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Irreversible aldolization of ketones with bisdicyclohexylboron enediolates

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ABSTRACT

Unlike the reported reversible addition of ketone enolborinates to ketones, the aldolization of ketones with bisboron enediolates derived from carboxylic acids proceeds without difficulty. A variety of α,β,β-trisubstituted-β-hydroxy acids have been thus synthesized in good to excellent yields and diastereoselectivities.

The presence of *tert*-alcohols in a large number of biologically active molecules, such as fluconazole, bedaquiline, brassinazole, tridihexethyl, fostriecin, venlafaxine, etc. [1–3] motivated synthetic chemists to commit considerable effort in developing diastereo- and enantioselective nucleophilic additions to ketones [4–10]. Unlike the stereoselective addition of metal enolates to aldehydes that delivers a *sec*-hydroxyl group β- to carbonyl functionalities [11], the stereoselectivies for a similar enolate addition to ketones yielding *tert*-alcohols have been subpar. This has been attributed to the decreased electrophilicity of ketones and the mandatory steric and/or electronic differences of their substituents [12,13]. Another major drawback associated with the reaction of ketone electrophiles is the complications associated with a *retro*-aldol process [11,14].

Additions of tin [15], cerium [16], lanthanide [17], samarium [18], zinc [19], and titanium [16,20] enolates to ketones have been realized with limited success due to unsatisfactory yields and diastereoselectivities. Reported successful diastereoselective (ds) synthesis of β,β-disubstituted β-hydroxy carbonyls via enolate chemistry involves the addition to selected class of α-hetero-substituted carbonyls; e.g., the aldolization of lactate-derived alkyl ketones with titanium enolates of α-benzyloxyketones [21] yielding *syn*-aldols (Fig. 1).

Boron enolates have been widely used for directed aldol synthesis for over four decades [22,23]. Yet, a boron-mediated cross-aldolization of ketones was reported only recently [24]. However, this was negated by another publication from the same group describing significant amounts of *retro*-aldol reaction [14]. Since these reports, to the best of our knowledge, there has been none on the aldolization of ketones using ketone enolborinates. Described herein is the first boron-mediated diastereoselective aldolization of ketones with enediolates, without any reversal, furnishing a variety of α,β,β-trisubstituted β-hydroxy acids in high yields and diastereoselectivities.

We have recently described the generation of bisboron enediolates from carboxylic acids and the subsequent stereoselective aldolization of aldehydes [25,26]. The focal features of this reaction are the easy purification and isolation of the product β-hydroxy acids and their utility as valuable precursors for β-lactones and alkenes [27]. We envisioned that extending the scope of the investigation to include ketone electrophiles will pave way for a diastereoselective synthesis of α,β,β-trisubstituted β-hydroxy acids, provided a *retro*-aldol reaction is non-existent or is curtailed. The details of our fruitful study follow.

Optimal conditions were selected by examining the effects of (i) solvent, (ii) concentration, (iii) enolization and aldolization temperatures, and (iv) amine base on the reaction. Adopting the reaction conditions of bisboron enediolates with aldehydes [26], aldolization of a representative ketone, acetophenone (**2a**), was carried out in diethyl ether (0.1 M) with bisdicyclohexylboron enediolate of propanoic acid (**1**) generated with *B*-bromodicyclohexylborane (**3**). The corresponding aldol, 3-hydroxy-2-methyl-3-phenylbutanoic acid **4a** was obtained in 86% yield with a 94:6 diastereomer ratio. The major isomer possessed an *anti*-relationship between the α-methyl and β-hydroxy substituents (Table 1,

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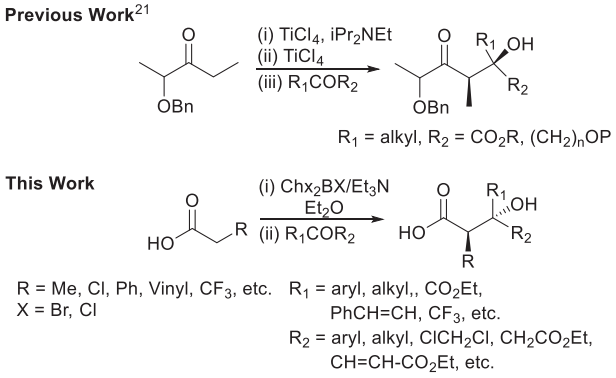


Fig. 1. Irreversible boron-mediated aldol reaction of ketones.

entry 1), confirmed by comparing with the reported ^{1}H NMR spectrum [28]. The *anti*-stereochemistry of all of the aldols produced during this study is assigned on the basis of reported structures of *anti*-aldols **4a**, **13a** and **13k** (see below).

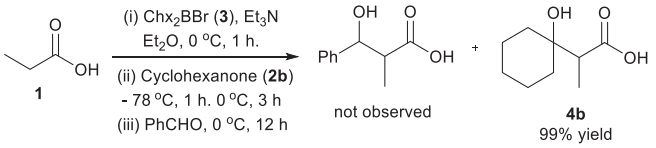
Diluting the reaction (0.066 M instead of 0.1 M) was necessary for consistency of the results. Increasing the aldolization time to 4 h at 0 °C, furnished an improved 92% yield of **4a** in 94% *anti*-selectivity (entry 3). Similar to the aldolization of aldehydes, changing the enolizing agent from **3** to the corresponding B-chlorodicyclohexylborane **5** decreased both the yield and selectivity (54%, 80:20, entry 4). Switching from triethylamine to the bulkier *N*,*N*-diisopropylethylamine also produced a deleterious effect on the yield, while the ds was maintained (35% yield, 91:9 dr, entry 5). Surprisingly, no aldol product was isolated when either THF or dichloromethane was used as the solvent for the reaction.

Aiming to probe the lack or presence of reversibility in the aldolization of ketones with bisboron enediolates, **1** was subjected to enolization, followed by aldolization of an equiv. of cyclohexanone (**2b**) for 3 h. The choice of the ketone was based on the *retro*-aldol reaction reported [14]. An equiv. of benzaldehyde was then added to the aldolate mixture and monitored for 12 h by ^{1}H NMR spectroscopy. Gratifyingly, none of the 3-hydroxy-2-methyl-3-phenylpropanoic acid resulting from sequential *retro*-keto-aldol-aldehyde aldol reaction was observed, verifying the absence of any reversal that afflicts the ketone aldol reactions [14]. The aldol (**4b**) from cyclohexanone was isolated in 99% yield (Scheme 1).

The optimized protocol for the aldolization of ketones with the enediolate of **1** (Table 1, entry 3) was then successfully extended to include representative examples of different classes of ketones. The results are summarized in Table 2. Substitution of **2a** with a bromine atom at the *para*-position (**2c**) provided similar ds for the hydroxy acid **4c** in 83% yield (entry 3). An α-haloketone, 2-chloroacetophenone (**2d**), provided the aldol **4d** in 90% yield, also with 94:6 diastereomer ratio (dr). A β-ketoester, ethyl benzoylacetate (**2e**) provided the aldol **4e** in 57% yield and 89:11 dr (entries 4–5). An α-keto ester, ethyl pyruvate **2f** provided the corresponding aldol, **4f** in 60% yield and 93% *anti*-selectivity (entry 6). An α,β-unsaturated ketone, (*E*)-4-phenylbut-3-en-2-one **2g** was aldolized to provide the corresponding hydroxy acid **4g** in a much decreased 54% yield and 85:15 dr favouring the *anti*-isomer (entry 7). No decrease in yield was observed with ethyl benzoylacrylate (**2h**), aldolized to **4h** in 89% yield and 89:11 dr (entry 8).

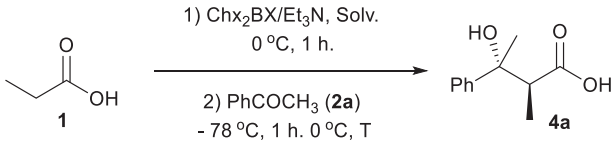
The diastereoselectivity appears to depend on the sterics on either side of the carbonyl group. For example, the aldolization of 4-methoxybenzophenone **2i** with bisdicyclohexylboron enediolate of **1a** provided the corresponding aldol in very high (95%) yield, with no diastereoselectivity (1:1 dr) (entry 9). A similar dr (1:1) was also observed for the aldolization of 3-hexanone (**2j**) (entry 10). The dr improved to 86:14 for 2-butanone (**2k**) and 76:24 for 3-methyl-2-butanone (**2l**) (entries 11–12). Further increasing the bulk of the ketone to 3,3-dimethyl-2-butanone (**2m**) provided essentially diastereopure *anti*-isomer of **4m** in 73% yield (entry 13).

The sterics and electronics of a trifluoromethyl group has been of interest to organic and biological chemists [29–31]. Given the



Scheme 1. Non-reversible addition of bisboron enediolate of propanoic acid to cyclohexanone.

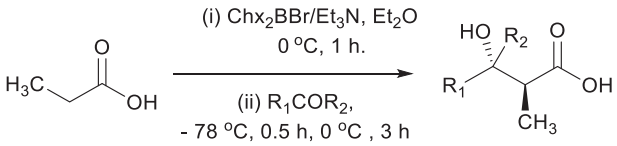
Table 1
Optimization of *anti*-selective aldolization of acetophenone with bisdicyclohexylboron enediolate of propanoic acid (**1**).



Entry	Chx_2BX		Cond.[a]	Solvent	Yield (%)[b]	*anti*:*syn*[c]
	#	X				
1	**3**	Br	A	Et_2O	86[d]	94:6
2	**3**	Br	B	Et_2O	85	94:6
3	**3**	**Br**	**C**	**Et_2O**	**92**	**94:6**
4	**5**	Cl	C	Et_2O	54	80:20
5[e]	**5**	Cl	C	Et_2O	35	91:9
6	**3**	Br	C	THF	–	–
7	**3**	Br	C	CH_2Cl_2	–	–

[a] Reaction conditions: A = concentration of **1**: 0.1 M, enolization: 0 °C, 1 h; aldolization: −78 °C, 0.5 h, 0 °C, 1 h. B = concentration of **1**: 0.066 M, enolization: 0 °C, 1 h, aldolization: −78 °C, 0.5 h, 0 °C, 1 h. C = concentration of **1**: 0.066 M, enolization: 0 °C, 1 h, aldolization: −78 °C, 0.5 h, 0 °C, 3 h.
[b] Combined yields of *syn* and *anti*-isomers.
[c] *syn* and *anti* ratios were determined by ^{1}H NMR analysis of the crude reaction mixture.
[d] Yields varied between 40% and 95%.
[e] *i*-Pr_2NEt was used as the base.

Table 2
Addition of ketones to bisboron enediolates of propanoic acid.



Entry	Ketone			Aldol		
	#	R_1	R_2	#	Yield[a]	*anti*:*syn*[b]
1	**2a**	C_6H_5	Me	**4a**	92	94:6
2	**2b**	$-(CH_2)_5-$		**4b**	99	–
3	**2c**	*p*-BrC_6H_4	Me	**4c**	83	94:6
4	**2d**	C_6H_5	CH_2Cl	**4d**	90	94:6
5	**2e**	C_6H_5	CH_2CO_2Et	**4e**	57	89:11
6	**2f**	CO_2Et	Me	**4f**	60	93:7
7	**2g**	C_6H_6CHCH	Me	**4g**	54	85:15
8	**2h**	C_6H_5	$CHCHCO_2Et$	**4h**	89	89:11
9	**2i**	*p*-$CH_3OC_6H_4$	C_6H_5	**4i**	95	50:50
10	**2j**	*n*-Pr	Et	**4j**	84	50:50
11	**2k**	Et	Me	**4k**	60	86:14
12	**2l**	*i*-Pr	Me	**4l**	62	76:24
13	**2m**	*t*-Bu	Me	**4m**	73	99:1
14	**2n**	CF_3	Et	**4n**	56	93:7

[a] Combined yields of *syn* and *anti*-isomers.
[b] *syn*- and *anti*-ratios were determined by ^1H NMR, occasionally ^{13}C NMR and where applicable ^{19}F NMR spectroscopy.

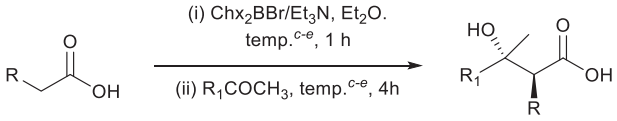
importance of fluoroorganic molecules in medicinal chemistry [32,33], as well as our longstanding interest in fluoroorganic synthesis via boranes [34,35], 1,1,1-trifluoro-2-butanone (**2n**) was subjected to the aldolization when the corresponding aldol, 3-hydroxy-2-methyl-3-(trifluoromethyl)pentanoic acid (**4n**) was isolated in 56% yield and 93:7 dr (entry 14).

To further validate the non-reversible nature of the reaction and to verify the effect of the enediolates on the diastereoselectivity, additional α-substituted acetic acids were included in the study. The aldolization of representative aromatic and aliphatic ketones, **2a** and **2k**, respectively, were carried out using bisdicyclohexyl boron enediolates derived from four representative acids possessing differing steric and electronic environments (Table 3). The reaction conditions were modified, as necessary, based on previously optimized protocols of the bisboron endiolates of these acids with aldehydes [25,26].

The optimal conditions for the enolization-aldolization with chloroacetic acid (**6**) and phenylacetic acid (**8**) were the same as that of **1**. 4-Methoxyphenylacetic acid (**10**), on the other hand, enolized under similar conditions but required higher temperature (rt) for aldolization. Enolization of but-3-enoic acid (**12**) and subsequent aldolization were carried out at −78 °C for optimal results.

The bisboron enediolate from **6** provided aldols in 83% yield and 99:1 dr with **2a** (Table 3, entry 1) and 75% yield and 85:15 dr with

Table 3
Addition of representative ketones to bisboron enediolates of selected substituted acetic acids.



Entry	Acid		Ketone		Aldol		
	#	R	**2**	R_1	#	Yield[a]	*anti*:*syn*[b]
1	**6**[c]	Cl	**2a**	C_6H_5	**7a**	83	99:1
2			**2k**	Et	**7k**	75	85:15
3	**8**[c]	C_6H_5	**2a**	C_6H_5	**9a**	95	99: 1
4			**2k**	Et	**9k**	85	86:14
5	**10**[d]	*p*-$CH_3OC_6H_4$	**2a**	C_6H_5	**11a**	80	94:6
6			**2k**	Et	**11k**	75	85:15
7	**12**[e]	$CH{=}CH_2$	**2a**	C_6H_5	**13a**	80	99:1
8			**2k**	Et	**13k**	87	82:18

[a] Combined yields of *syn* and *anti*-isomers.
[b] *syn* and *anti* ratios were determined by ^1H NMR spectroscopy.
[c] Reaction conditions: concentration of acid: 0.66 M, enolization: 0 °C, 1 h; aldolization: −78 °C, 0.5 h, 0 °C, 3 h.
[d] Reaction conditions: concentration of acid: 0.66 M, enolization: rt, 1 h; aldolization: 0 °C, 0.5 h, rt, 3 h.
[e] Reaction conditions: concentration of 0.66 M: enolization: −78 °C, 1 h; aldolization: −78 °C, 4 h.

2k (entry 2). Acid **8** provided near perfect diastereoselectivity (99:1 dr) in 95% yield with **2a** (entry 3) and 86:14 dr in 85% yield with **2k** (entry 4). The enolization of *p*-methoxyphenylacetic acid, followed by aldolization of **2a** and **2k** provided the aldols in 80% and 75% yields, respectively (entries 5–6). The aromatic ketone revealed a dr of 94:6, whereas the aliphatic ketone showed only a dr of 85:15. But-3-enoic acid provided essentially diastereopure *anti*-aldol in 80% yield with **2a**. However, an 87% yield and a dr of 82:18 was observed with **2k** (entries 9–10). The *anti*- relationship between the α-vinyl and β-hydroxy groups was confirmed based on the ^{1}H NMR spectrum of **13a** and **13k** reported in the literature [36]. It is noteworthy that in all of the cases the aldols from the representative arylalkyl ketones possessed higher diastereoselectivity compared to those from dialkyl ketones.

In conclusion, the aldolization of various ketones with bisdicyclohexylboron enediolates of a series of substituted acetic acids have been achieved to provide β,β-disubstituted β-hydroxy acids, generally, in very good yields and high anti-selectivity. Unlike the aldolization of ketones with enolborinates derived from ketones [14], there is no *retro*-aldol reaction with the boron enediolates. Further studies to expand the scope of this reaction are under way.

A typical experimental procedure is as follows: All operations were carried out in a nitrogen atmosphere. B-bromodicyclohexylborane (Chx_2BBr) (4.8 mmol) was transferred to a 50 mL round-bottom flask and dissolved in anhydrous ether (30 mL) followed by dropwise addition of triethylamine (0.67 mL, 4.8 mmol) to the stirred solution at 0 °C. The acid (2.0 mmol) dissolved in 2 mL of anhydrous Et_2O was then added, dropwise, to the above solution at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, cooled to −78 °C, followed by the dropwise addition of the ketone (2.4 mmol). The reaction mixture was stirred for 1 h at the same temperature (−78 °C), warmed to 0 °C and stirred for 3 h. The reaction was then quenched by the addition of a saturated aqueous solution of sodium bicarbonate (5 mL) and stirred for 1 h at room temperature. After separation of the layers, the organic phase was treated with additional saturated aqueous sodium bicarbonate solution. The combined aqueous layers were washed with ether, acidified with 6 M HCl, saturated with NaCl, and extracted with ether (3 × 10 mL). The combined ether layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to obtain the *anti*-aldol products.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151102.

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