

Stereoselective Crossed Aldol Reaction via Boron Enolate Generated from α -Iodoketones and 9-BBN-H

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Boron enolates were in situ generated smoothly by treating α -iodo ketones with 9-BBN-H, and aldols were produced in highly diastereoselective manner by successive reaction with various aldehydes at low temperature.

Aldol reaction is frequently employed in organic synthesis as one of the most important and useful tools for carbon-carbon bond formation. The reaction is generally carried out under basic or acidic conditions by generating active enolates from donor carbonyl compounds or by activating acceptor carbonyl compounds, respectively. It was reported from our laboratory in 1973 that boron enolates reacted smoothly with aldehydes and gave the aldol adducts under neutral conditions.¹

Metal enolates were generated under nearly neutral conditions with high regioselectivities by reduction of α -halo carbonyl compounds with low-valent metals as is represented in the Reformatsky and related reactions.² α -Halo carbonyl compounds afforded the corresponding aldols in stereoselective manner on treatment with acceptor carbonyl compounds by using a variety of metals or low-valent metals such as Sn,³ Co,⁴ Cr,⁵ or Sm.⁶ It was recently reported from our laboratory that the aldol reactions of titanium enolates generated from α -halo carbonyl compounds and low valent titanium compounds such as TiCl_2 gave the corresponding aldols with high diastereoselectivities.⁷ In these cases, however, difficulty in preparing reducing metallic reagents which were employed in the generation of key enolates and also limitation concerning the substrates were pointed out.

It was then considered that highly regioselective and diastereoselective aldol reaction would be achieved if boron enolates were generated from α -halo carbonyl compounds under mild conditions since boron enolates were known to react with aldehydes resulting in the formation of the corresponding aldols.⁸ The aldol reaction of α -iodoketones with several aldehydes by using Et_3B as a reductant was already reported⁹ although satisfactory results were not shown concerning the diastereoselectivities.

In this communication, we would like to describe highly diastereoselective aldol reaction of several aldehydes and boron enolates, generated by hydride reduction of α -iodoketones with 9-BBN-H.

In the first place, the following evidences were confirmed; 1) generation of boron enolate on treating pinacolborane¹⁰ and 2-iodopropiophenone where boron hydride coordinated to the carbonyl oxygen first, and hydride reduction spontaneously took place to form the enolate along with hydroiodic acid (Figure 1),¹¹ 2) reduction of various aldehydes by the boron hydrides did not proceed under the reaction conditions.

The aldol reaction of 2-iodopropiophenone with benzaldehyde was tried in the presence of catecholborane and K_2CO_3 at

-78°C in toluene, and the desired aldol was obtained in 92% yield though diastereoselection was quite low. When the reaction was carried out at 0°C using 9-BBN-H, on the other hand, the corresponding aldol was obtained in 45% yield with high diastereoselectivity. Further, in order to complete the generation of boron enolate from 2-iodopropiophenone at room temperature, 2,6-lutidine was used as a hydroiodic acid acceptor. Then, the desired aldol was obtained in 85% yield with high diastereoselectivity. The combined use of 2,6-lutidine and THF afforded the corresponding aldol in the highest yield with high diastereoselectivity.

A proposed reaction mechanism is shown in Figure 1: i.e., α -iodoketone was reduced with 9-BBN-H to generate boron enolate in the presence of 2,6-lutidine. The formation of boron enolates from α -iodoketones and boron hydrides was confirmed by the NMR measurement.¹²

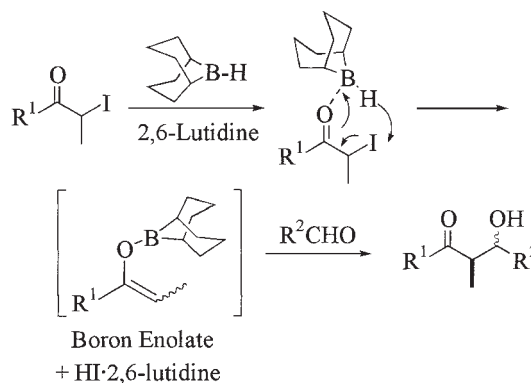


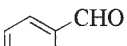
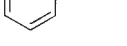
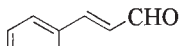

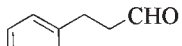



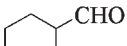
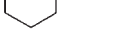
Figure 1.

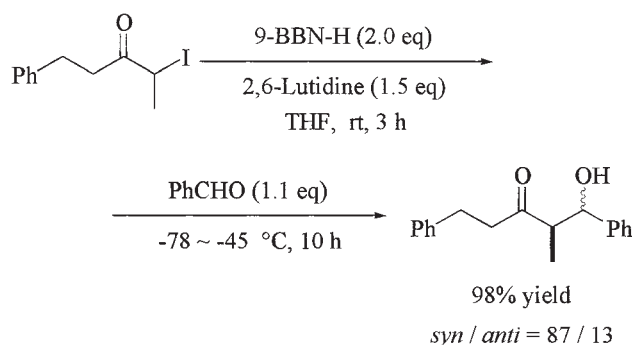
The yields and diastereoselectivities of aldol products by the present procedure are summarized in Table 1. Both aromatic and aliphatic α -iodo ketones reacted smoothly with acceptor aldehydes to give the corresponding *syn*-aldol products predominantly in high yields.

The regioselectivity of the reaction is shown by the following example (Scheme 1). Treatment of 2-iodo-5-phenyl-3-pentanone and benzaldehyde with 9-BBN-H and 2,6-lutidine expectedly gave β -hydroxy ketone as a single product without contaminating the opposite regioisomer at all.

A typical procedure is described for the reaction of 2-iodopropiophenone with benzaldehyde: To a solution of 2-iodopropiophenone (0.3 mmol) and 2,6-lutidine (0.4 mmol) in THF (5.0 ml) at room temperature was added 0.8 ml of a 0.5 M solution of 9-BBN-H (0.4 mmol) in THF under argon atmosphere. After the resulted solution was stirred for 3 h at the same temperature, it was cooled down to -78°C and benzaldehyde was added. Then stirring was continued another for 5 h and the

Table 1. Aldol reaction of α -iodo ketones with aldehydes in the presence of 9-BBN-H and 2,6-lutidine

| $\text{R}^1-\text{C}(=\text{O})-\text{CH}_2-\text{I} \xrightarrow[\text{THF, rt}]{\text{9-BBN-H (1.5 eq), 2,6-Lutidine (1.5 eq)}} \xrightarrow[\text{Conditions}]{\text{R}^2\text{CHO (1.1 eq)}} \text{R}^1-\text{C}(=\text{O})-\text{CH}(\text{OH})-\text{CH}(\text{R}^2)-\text{R}^1$ | | | | | |
|--|----------------|--|--------------------|----------------------|-----------------------|
| Entry | R ¹ | R ² CHO | Conditions | Yield/% ^a | syn/anti ^b |
| 1 | Ph |  | -78 °C, 5 h | 95 | 99 / 1 |
| 2 | Et |  | -78 ~ -45 °C, 10 h | 90 | 93 / 7 |
| 3 | Ph |  | -78 °C, 2 h | 96 | 99 / 1 |
| 4 | Et |  | -78 ~ -45 °C, 10 h | 94 | 94 / 6 |
| 5 | Ph |  | -78 °C, 10 h | 97 | 98 / 2 |
| 6 | Et |  | -78 ~ -45 °C, 10 h | 95 | 99 / 1 |
| 7 | Ph |  | -78 °C, 10 h | 94 | 98 / 2 |
| 8 | Et |  | -78 ~ -45 °C, 10 h | 92 | 99 / 1 |
| 9 | Ph |  | -78 °C, 10 h | 95 | 97 / 3 |
| 10 | Et |  | -78 ~ -45 °C, 10 h | 90 | 88 / 12 |

^aIsolated yield. ^bDetermined by ¹H NMR (300 MHz) and by HPLC analysis.**Scheme 1.**

reaction mixture was poured into phosphate buffer of pH 7.0 (5.0 ml) and was extracted with ether. Next, ether was removed, and methanol (2.0 ml) and 30% H₂O₂ (2.0 ml) were added at 0 °C and was left for 15 min. The mixture was concentrated in vacuo in order to remove most of the methanol and then was extracted with

ether. The combined organic layer was washed with saturated aqueous sodium hydrogencarbonate and brine, dried over Na₂SO₄, and the solvent was removed. The crude product was purified by TLC to afford the *syn*- and *anti*-3-hydroxy-2-methyl-1,3-diphenyl-1-propanone (95%, *syn/anti* = 99/1).

Reaction conditions described here are not yet sufficiently been optimized, and further studies on scope and limitation of these reactions are in progress.

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References and Notes

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- 11 In the presence of pyridine, the boron enolate was formed from pinacolborane and 2-iodopropiophenone, and was isolated by distillation in vacuo under argon. bp 91 °C/0.1 mmHg. ¹H NMR (C₆D₆, 270 MHz): δ 0.91 (s, 12H), 1.71 (d, 6.9 Hz, 3H), 5.40 (q, 6.9 Hz, 1H), 7.1 (m, 3H), 7.5 (d, 8.1 Hz, 2H); ¹³C NMR (C₆D₆, 67.5 MHz): δ 11.4, 24.5, 83.1, 106.5, 124.7, 127.7, 128.5, 137.5, 149.1. Several boron enolates were stereoselectively formed by oxidation of vinylboronates and were isolated by bulb to bulb distillation. See: R. W. Hoffmann and K. Dittrich, *Tetrahedron Lett.*, **25**, 1781 (1984). R. W. Hoffmann, K. Dittrich, and S. Fröch, *Liebigs Ann. Chem.*, **1987**, 977.
- 12 The NMR spectrum of the reaction mixture showed a signal at δ 5.20 assigned to a vinyl proton of the boron enolate.