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anti-Selective enolboration–aldolization of propanoic acid

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ABSTRACT

A systematic examination of enolboration–aldolization of propanoic acid has led to an efficient synthesis of *anti*-β-hydroxy-α-methyl carboxylic acids in consistently high yields and diastereoselectivities by using *B*-bromodicyclohexylborane as the enolization reagent and triethylamine as the base.

The preparation of β-hydroxy carbonyls via boron-mediated aldol reaction of a variety of carbonyl class has been well studied and utilized in organic synthesis for over three decades.[1] Nonetheless, an extremely useful class of carbonyl compounds that has not received its due attention is carboxylic acids. Indeed, while the aldol reaction of dimagnesium ene-1,1-diolates of carboxylic acids, the Ivanov reaction,[2] and the corresponding dilithium[3] and disilicon[4] enediolates have been well explored,[5] the diboron ene-1,1-diolates has only been sparingly reported.[6–8]

As part of a comprehensive study on cross aldol reactions using dialkylboron triflates, Evans et al. had included an example each of the aldol reaction of propanoic acid and benzyloxyacetic acid with dibutylboron triflate (*n*-Bu_2BOTf, **1**) and dicyclopentylboron triflate (Cyp_2BOTf, **2**).[6] Again, while introducing dialkylhaloboranes for the enolboration of different classes of carbonyl compounds, the Brown group alluded to the enolization of propanoic acid (**3**) and phenylacetic acid (**4**) with *B*-chlorodicyclohexylborane (Chx_2BCl, **5**) in the presence of triethylamine with no details or follow-up.[7] Later, Fringuelli et al. prepared dibora ene-1,1-diolates using *B*-chlorodialkylboranes via a *trans*-metalation of the corresponding dilithio enediolates, derived from carboxylic acids and LDA.[8] Although direct enolization of carbonyls using haloboranes in the presence of amines could achieve the same intermediates, no reasoning was provided for the need for the *trans*-metalation.[9] Surprisingly, none of these protocols have become part of the synthetic organic chemist's toolbox. The success of boron-mediated aldol reactions beseeched the development of such a reaction for this ubiquitous carbonyl class.

The rich chemistry of β-lactone bearing bio-active molecules, such as (−)-ebelactone A[10] and (−)-tetrahydrolipstatin,[11] coupled with a simple basic work-up for the purification of *anti*-α-alkyl-β-hydroxyl carboxylic acids provided additional impetus to develop the boron-mediated aldol chemistry of carboxylic acids.

Accordingly, a systematic investigation of the enolboration–aldolization of carboxylic acid functionality was initiated. The resultant successful *anti*-selective aldol reaction of **3** using *B*-bromodicyclohexylborane-triethylamine is described herein.

We began the project by carrying out the enolization of **3** with dicyclohexylboron triflate (**6**), under Evans' conditions,[6] in Et_2O at 0 °C in the presence of *i*-Pr_2NEt as the base, followed by aldolization of benzaldehyde (**7a**) at −78 °C. The work-up of the hydroxy acid aldol borinate intermediate was carried out according to the literature protocol[6] by quenching with saturated aqueous $NaHCO_3$ and acidifying with 6 M HCl. Surprisingly, the isolated yield of the product 3-hydroxy-2-methyl-3-phenylpropanoic acid (**8a**) separated via ether extraction was more than quantitative. Although the ^{1}H NMR was clean and revealed 89% *anti*-selectivity[12] (in comparison to 65% *anti*-isomer with **1**),[6] the >100% yield was a concern. Our suspicion that the product might be contaminated with triflic acid (a byproduct from two equivalents of **6**) was proven correct by examining the ^{19}F NMR of the product.[13] Thus, we faced an inherent problem in the aldol reaction of carboxylic acids with boron triflate reagents necessitating a tedious column chromatography to separate the product hydroxyl acid from triflic acid. However, it is noteworthy that the boron triflate reagents which provide *syn*-aldols for ketone enolates do provide *anti*-aldols from the ene-1,1-diolate derived from propanoic acid.

To overcome this difficulty and to achieve the product acid via simple basic work-up, we envisioned that dialkylhaloboranes

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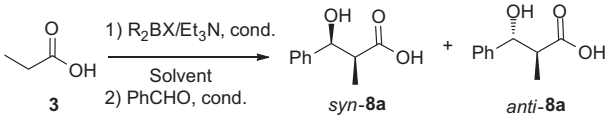
could be better reagents. Thus, propanoic acid was enolized with a mixture of **5**/*i*-Pr_2NEt in tetrahydrofuran (THF) at −78 °C, followed by aldolization of **7a** at the same temperature.[8] Although **8a** was isolated in pure form with 78% *anti*-selectivity, the yield was a dismal 9% (Table 1, entry 2), which could be improved to 56% at the cost of the diastereoselectivity (62% *anti*) by replacing *i*-Pr_2NEt with Et_3N (Table 1, entry 3). It is noteworthy that *B*-chlorodialkylboranes do not enolize alkyl propanoates, whereas it is capable of enolizing dialkylboryl propanoates. On the basis of the demonstrated influence of solvents on aldol reactions,[14] the effect of diethyl ether, pentane, and dichloromethane on the reaction with **5** was examined (Table 1, entries 3–6). A positive influence of diethyl ether on the diastereoselectivity was observed (58% yield, 82% *anti*-selectivity, Table 1, entry 6).

The effect of the leaving halogen group of the dialkylboron halide was then evaluated (Table 1, entries 6–8). The reaction with *B*-bromodicyclohexylborane (Chx_2BBr, **9**) was carried out in diethyl ether and the reaction with *B*-iododicyclohexylborane (Chx_2BI, **10**) was performed in pentane since **10** is known to cleave ether almost instantaneously.[15] Although tribromoborane is a commonly used reagent for ether cleavage, and dialkylbromoboranes typically cleave ethers over two weeks,[15] we were pleased to note that the aldol reaction with **9** proceeded well in diethyl ether and yielded 86% of the product with an improved (86%) diastereoselectivity (Table 1, entry 7). When this reaction was carried out under conditions with shorter reaction time (Condition A, Table 1), the yield improved to 92% with no change in the *anti*-selectivity (Table 1, entry 9). *B*-Bromobis-*exo*-2-norbornylborane (**11**), under similar conditions, provided the same diastereoselectivity in slightly lesser yield than obtained with **9** (86% *anti*, 86% yields, Table 1, entry 10). Due to the lower cost and ready availability of cyclohexene, reagent **9** was chosen for further studies. Thus, we achieved an efficient protocol for aldol reaction of propanoic acid with Chx_2BBr/Et_3N.

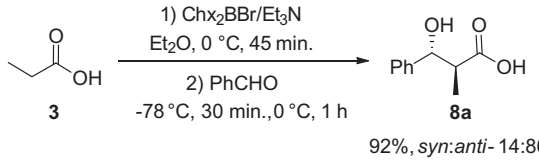
With the optimum conditions in hand (shown in bold face in Table 1) (Scheme 1), the generality of the reaction was examined by employing a series of aromatic and aliphatic aldehydes. The results summarized in Table 2 illustrate that electron-rich and -deficient aromatic aldehydes gave similar yields and diastereoselectivities (Table 2, entries 2–4). An α,β-unsaturated aldehyde, cinnamaldehyde, provided 86% yield and 94:6 selectivity

Table 1
Optimization for *anti*-selective aldol reaction of propanoic acid (**3**)



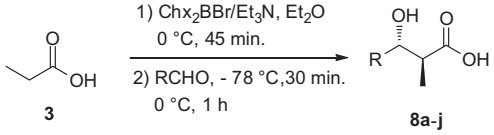
No.	R_2BX	#	Cond.[a]	Solvent	Yield[b] (%)	*syn*:*anti*[c]
1[d]	Chx_2BOTf	**6**	A	Et_2O	>100[e]	11:89
2[d]	Chx_2BCl	**5**	B	THF	9	22:78
3	Chx_2BCl	**5**	B	THF	56	38:62
4	Chx_2BCl	**5**	B	CH_2Cl_2	47	23:77
5	Chx_2BCl	**5**	B	Pentane	49	23:77
6	Chx_2BCl	**5**	B	Et_2O	58	18:82
7	Chx_2BBr	**9**	B	Et_2O	86	14:86
8	Chx_2BI	**10**	B	Pentane	90	18:82
9	**Chx_2BBr**	**9**	**A**	**Et_2O**	**92**	**14:86**
10	Nrb_2BBr	**11**	A	Et_2O	86	14:86

[a] Reaction conditions: A = enolization: 0 °C, 45 min; aldolization: −78 °C, 30 min, 0 °C, 1 h. B = enolization: −78 °C, 1 h, 0 °C, 1 h; aldolization: −78 °C, 1 h, 0 °C, 15 h.
[b] Combined isolated yields of *syn* and *anti*-isomers.
[c] *syn* and *anti* ratios were determined by ^1H NMR analysis of the crude reaction mixture.
[d] *i*-Pr_2NEt was used as amine.
[e] Crude yield.



Scheme 1. Optimum conditions for aldol reaction of propanoic acid (**3**).

Table 2
Examination of aldehydes for the *anti*-selective aldol reaction of propanoic acid (**3**)



No.	RCHO		Aldol		
	7	R	**8**	Yield[a] (%)	*syn*:*anti*[b]
1	**7a**	C_6H_5	**8a**	92	14:86
2	**7b**	4-MeC_6H_4	**8b**	86	15:85
3	**7c**	4-$MeOC_6H_4$	**8c**	82	15:85
4	**7d**	4-FC_6H_4	**8d**	85	14:86
5	**7e**	(*E*)-PhCH=CH	**8e**	86	6:94
6	**7f**	2-Thioph	**8f**	82	2:98
7	**7g**	Chx	**8g**	82	7:93
8	**7h**	*n*-Pr	**8h**	80	10:90
9	**7i**	*i*-Pr	**8i**	84	6:94
10	**7j**	*t*-Bu	**8j**	86	3:97

[a] Combined isolated yields of *syn* and *anti*-isomers.
[b] *syn* and *anti* ratios were determined by ^1H NMR spectroscopy.

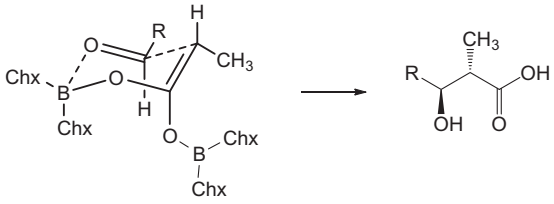


Figure 1. Proposed transition state for the formation of *anti*-aldols via the aldolization of aldehydes with dibora ene-1,1-diolates.

in favor of the *anti*-aldol (Table 2, entry 5). A heteroaromatic aldehyde, such as 2-thiophene carboxaldehyde, provided very high *anti*-selectivity (98% *anti*, Table 2, entry 6). All of the aliphatic aldehydes provided ≥90% *anti*-selectivity in 80–86% yields (entries 7–10). While the yields remained similar, the diastereoselectivity improved with the increase in steric requirements (Table 2, entries 9 and 10). Pivalaldehyde provided 97% diastereoselectivity for the product aldol.

It is fascinating that the aldol reaction proceeds with high stereoselectivities (Table 2), although the ene-1,1-diolates cannot be classified as *E* or *Z*. While the aldol reaction of dimagnesium ene-1,1-diolates, which led to the conventional Zimmerman–Traxler transition state,[16] gave poor selectivities, the reaction of diboraene-1,1-diolates provided up to 98% selectivity. These selectivities could be rationalized due to a tighter transition state, common in boron-mediated aldol reactions,[1a] involving the bulky cyclohexyl ligands (Fig. 1). The methyl group of propanoic acid and the R group of the aldehyde occupy equatorial positions in the proposed transition state.

In conclusion, a systematic study of the enolization and aldol reactions of propanoic acid revealed that *B*-bromodicyclohexylborane-triethylamine is the choice reagent-base combination for highly *anti*-selective[17] aldol reactions of this carboxylic acid. Our study identified an inherent problem of contamination by triflic acid during the aldol reaction of carboxylic acids with dialkylboron triflates. This can be circumvented by the reaction with the *B*-halodialkylborane reagents. We expect this protocol to receive wide acceptance due to the ubiquity of carboxylic acids, particularly for the synthesis of β-hydroxyl carboxylic acids and β-lactones.[18] We are continuing our explorations with other 2-substituted acetic acids.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.048.

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12. The diastereoselectivity was determined from the peak areas of *syn*- and *anti*-β-proton in ^{1}H NMR spectrum of the crude reaction mixture. Chemical shift of the carbinol proton of the *syn*-isomer is δ 5.17 ppm (J = 3.9 Hz) and that of the *anti*-isomer is δ 4.73 ppm (J = 9.0 Hz).
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17. *General procedure for anti-selective aldol reactions of propanoic acid*: Under nitrogen and stirring, 15 mL of anhydrous ether was transferred to a 50 mL round-bottom flask containing *B*-bromodicyclohexylborane (Chx_2BBr, **9**) (1.23 g, 4.8 mmol) and cooled to 0 °C, followed by dropwise addition of triethylamine (0.67 mL, 4.8 mmol). Propanoic acid (**3**) (0.15 g, 2.0 mmol) dissolved in 2 mL anhydrous ether, was then added dropwise to the same solution. The reaction mixture was stirred at 0 °C for 45 min. and then cooled to −78 °C. Aldehyde **7** (2.4 mmol) was added dropwise to the above reaction mixture and stirred for 30 min. at the same temperature (−78 °C) and 1 h at 0 °C. The reaction was quenched by the addition of saturated aq solution of sodium bicarbonate (5 mL) and was left stirring for 1 h at room temperature. After separation of the layers, the organic phase was extracted with additional saturated aqueous sodium bicarbonate solution (2 × 5 mL). The combined aqueous layers were washed with ether (10 mL), acidified with 6 M HCl, saturated with NaCl, and extracted with ether (3 × 10 mL). The combined ether layers was dried (anhydrous Na_2SO_4), filtered, and concentrated in vacuo to obtain *anti*-aldol products **8a–j**.
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