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Concerning the Boron-Mediated Aldol Reaction of Carboxylic Esters

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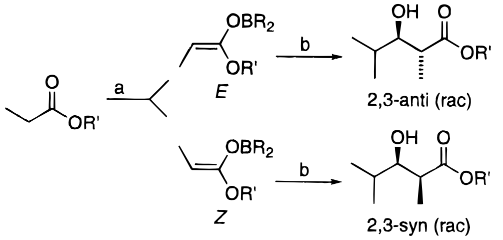
For many years, it has been assumed as a rule that simple carboxylic esters and amides cannot be enolized with the use of a dialkylboron trifluoromethanesulfonate (dialkylboron triflate) and an amine,[1] reagents which are commonly used for enolization of other carbonyl compounds, such as ketones, thioesters, and others.[2] Recorded boron-mediated aldol reactions of esters and amides are very few and use special reagents and conditions; e.g., (1) Corey reported asymmetric aldol reactions of propionate esters with aldehydes, using a chiral bis-sulfonamide derivative of boron bromide and an amine for enolization,[3] and (2) Brown developed dicyclohexylboron iodide for the aldol reaction of esters and amides.[1c,4] During our recent reinvestigation of the aldol reaction, we have unexpectedly found that carboxylic esters can be enolized under the usual conditions (dialkylboron triflate and amine) and react with aldehydes.[5] In this report, we describe our findings to correct the long-held misconception as to the reactivity of the esters. Another significant discovery concerns the *E*−*Z*[6] isomerization of an enol borinate at 0 °C or below, and this process, under the standard enolization conditions, has never been observed previously.

Treatment of benzyl propionate with *certain* pairs of dialkylboron triflate (1.3 equiv) and an amine (1.5 equiv) in dichloromethane at −78 °C for 2 h and then with isobutyraldehyde[7] provided the corresponding aldol product in high yield, as summarized in Scheme 1 and Table 1. From Table 1 the adequate reactivity of esters is evident. It is noted that both the size of the boron triflate and that of the amine are very important for successful aldol reactions and that the combination of a smaller boron triflate (Et_2BOTf, Bu_2BOTf) and a smaller amine (Et_3N, Bu_3N) led to failure of enolization of the ester, *vide infra*.

Scheme 1[a]



[a] Key: (a) R_2BOTf (1.3 equiv), amine (1.5 equiv), CH_2Cl_2, −78 °C, 2 h; (b) *i*-PrCHO, −78 °C, 1 h; 0 °C, 1 h.

The syn:anti selectivities of various propionate esters are summarized in Table 2. The selectivity is sensitive to the alcohol residue of the ester and the enolization reagents. To the exclusion of row 5, the bulkier the ester (rows 1−4 of each column of Table 2), or the smaller the amine (columns B and C, Table 2), the more anti isomer is produced. However, the bulkiness of the boron reagent has a less significant effect on the selectivity (columns A and B, Table 2). These observations could be rationalized on the basis of conformations similar to those proposed earlier for the enolization of ketones.[1a,2a] As noted above, Et_3N (a small amine) with Bu_2BOTf did not deprotonate esters, but instead the amine irreversibly formed a complex with Bu_2BOTf (not shown in Table 2, but see Table 1). It should be noted that with respect to the selectivity benzyl ester behaved differently from the other esters as described previously.[3c] The reaction of *tert*-butyl propionate did not proceed at −78 °C, and this ester decomposed under the reaction conditions at 0 °C.

No asymmetric boron-mediated aldol reaction of *chiral* carboxylic esters has been recorded, perhaps because of the misbelief as to the reactivity of esters. With information as to the reactivity and syn:anti selectivity of esters now in hand, we have investigated the aldol reaction of various chiral propionate esters with isobutyraldehyde, in particular using 8-phenylmenthyl propionate (Scheme 2).[8] As enolization reagents, dicyclohexylboron triflate and triethylamine were found to be superior to other combinations of boron triflates and amines. This investigation has disclosed several interesting phenomena, and the results are summarized in Table 3.

In order to achieve a quantitative conversion of the ester, 2.0 equiv of the boron triflate had to be used (entries 7−10, Table 3).[9] In the generation of the enol borinate under kinetically controlled conditions (−78 °C, 3 h), the anti isomer was formed predominantly irrespective of the amount of boron triflate and the amine (entries 1 and 7, Table 3). Unfortunately, a negligible facial selectivity was observed for the aldol reaction leading to the anti products. In contrast, when enolboration was

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[1] For the failure of aldol reactions of carboxylic esters and amides, see: (a) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099. (b) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 499. (c) Ganesan, K.; Brown, H. C. *J. Org. Chem.* **1994**, *59*, 2336. (d) Ganesan, K.; Brown, H. C. *J. Org. Chem.* **1994**, *59*, 7346.

[2] For reviews of boron-mediated aldol reaction, see: (a) Kim, B. M.; Williams, S. F.; Masamune S. *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2 (Heathcock, C. H., Ed.), Chapter 1.7, p 239. (b) Heathcock, C. H. *Modern Synthetic Methods;* Scheffold, R., Ed.; VCH: New York, 1992; p 1. Also see ref 1d and references cited therein.

[3] (a) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493. (b) Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976. (c) Corey, E. J.; Lee, D.-H. *Tetrahedron Lett.* **1993**, *34*, 1737.

[4] Brown, H. C.; Ganesan, K. *Tetrahedron Lett.* **1992**, *33*, 3421.

[5] Reaction of an amide proceeded less efficiently. Thus, enolization of *N,N*-diethylpropionamide with dicyclohexylboron triflate and triethylamine in CH_2Cl_2 at −78 °C for 2 h, followed by the addition of isobutyraldehyde at −78 °C for 1 h and then 0 °C 1 h, afforded the aldol product in 50% yield with a ratio of syn:anti = 1:1.

[6] In this paper the *Z* and *E* stereochemical descriptors of enol borinates are defined on the assignment of the highest priority designation to the OBR_2 group (Scheme 1). Also, the *E:Z* ratio of an enol borinate is equated to the syn:anti ratio of the aldol products which are derived from the borinate. See ref 1c. Due mainly to the facile *E*−*Z* isomerization of the enol borinate, the precise spectral characterization of either isomer (*E* or *Z*) has not been completed.

[7] Isobutyraldehyde (instead of benzaldehyde) was used in order to avoid the Lewis acid-catalyzed aldol reaction, which is sometimes the main reaction pathway. See: Danda, H.; Hansen, M. N.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173.

[8] Corey, E. J.; Peterson, R. T. *Tetrahedron Lett.* **1985**, *26*, 5025.

[9] Dicyclohexylboron triflate formed a complex with the amine in competition with deprotonation, and there existed no *free* cyclohexylboron triflate after 3 h at −78 °C in the experiments using either 1.3 or 2.0 equiv of the triflate.

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Table 1. Aldol Reaction of Benzyl Propionate and Isobutyraldehyde[a]

triflate	$\mathrm{Et_2BOTf}$[b]	$\mathrm{Bu_2BOTf}$[c]	$\mathrm{cPen_2BOTf}$[c]	$\mathrm{cHex_2BOTf}$[b]
amine	yield (%) (syn:anti)	yield (%) (syn:anti)	yield (%) (syn:anti)	yield (%) (syn:anti)
$\mathrm{iPr_2NEt}$	96 (92:8)	97 (95:5)	97 (95:5)	84 (90:10)
$\mathrm{cHex_2NMe}$	93 (95:5)	95 (95:5)	96 (92:8)	
$\mathrm{nBu_3N}$	0[d]	<10		
$\mathrm{Et_3N}$	0[d]	<10	94 (22:78)	92 (10:90)

[a] Enolization: at -78 °C for 2 h in $\mathrm{CH_2Cl_2}$. Aldol reaction: at -78 °C for 1 h and then 0 °C for 1 h. Yield and syn:anti ratio by HPLC analysis. [b] Freshly prepared. [c] Purchased from Aldrich Chemical Co. [d] Enolization at rt.

Table 2. Aldol Reaction of Propionate Esters[a]

	A	B	C
enolization reagents	$\mathrm{Bu_2BOTf/iPr_2NEt}$	$\mathrm{cHex_2BOTf/iPr_2NEt}$	$\mathrm{cHex_2BOTf/Et_3N}$
propionate ester	yield (%) (syn:anti)	yield (%) (syn:anti)	yield (%) (syn:anti)
$\mathrm{EtCO_2Me}$	85 (>95:5)	75 (95:5)	84 (>95:5)
$\mathrm{EtCO_2Et}$	81 (95:5)	72 (>95:5)	86 (60:40)
$\mathrm{EtCO_2CH_2cHex}$	89 (80:20)	73 (>95:5)	92 (70:30)
$\mathrm{EtCO_2iPr}$	65 (75:25)	60 (85:15)	63 (30:70)
$\mathrm{EtCO_2Bn}$[b]	97 (95:5)	84 (90:10)	92 (10:90)

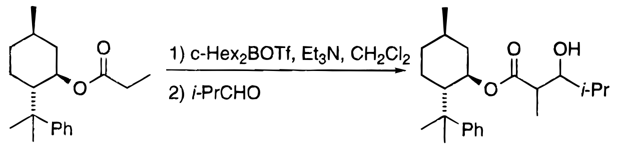
[a] The reaction was carried out with 1.3 equiv of the boron triflate and 1.5 equiv of the amine, -78 °C for 2 h, followed by isobutyraldehyde (-78 °C for 1 h and then 0 °C for 1 h). Yield:isolated yield. Syn:anti ratio by NMR. For the source of the triflates, see Table 1. [b] See Table 1.

Table 3. Asymmetric Aldol Reaction of 8-Phenylmenthyl Propionate[a]

entry	$\mathrm{cHex_2BOTf}$[b] (equiv)	$\mathrm{Et_3N}$ (equiv)	enolization condns (T (°C), time)	syn:anti	ds for syn[c]	yield (%)
1	1.3	1.5	−78, 3 h	2:98	(48:52)	58
2	1.3	1.5	−40, 3 h	60:40	97:3	58
3	1.3	1.5	0, 1 h	84:16	98:2	58
4	1.3	1.5	0, 2 h	82:18	97:3	57
5	1.3	1.5	0, 14 h	83:17	98:2	59
6	1.3	1.5	−78, 3 h: 0, 1 h	81:19	97:3	57
7	2.0	3.0	−78, 3 h	2:98	(48:52)	87
8	2.0	3.0	0, 30 min	78:22	97:3	92
9	2.0	3.0	−78, 3 h; −40, 10 min	38:62	97:3	85
10	2.0	3.0	−78, 3 h; 0, 1 h	80:20	97:3	92

[a] After enol borinate was formed, isobutyraldehyde (1.2 equiv) was added at -78 °C. Aldol conditions: -78 °C for 1 h, 0 °C for 1 h. [b] Freshly prepared. [c] Numbers in parentheses are ds for anti isomer.

Scheme 2



carried out at higher enolization temperatures (-40 and 0 °C), the syn isomer was produced with high facial selectivity as the major product with a ratio of syn:anti = 60:40 and ~80:20, respectively (entries 2−5 and 8, Table 3). The prolonged enolization time affected neither the yield nor the syn:anti ratio (entry 5, Table 3). The varying syn:anti ratios from 2:98 to 80:20 through 60:40 (entries 1−3, 7, and 8, Table 3) depending on the enolization temperature would indicate the isomerization of the enol borinate. The results of Entries 6, 9, and 10 (Table 3) are revealing and strongly support this inference. In entries 6 and 10 (Table 3), enolization was conducted in two steps: first enolization at -78 °C for 3 h, [providing the enolate with Z:E = 2:98 (entries 1, 7, Table 3)], and then standing at 0 °C for 1 h. The aldol reaction in the standard manner afforded the product with syn:anti = 81:19 (80:20), which corresponds to the enolate with Z:E = 81:19 (80:20). In entry 9 (Table 3) the enolate prepared at -78 °C was allowed to stand at -40 °C for 10 min. The syn:anti ratio of the aldol product was 38:62, which is equated to the enolate Z:E ratio. The E−Z isomerization appears to be promoted mainly by $\mathrm{Et_3NHOTf}$ present in the reaction mixture[9] and brings about an 80:20 equilibrated mixture of the two isomers. Detailed mechanistic studies are now underway.

In conclusion, the boron aldol reaction of carboxylic esters, which was believed to be an ineffective process, has now been found to be a rather useful variation of the aldol reaction. Under standard enolization conditions enol borinates have been found to undergo facile isomerization at 0 °C or below.[10]

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Supporting Information Available: A typical experimental procedure for the aldol reactions and characterization of new compounds (3 pages).

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(10) Isomerization of enol borinates under rather forcing conditions. (a) Masamune, S.; Mori, S.; van Horn, D.; Brooks, D. W. *Tetrahedron Lett.* **1979**, 1665. (b) Reference 1a.