[12]

A search of the literature revealed that, unlike the aldol reaction of propanoates, there has been no systematic investigation of the boron-mediated aldol reaction of phenylacetates.[12,13] A lone example of a *syn*-selective aldol reaction of methyl phenylacetate (**3**)[14] with **2** and one of an *anti*-selective aldol reaction of ethyl phenylacetate via a Chx_2BI-mediated reaction[11] have been described.[15,16] However, Chx_2BI is relatively unstable and very sensitive to ethereal solvents. This prompted a systematic examination of the stereoselective boron-mediated enolization−aldolization of phenylacetate[17] with **1** (chosen due to its ease of preparation). This study has revealed the complete control of diastereoselectivity in the enolization of methyl phenylacetate with **1** by modifying either the temperature or the solvent. The details are as follows.

The enolization of **3** with **1**, in CH_2Cl_2, in the presence of Et_3N at 0 °C, followed by aldolization with benzaldehyde (**6a**), at the same temperature provided methyl 3-hydroxy-2,3-diphenylpropanoate (**7a**) in 88% yield with a *syn*/*anti* ratio of 80:20 (Table 1, entry 1), as was determined from the ^1H NMR spectrum of the crude reaction mixture.[18] The reaction of isopropyl phenylacetate (**4**) yielded 81% of isopropyl 3-hydroxy-2,3-diphenylpropanoate (**8a**) with an increased *anti*-diastereomer (*syn*/*anti* 58:42, Table 1, entry 2). On the basis of the reported *anti*-selectivity for bulky *tert*-butyl propanoates[12b] with **1**, a higher *anti*-selectivity was expected for the enolization−aldolization of *tert*-butyl phenylacetate (**5**). Unfortunately, the enolization of **5** with **1** in CH_2Cl_2 and aldolization with benzaldehyde (**6a**), under the above conditions, did not yield the desired aldol product (Table 1, entry 3).

The next approach was to examine the influence of the solvent on the diastereoselectivity of the reaction. The basis for our approach was the reported solvent effect on the diastereoselectivity of the aldol reaction of tertiary amides.[19] Thus the enolization of the methyl ester **3** was examined with **1** in CCl_4, pentane, and ether, and indeed, the reaction yielded ∼90% *anti*-**7a** in all of these solvents (79−84% yields, Table 1, entries 4−6). This demonstrates that less polar solvents favor *anti*-selectivity. To the best of our knowledge, this is the first report of a solvent-controlled, diastereoselective boron-mediated aldol reaction of esters.

Assuming that lowering the temperature would achieve higher selectivity, the enolization of **3** with **1** was carried out in pentane (*anti*-selective solvent) at −78 °C, followed by aldolization with **6a** at the same temperature, whereas a selectivity of 3:97 favoring the *anti*-isomer was achieved (Table 1, entry 7). Expecting higher *syn*-selectivity,[12b] a −78 °C reaction was performed in CH_2Cl_2 (*syn*-selective solvent) when, surprisingly, 98% *anti*-selectivity was observed for **7a** (91% yield, Table 1, entry 8)!

The limits of this temperature effect on the reaction were then examined, and we noticed that increasing the enolization−aldolization temperature to rt or to reflux, in CH_2Cl_2, provided an 88:12 *syn*/*anti* ratio for **7a** (78−84% yields) (Table 1, entries 10 and 14). This effect was not observed in other solvents, which favored the *anti*-isomer at rt (Table 1, entries 11−13). At reflux temperatures, however, all of the solvents produced predominantly the *syn*-product (Table 1, entries 14−17). Clearly, all of the solvents favor the kinetic enolate at very low temperature (−78 °C) and the thermodynamic enolate at refluxing temperature. The solvent effect is pronounced at 0 °C (Table 1, entry 1 vs entries 4−6) and rt (Table 1, entry 10 vs entries 11−13).

Since there is no literature report on the effect of solvents for the enolization−aldolization of methyl propanoate (**10**), we carried out such a reaction in different solvents, at varying temperatures, to understand this phenomenon further. Interestingly, we failed to observe a similar effect on the diastereoselectivity in the case of **10**.[20] Obviously, the presence of the phenyl group controls the stereochemistry of enolization.

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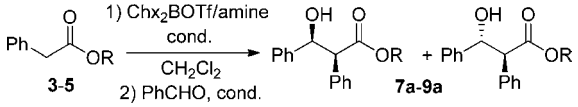
(20) See Supporting Information for details.

Table 1. Optimization of *Syn*- and *Anti*-Selectivity by Using Reagent **1**



	ester		cond.[a]				aldol products		
entry	**3**–**5**	R	amine	solvent	enolization temperature	aldolization temperature	**7a**–**9a**	yield (%)[b]	*syn*/*anti*[d]
1	**3**	Me	Et_3N	CH_2Cl_2	0 °C	0 °C	**7a**	88	80:20
2	**4**	*i*-Pr	Et_3N	CH_2Cl_2	0 °C	0 °C	**8a**	81	58:42
3	**5**	*t*-Bu	Et_3N	CH_2Cl_2	0 °C	0 °C	**9a**	NR[c]	NR[c]
4	**3**	Me	Et_3N	CCl_4	0 °C	0 °C	**7a**	82	12:88
5	**3**	Me	Et_3N	Et_2O	0 °C	0 °C	**7a**	84	10:90
6	**3**	Me	Et_3N	pentane	0 °C	0 °C	**7a**	79	9:91
7	**3**	Me	Et_3N	pentane	−78 °C	−78 °C	**7a**	78	3:97
8	**3**	**Me**	**Et_3N**	**CH_2Cl_2**	**−78 °C**	**−78 °C**	**7a**	**91**	**2:98**
9	**3**	Me	Et_3N	CH_2Cl_2	−30 °C	−30 °C	**7a**	85	18:82
10	**3**	Me	Et_3N	CH_2Cl_2	rt	rt	**7a**	78	88:12
11	**3**	Me	Et_3N	CCl_4	rt	rt	**7a**	80	22:78
12	**3**	Me	Et_3N	Et_2O	rt	rt	**7a**	77	34:66
13	**3**	Me	Et_3N	pentane	rt	rt	**7a**	76	15:85
14	**3**	Me	Et_3N	CH_2Cl_2	reflux	reflux	**7a**	84	88:12
15	**3**	Me	Et_3N	CCl_4	reflux	reflux	**7a**	79	84:16
16	**3**	Me	Et_3N	Et_2O	reflux	reflux	**7a**	76	68:32
17	**3**	Me	Et_3N	pentane	reflux	reflux	**7a**	77	68:32
18	**3**	Me	Et_3N	CH_2Cl_2	−78 °C	0 °C	**7a**	85	10:90
19	**3**	Me	Et_3N	CH_2Cl_2	−78 °C	rt	**7a**	76	60:40
20	**3**	Me	Et_3N	CH_2Cl_2	rt	−78 °C	**7a**	78	88:12
21	**3**	Me	*i*-Pr_2NEt	CH_2Cl_2	−78 °C	−78 °C	**7a**	92	4:96
22	**3**	**Me**	***i*-Pr_2NEt**	**CH_2Cl_2**	**rt**	**rt**	**7a**	**79**	**90:10**

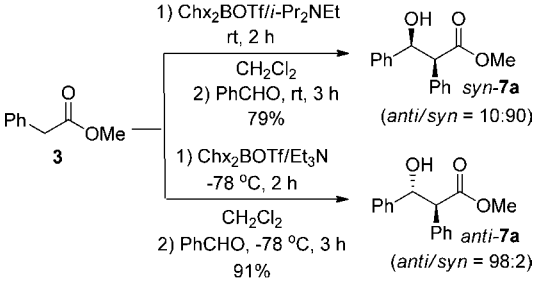
[a] Enolization and aldolization times were 2 and 3 h, respectively. [b] Combined yield of *syn* and *anti* isomers. [c] NR = No reaction. [d] *Syn* and *anti* ratios were determined by ^1H NMR spectroscopy.

It is noteworthy that aldolization temperature also is critical for high selectivity. For example, the enolization of **3** with **1** at −78 °C, followed by aldolization at 0 °C, or rt decreased the diastereoselectivity to 90% and 40% *anti*, respectively (Table 1, entries 18 and 19). Once the enolate is formed at rt, cooling the reaction for aldolization had no effect on the diastereoselectivity (Table 1, entry 20).

We examined the influence of the amine by carrying out the reaction in CH_2Cl_2 at −78 °C and rt in the presence of *i*-Pr_2NEt and found no major effect, although we obtained a slightly improved *syn*-selectivity (*syn*/*anti* 90:10, Table 1, entry 22) at rt. Thus, we have achieved a boron-mediated aldol reaction of methyl phenylacetate with **1**, wherein the diastereoselectivity can be efficiently controlled by a simple change of solvent or reaction temperature, the latter condition providing optimal results (Scheme 2).

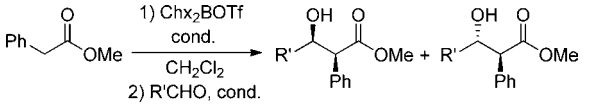
The generality of the reaction was demonstrated under the standardized conditions for the *syn*-selection (CH_2Cl_2, rt) and *anti*-selection (CH_2Cl_2, −78 °C). A series of aldehydes of varying steric and electronic requirements were converted to the corresponding *β*-hydroxy-α-phenyl esters in high yields and diastereoselectivities. Thus, methyl phenylacetate, when treated with reagent **1** in the presence of Et_3N at −78 °C, followed by aldolization with benzaldehyde bearing electron-donating 4-methyl and 4-methoxy

Scheme 2. Optimization of *Syn*- and *Anti*-Selective Aldol Reactions of Methyl Phenylacetate (**3**) with **1**



groups (**6b**, **6c**), or electron-withdrawing 4-fluoro and 4-nitro groups (**6d**, **6e**), cinnamaldehyde (an α,*β*-unsaturated aldehyde, **6f**), heteroaromatic thiophene-2-carbaldehyde (**6g**), and hindered and unhindered aliphatic aldehydes (**6h**–**k**), provided the corresponding *anti*-*β*-hydroxy-α-phenyl esters (*anti*-**7a**–**7k**) in 81–96% yields and 95–99% diastereoselectivity. The same series of aldehydes, except pivalaldehyde, provided 76–90% *syn*-aldol in 79–90% yields with **3** and **1** in the presence of *i*-Pr_2NEt at ambient temperature. Pivalaldehyde provided

Table 2. Temperature-Controlled Preparation of *Syn*- and *Anti*-Aldols from Methyl Phenylacetate in CH_2Cl_2 with **1**



		R′CHO			aldol	
entry	cond.[a]	**6**	**R′**	**7**	yield (%)[b]	*syn*/*anti*[c]
1	**A**	**6a**	C_6H_5	**7a**	91	2:98
2	**A**	**6b**	4-MeC_6H_4	**7b**	87	2:98
3	**A**	**6c**	4-$MeOC_6H_4$	**7c**	81	3:97
4	**A**	**6d**	4-FC_6H_4	**7d**	81	4:96
5	**A**	**6e**	4-$NO_2C_6H_4$	**7e**	93	4:96
6	**A**	**6f**	*E*-PhCH=CH	**7f**	82	5:95
7	**A**	**6g**	2-Thioph	**7g**	92	4:96
8	**A**	**6h**	*t*-Bu	**7h**	89	4:96
9	**A**	**6i**	*i*-Pr	**7i**	86	4:96
10	**A**	**6j**	*n*-Pr	**7j**	96	2:98
11	**A**	**6k**	TBSO-$(CH_2)_2$	**7k**	90	1:99
12	**B**	**6a**	C_6H_5	**7a**	79	90:10
13	**B**	**6b**	4-MeC_6H_4	**7b**	83	85:15
14	**B**	**6c**	4-$MeOC_6H_4$	**7c**	88	79:21
15	**B**	**6d**	4-FC_6H_4	**7d**	83	87:13
16	**B**	**6e**	4-$NO_2C_6H_4$	**7e**	79	85:15
17	**B**	**6f**	*E*-PhCH=CH	**7f**	89	81:19
18	**B**	**6g**	2-Thioph	**7g**	87	76:24
19	**B**	**6h**	*t*-Bu	**7h**	89	62:38
20	**B**	**6i**	*i*-Pr	**7i**	82	85:15
21	**B**	**6j**	*n*-Pr	**7j**	87	89:11
22	**B**	**6k**	TBSO-$(CH_2)_2$	**7k**	90	88:12

[a] *Anti*-selective condition A = Enolization: −78 °C, Et_3N, 2 h; aldolization: −78 °C, 3 h. *Syn*-selective condition B = Enolization: rt, *i*-Pr_2NEt, 2 h; aldolization: rt, 3 h. [b] Combined yield of *syn* and *anti* isomers. [c] *Syn* and *anti* ratios were determined by ^1H NMR or GC analysis.

a *syn*/*anti* ratio of 62:38. The results are summarized in Table 2.

In conclusion, a detailed study of the effects of temperature, solvent, amine, and an ester alkyl group for diastereoselective aldol reactions of phenylacetates with **1** has revealed that the aldol reaction of methyl phenylacetate can provide either the *anti*- or *syn*-aldol product by the appropriate choice of solvent and/or temperature.[21] This methodology will provide ready access to molecular synthesis containing a β-hydoxy-α-phenyl moiety. The role of the phenyl group in influencing the stereochemistry in different solvents and at variable temperature is being probed further. An asymmetric version of this reaction will be reported in due course.

Acknowledgment. We thank the Herbert C. Brown Center for Borane Research for financial assistance of this project.

Supporting Information Available. Experimental details and spectral data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org

(21) Typical procedure for *anti*- or *syn*-selective aldol reaction. Freshly prepared dicyclohexylborane (Chx_2BH) (0.267 g, 1.5 mmol) was transferred to a 50 mL round-bottom flask and suspended in 3 mL of dichloromethane. Trifluoromethanesulfonic acid (TfOH) (0.15 mL, 1.69 mmol) was then added dropwise at 0 °C. The reaction mixture was stirred at rt for 1 h followed by cooling to −78 °C. Methyl phenylacetate (1 mmol), dissolved in 1 mL of dichloromethane, was slowly added to the cooled reaction mixture. Triethylamine (0.30 mL, 2.2 mmol) was then added dropwise to the reaction mixture and stirred for 2 h at −78 °C. Aldehyde (1.5 mmol) was added dropwise to the solution of enolate and stirred for 3 h at the same temperature (−78 °C). The reaction was quenched by addition of pH 7 buffer solution (2 mL). The mixture was diluted with MeOH (2 mL) followed by slow addition of 30% hydrogen peroxide (2 mL) and stirred for 4 h at rt. The organic layer was separated, and the aqueous layer was washed with dichloromethane (3 × 10 mL). Combined organic layers were then washed with saturated brine solution (5 mL), dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo, and purified by silica gel column chromatography to obtain pure *anti*-aldol product. A similar reaction was carried out at rt and in the presence of *N*,*N*-diisopropylethylamine to obtain pure *syn*-aldol product.

The authors declare no competing financial interest.