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THREO-SELECTIVE ALDOL CONDENSATIONS OF LITHIUM ENOLATES IN THE PRESENCE OF TRIALKYLBORANES

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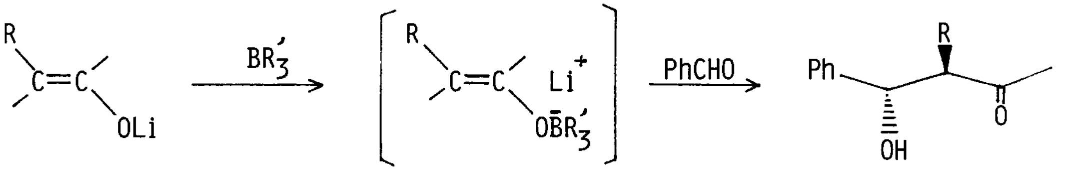
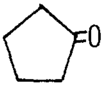
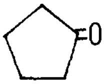
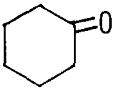
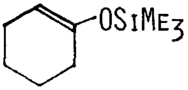
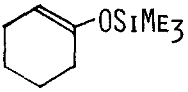
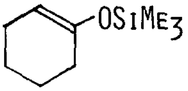
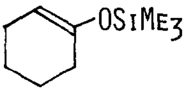
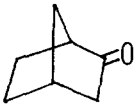
Summary The reaction of preformed lithium enolates in the presence of trialkylboranes, such as Et_3B and $n\text{-}Bu_3B$, with aldehydes leads to product mixtures rich in the more stable threo aldol.

The development of the diastereoselective synthesis of β-hydroxycarbonyl compounds as a basic synthetic block for macrolide, polyether, or ansamycin antibiotics has seen rapid growth in the past few years.[1] The aldol condensation is a method of choice for this purpose. In general, the threo product is favored under the conditions of thermodynamic control, and stereochemically defined E-enolates or quaternary ammonium enolates give preferentially the threo product.[2] We wish to report a new and convenient method to produce the threo-selectivity, which well complements the many existing methods for generating erythro isomers. Our method is very simple; merely the addition of commercially available trialkylboranes to preformed lithium enolates produces the threo selectivity (eq 1).

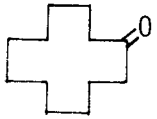
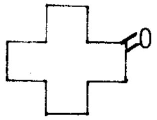
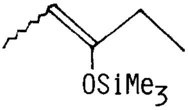
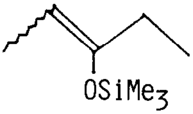


(eq 1)

Table. Threo-Selective Aldol Condensation of Lithium Enolates in the Presence of Trialkylboranes[a]

Ketone or Enol	Reaction Conditions	Threo/Erythro[b]	Yield,%[c]
	iPr_2NLi/THF, 1eq BEt_3	50/50	90
	iPr_2NLi/THF, 2eq BEt_3	91/9	90
	iPr_2NLi/THF, 3eq BEt_3	97/3	90
	iPr_2NLi/THF, 3eq BEt_3	88/12	91
	nBuLi/THF, 1eq BEt_3	92/8	90
	nBuLi/THF, 1eq nBu-9-BBN	75/25	85
	nBuLi/THF, 1eq $AlEt_3$	50/50	91
	1eq $TiCl_4/CH_2Cl_2$	64/36	(75)
	iPr_2NLi/THF, 3eq BEt_3	92/8	(88)

(Table. continued)

	iPr$_2$NLi/THF, 3eq BEt$_3$	80/20	(70)
	iPr$_2$NLi/THF, 3eq B(n-Bu)$_3$	80/20	78
	nBuLi/THF, leq BEt$_3$	60/40[d]	85
	nBuLi/THF, leq AlEt$_3$	77/23	80

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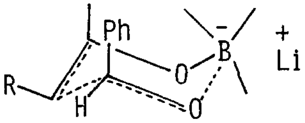
[a] All reactions were performed on a 1 mmol scale. Lithium enolates, generated from ketones or enol silyl ethers, were treated with Lewis acids at -78°C, and then benzaldehyde was added. After 30 min, the reaction was quenched with methanol at -70°C. Trialkylboranes were oxidized by treatment with H_2O_2 at this temperature. It was not necessary to add aq. NaOH. Et_3Al was decomposed by slow addition of H_2O at 0°C. [b] Determined by ^{1}H NMR spectra. [c] ^{1}H NMR yield based on an appropriate internal standard (isolated yield). [d] The reaction was quenched at room temperature.

The results are summarized in the Table. Clearly, threo-selective aldol condensation is realized by use of triethylborane or tri-n-butylborane; use of the former is more convenient since ethanol formed after oxidation is easily separated. Although the results of benzaldehyde are indicated in the Table, similar threo selective condensations are observed in the reaction with other aldehydes, such as n-butyraldehyde and i-butyraldehyde. When lithium enolates are generated from silyl enol ethers, use of one equivalent of Et_3B is enough to produce threo selectivity. On the other hand, three equivalents of Et_3B are required in the reaction of lithium enolates generated from ketones, presumably because of formation of the borane-amine (iPr_2NH) complex. Sterically less hindered n-Bu-9-BBN and sterically bulky $B(sec\text{-}Bu)_3$ are not so effective for producing threo selectivity, suggesting that the steric circumstances between these two extremes are important for the transition state leading to the threo product.[3] Presumably, T_1 of the 9-BBN may be more stable than that of Et_3B.



T_1

Finally it should be mentioned that the present method is useful for cyclic systems. Unfortunately, the threo selectivity is not high for acyclic systems, and in such a case the use of Et_3Al produces an allowable threo selectivity. Although use of dialkylboron triflate is a very useful procedure for threo selective condensations[4], our method does not require to prepare dialkylborinate derivatives in advance.

References

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2) a) W. A. Kleschick, C. T. Buse, C. H. Heathcock, J. Am. Chem. Soc., 99, 247 (1979); b) Y. Yamamoto and K. Maruyama, Tetrahedron Lett., 2895 (1981) and references cited therein; c) For review articles, see A Suzuki and S. Hara, Kagaku, 35, 406 (1980) and I. Kuwajima, ibid., 37, 151 (1982).
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4) D. E. V. Horn and S. Masamune, Tetrahedron Lett., 2229 (1979); D. A. Evans, E. Vogel, J. V. Nelson, J. Am. Chem. Soc., 101, 6120 (1979); T. Inoue and T. Mukaiyama, Bull. Chem. Soc. Jpn., 53, 174 (1980).

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