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Asymmetric double aldol reaction of chiral acetyloxazolidinone

Hiroshi Furuno, Tadashi Inoue and Atsushi Abiko*

Venture Laboratory, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606-8585, Japan

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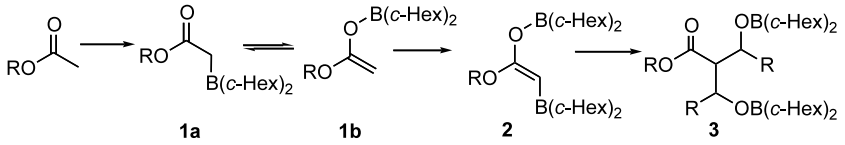
Abstract—Treatment of chiral oxazolidinone with Bu_2BOTf (2.5 equiv.) and Et_3N (3.0 equiv.) quantitatively produced the doubly borylated enolate, which afforded the double aldol products with high diastereoselectivity after reaction with aldehydes.

Recently, we have reported a new asymmetric boron-mediated double aldol reaction.[1] From an extensive spectroscopic investigation of the double aldol reaction of acetate esters, we found and characterized carbon-bound boron enolates (**1a**) as equilibrium mixtures of oxygen-bound enolates (**1b**) for the first time.[2] Furthermore, the novel doubly borylated enolates (**2**) were identified as intermediates of the double aldol reaction (Scheme 1).[3] We also found that the corresponding doubly borylated enolates could be prepared from a variety of carbonyl compounds, such as *N*,*N*-dimethylacetamide, acetic acid, methoxyacetone, and phenyl thioacetate.[2]

Further investigation of the boron mediated aldol reaction of acetyl derivatives unexpectedly led us to discover that 3-acetyl-2-oxazolidinone produced the corresponding doubly borylated enolate and was actually a substrate of the double aldol reaction. Herein, we report preliminary results of the asymmetric double aldol reaction of a chiral acetyl oxazolidinone (Evans' auxiliary).

Undoubtedly, the chiral 2-oxazolidinone auxiliaries are the most useful and reliable reagents in the boron-mediated aldol reaction.[4] Besides the well-established asymmetric aldol reaction of the propionate derivative of chiral oxazolidinones, a few examples of asymmetric aldol reaction of acetyl oxazolidinones have been reported to afford the corresponding mono aldol products under the 'standard conditions'.[5] Contrary to the reported normal aldol reactions, we have found that both the conventionally assumed mono enolates and the doubly borylated enolate species could be produced depending on the enolization reagent and the amount of the boron triflate.

When **4** was treated with 1 equiv. of n-Bu_2BOTf and 1.2 equiv. of Et_3N in $CDCl_3$ at 0°C, formation of both mono enolate **5a** ($R' = n$-Bu; 42%) and doubly borylated enolate **6a** ($R' = n$-Bu; 15%) was observed (Table 1, entry 1). Enolization at the lower temperature (−65°C) made **5a** predominate over **6a** (entry 2). The use of i-Pr_2EtN did not affect the result very much (entries 3 and 4). Similarly, with 1 equiv. of c-Hex_2BOTf and 1.2 equiv. of a base, **4** afforded a mixture of **5b** and **6b** favoring **5b** (entries 5 and 6). The mixtures of **5** and **6** were quantitatively converted to the doubly borylated enolate **6** with an additional 1.5 equiv. of the corresponding boron triflate. With 2.5 equiv. of n-Bu_2BOTf and 3 equiv. of triethylamine, **6a** formed as a sole product irrespective of the reaction conditions (entry 7). The doubly borylated enolates **6b** and **6c** were prepared



Scheme 1.

Keywords: aldol reaction; boron-mediated aldol reaction; double aldol reaction; asymmetric aldol reaction; oxazolidinone; doubly borylated enolate; boron triflate.

* Corresponding author.

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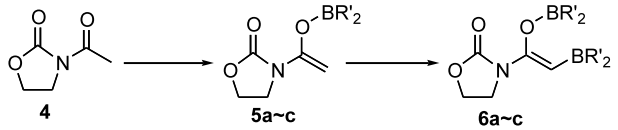
Table 1. Composition of the enolates prepared from acetyloxazolidinone (**4**) with boron triflate and amine



a R'= *n*-Bu, **b** R'= *c*-Hex, **c** BR'_2= 9-BBN

Entry	Enolization reagents (equiv.)	Temp. (°C)[a]	Yield% (ratio of **5**:**6**:**4**)
1	*n*-Bu_2BOTf (1.0), Et_3N (1.2)	0	**5a**:**6a**:**4** = 42:15:43
2	*n*-Bu_2BOTf (1.0), Et_3N (1.2)	−65	**5a**:**6a**:**4** = 61:12:27
3	*n*-Bu_2BOTf (1.0), *i*-Pr_2EtN (1.2)	0	**5a**:**6a**:**4** = 57:3:40
4	*n*-Bu_2BOTf (1.0), *i*-Pr_2EtN (1.2)	−65	**5a**:**6a**:**4** = 60:18:22
5	*c*-Hex_2BOTf (1.0), Et_3N (1.2)	0	**5a**:**6b**:**4** = 76:8:15
6	*c*-Hex_2BOTf (1.0), *i*-Pr_2EtN (1.2)	0	**5a**:**6b**:**4** = 80:8:12
7	*n*-Bu_2BOTf (2.5), Et_3N (3.0)	0	**6a**, 100
8	*c*-Hex_2BOTf (2.5), Et_3N (3.0)	0	**6b**, 100
9	9-BBN-OTf[b] (3.8), Et_3N (4.5)	0	**6c**, 100

[a] Enolization was conducted at the indicated temperature for 5 min, then the ratio was measured by ^1H NMR spectroscopy at 23°C.
[b] Commercial solution of 9-BBN-OTf in hexane from Aldrich was used as received.

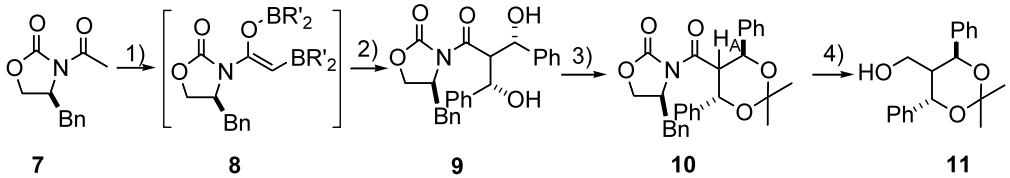
in the same manner with *c*-Hex_2BOTf and 9-BBN-OTf, respectively (entries 8 and 9). The doubly borylated enolates showed a characteristic singlet (**6a** 4.26 ppm, **6b** 4.00 ppm, **6c** 4.27 ppm) of the olefinic proton in the ^1H NMR spectra, and the structure was determined on the basis of NMR spectroscopies (^1H, ^{13}C, ^{11}B, [^{13}C–^1H] COSY, and [^1H–^{13}C] HMBC).[6]

The asymmetric double aldol reaction of (*R*)-**7** with benzaldehyde was investigated. The chiral auxiliary exhibited excellent stereocontrol ability even at room temperature to afford (*S*,*S*)-diol **9** as a major product (>95% ds).[7] The doubly borylated enolates derived from *c*-Hex_2BOTf and 9-BBN-OTf were rather unreactive and 14 h of the reaction time was necessary for completion. Naturally, *n*-Bu_2BOTf and Et_3N were selected as enolization reagents. It is important to note that the reaction of **8b** (R′ = *c*-Hex), prepared from **7** with *c*-Hex_2BOTf (2.5 equiv.) and Et_3N (3 equiv.), proceeded 24% after 1.5 h with recovery of **7** (71%). This result implies the rate determining step of this double aldol reaction is the reaction of the doubly borylated enolate (**8**) with aldehyde.

The relative stereochemistry of the double aldol product **9** was determined from the analysis of the coupling constants of the acetonide derivative **10**[8] and the further transformation. The absolute stereochemistry was established after conversion to the known alcohol **11**[1] with $LiAlH_4$ reduction (Scheme 2). The stereochemical outcome shows that the sense of diastereofacial selectivity is same as that of the conventional asymmetric aldol reaction of the corresponding propionate derivative. The high *Z*(O)-enolate preference of the boron-enolate of propionyloxazolidinone strongly suggests that **9** was produced from the *Z*(O)-enolate at the both first and second aldol reactions under the stereochemical control by the auxiliary.

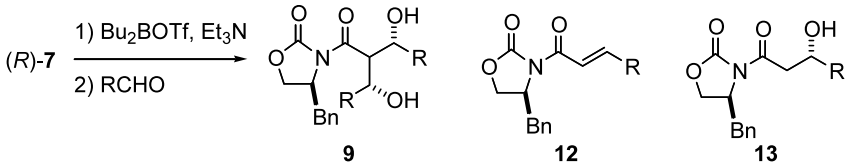
The asymmetric double aldol reaction of **7** with various aldehydes proceeded with excellent selectivities (ds > 95%) (Table 2). With most of aromatic aldehydes, the double aldol products (**9**)[9] could be isolated in high yields. With certain electron rich aldehydes, however, such as *p*-anisaldehyde or 1-naphthaldehyde, elimination products (**12**) also formed as side products (entries 3 and 5). Isobutyraldehyde and methacrolein afforded the double aldol products with high selectivity as major products (70–80%), and the mono aldols (**13**) with low selectivities and/or elimination products (**12**) as minor products (entries 8 and 9). The reaction of **8b** (R′ = *c*-Hex) with isobutyraldehyde afforded diastereomers of the mono aldol products as sole products in 3.3:1 (Table 2, entry 10).[10]

In summary, contrary to the reported normal mono aldol reaction, we have discovered that the acetyloxazolidinone caused the double aldol reaction. The excellent diastereoselectivities were achieved with a variety of aldehydes using a conventional chiral oxazolidinone. The present results made a variety of chiral triols of C_3-symmetry more accessible.[11]



Scheme 2. *Reagents and conditions*: (1) R'_2BOTf, Et_3N; (2) PhCHO; (3) 2,2-dimethoxypropane, PTS, CH_2Cl_2, rt; (4) $LiAlH_4$, ether.

Table 2. Asymmetric double aldol reaction of (*R*)-**7** with aldehydes



Entry	Aldehyde	Product (yield%)	Entry	Aldehyde	Product (yield%)
1	Benzaldehyde	**9a** (93)	6	4-CF_3-C_6H_4CHO	**9f** (94)
2	Tolualdehyde	**9b** (95)	7	4-Br-C_6H_4CHO	**9g** (98)
3	1-Naphthaldehyde	**9c** (85)[a]	8	Methacrolein	**9h** (81)[c]
4	2-Naphthaldehyde	**9d** (93)	9	Isobutyraldehyde	**9i** (72)[d]
5	4-MeO-C_6H_4CHO	**9e** (71)[b]	10[e]	Isobutyraldehyde	**13i** (95; 3.3:1)

[a] **12c** (11%).
[b] **12e** (22%).
[c] **12h** (8%).
[d] **12i** (6%), **13i** (20%).
[e] *c*-Hex_2BOTf/Et_3N were used as enolization reagents.

Acknowledgements

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6. Compound **6b** shows the following spectroscopic properties: ^{1}H NMR: δ 4.00 (1H, s), 4.11 (2H, t, J=8.5 Hz), 4.65 (2H, t, J=8.5 Hz), 8.16 (2H, s, N*H*); ^{13}C NMR: δ 33.4, 44.4, 64.8, 85.0, 156.6, 159.4; ^{11}B NMR: δ 50.5, 70.4; [^{13}C, ^{1}H] COSY 33.4–1.7, 44.4–4.11, 64.8–4.65, 85.0–4.00; [^{1}H, ^{13}C] HMBC ~1.7–85.0, 4.00–33.4, 4.00–156.6, 4.11–64.8, 4.11–159.4, 4.65–44.4, 4.65–159.4.
7. *Typical reaction procedure*: Commercial solution of *n*-Bu_2BOTf in CH_2Cl_2 (Aldrich, 1 M, 100 ml) was transferred to CH_2Cl_2 (200 ml) via cannula and then Et_3N (120 mmol) was added dropwise. To this solution, (*R*)-**7** (8.80 g, 40 mmol) in CH_2Cl_2 (20 ml) was added at 0°C during 20 min, and the mixture was stirred at 0°C for 15 min. Benzaldehyde (12.7 g, 120 mmol) was added dropwise, and the reaction was let to warm to room temperature and stirred for 1.5 h. A pH 7 buffer solution (200 ml) was added and the organic layer was separated. Aqueous layer was extracted with CH_2Cl_2 (2×100 ml) and the combined organic extracts were concentrated under vacuum. The residue was diluted with MeOH (150 ml) and tartaric acid (30 g) was added. To the mixture, 30% H_2O_2 solution (100 ml) was carefully added with cooling in an ice-water bath. After exothermic reaction subsided, the mixture was stirred at room temperature for 1 h and concentrated. Usual extractive workup afforded **9** (16.0 g, 37 mmol, 93%) after crystallization from ethyl acetate and hexane.
8. H_A appeared at δ 5.14 as a double doublet (J=8.2, 10.0 Hz).
9. The absolute stereochemistry of the double aldol products were assigned on the analogy of that of **9a**.
10. ^{1}H NMR showed the increase of the enolate of isobuyraldehyde was accompanied with the consumption of **8b** and isobutyraldehyde, and formation of the (mono) aldolate. Thus, the mono aldol product is attributed to the reversion of **8b** to the mono enolate by proton transfer. See Ref. 2.
11. The following chiral triols of C_3-symmetry [HC(CH(OH)-R)$_3$] have been synthesized: R=4-Me-C_6H_4, mp 119–120°C, $[\alpha]_D^{22}$=131.8 (*c* 1.24); R=4-MeO-C_6H_4, mp 203–204°C, $[\alpha]_D^{22}$=119.4 (*c* 0.50); R=4-Br-C_6H_4, mp 172–173°C, $[\alpha]_D^{22}$=177.9 (*c* 1.00); R=4-CF_3-C_6H_4, mp 130–131°C, $[\alpha]_D^{22}$=39.8 (*c* 0.50); R=1-naphthyl, mp 233–234°C, $[\alpha]_D^{22}$=−407.3 (*c* 1.00); R=2-naphthyl, mp 156–157°C, $[\alpha]_D^{22}$=342.6 (*c* 1.00). Details of the synthesis will be reported elsewhere.