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Major Effect of the Leaving Group in Dialkylboron Chlorides and Triflates in Controlling the Stereospecific Conversion of Ketones into Either [E]- or [Z]-Enol Borinates

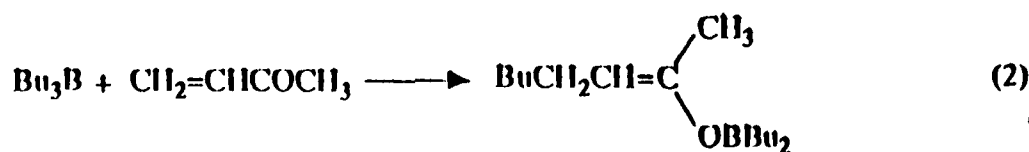
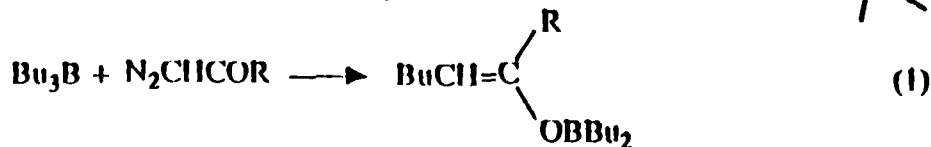
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The ready synthesis and ease of handling of dialkylboron chlorides, R_2BCL , compared to triflates, R_2BOTf , give the chlorides a significant advantage as reagents to achieve the conversion of ketones into enol borinates, regiospecifically and quantitatively. This made possible the first study of the effect of changes in the leaving group on the ratios of [E]-:[Z]-enol borinates produced. Indeed, a systematic study of the effect of the steric requirement of the R group ($R = 9\text{-BBN}$ vs Chx_2), the amine (Et_3N vs $i\text{-Pr}_2EtN$), and the leaving group (Cl vs OTf), with two representative ketones, propiophenone and diethyl ketone, revealed a controlled shift from preferential formation of the [Z]-enol borinates to the [E]-enol borinates. The technique was applied to other representative ketones and selective conversion to both [E]-enol borinates (~80-99%) and [Z]-enol borinates (97-99%) has been achieved.

Enol borinates are valuable intermediates in organic synthesis. A number of published methods have been described for their generation (eqs 1 and 2).⁴

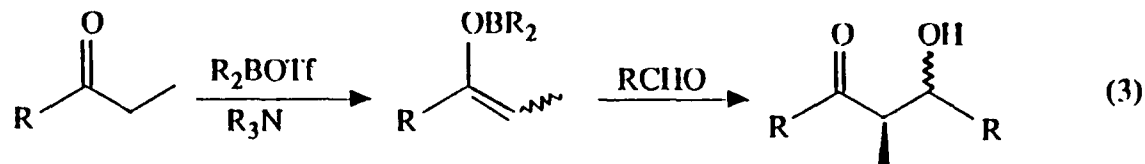


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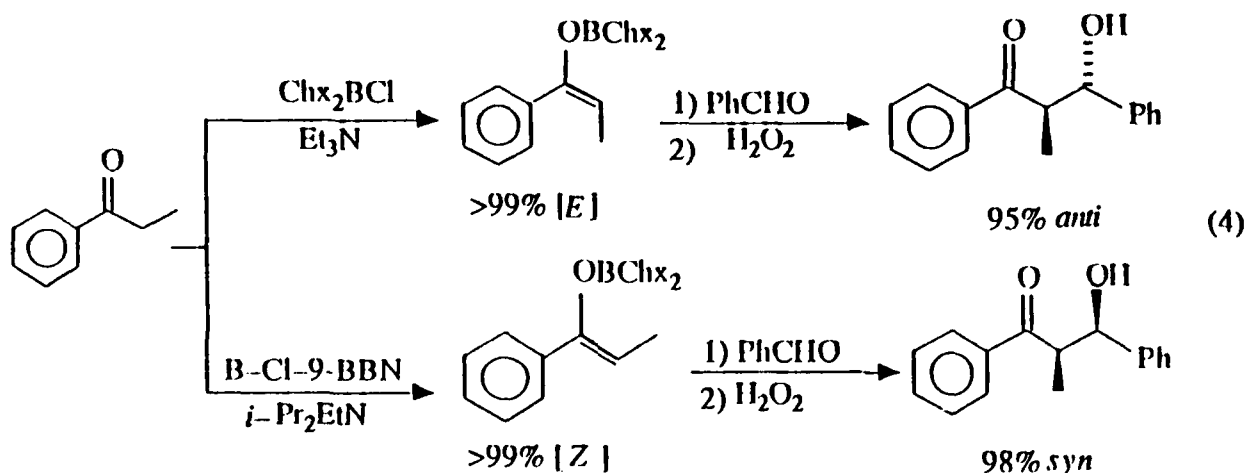
The introduction of dialkylboron triflates, R_2BOTf , by Mukaiyama greatly facilitated the conversion of ketones directly into the corresponding enol borinates for subsequent conversion into the corresponding aldols (eq 3).^{5a}



Fenzl and Köster demonstrated that boron enolate additions are highly stereoselective with the [Z]- and [E]-enolates giving *syn* and *anti* aldols respectively.⁶ Later Masamune and Evans used an R_2BOTf with larger steric requirements, dicyclopentylboron triflate (Cpn_2BOTf) and achieved an appreciable change in the [Z]- to [E]- ratio of the enol borinate produced from cyclohexyl ethyl ketone.^{1,2} Evans subsequently increased the steric requirements of the alkyl group utilizing thexylcyclopentylboron triflate (ThxCpnBOTf), but did not test its effect upon comparable ketones.^{2b} Evans and Masamune also examined the effect varying the steric requirements of the amine, but achieved only minor variations in the [Z]- to [E]-enolate product from diethyl ketone. However, Evans and Masamune succeeded in obtaining highly pure [E]-enol borinates (giving *anti* aldol) from thioesters,^{1,2} but the synthesis of either pure or predominant [E]-enolates from ketones has remained an unrealized goal.

Thus changes in the steric requirements of both the amine and of the alkyl groups on boron have been examined, but no attention has been given to the effect of the leaving group.

We wish to report that the dialkylboron chlorides in the presence of tertiary amines rapidly and quantitatively convert ketones into the corresponding enol borinates. Moreover, the $R_2\text{BCl}$ reagents greatly influence the stereochemistry of the enol borinate formed, making it possible to produce preferentially either [Z]- or [E]-enol borinate, leading to the corresponding *syn* or *anti* aldols (eq 4).



Both B-chloro-9-borabicyclo[3.3.1]nonane, B-Cl-9-BBN, and dicyclohexylchloroborane, Chx_2BCl , are readily synthesized.⁷ They react readily with ketones in the presence of either Et_3N or $i\text{-Pr}_2\text{EtN}$. The reaction is essentially complete in minutes at 0°C , as indicated by rapid formation and precipitation of the amine hydrochloride, along with regiospecific quantitative formation of enol borinate.

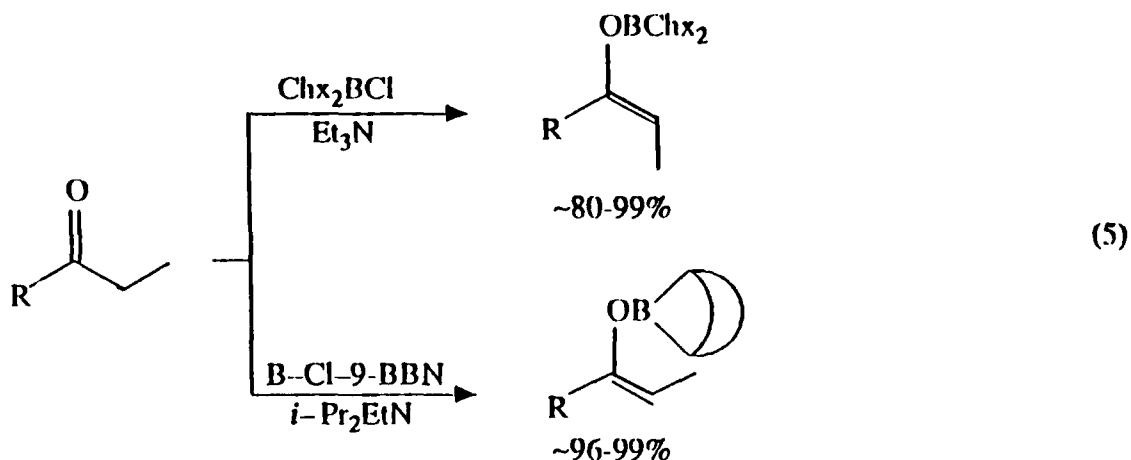
We undertook to make a detailed comparison of the stereochemistry of enolization by triflates and chlorides. The preparation of B-O-Tf-9-BBN was carried out as reported in the literature^{5b} and the new reagent, Chx_2BOTf , was prepared as a crystalline solid, mp 88°C .

We adopted diethyl ketone and propiophenone (both previously studied in detail),^{1,2} as model ketones, B-X-9-BBN and Chx_2BX ($\text{X} \approx \text{OTf}$ and Cl) for the boron reagents, and Et_3N and $i\text{-Pr}_2\text{EtN}$ for the amines, to examine the effect of these factors on the stereochemistry of enolization. The enolization was carried out at 0°C and the aldol reaction was carried out at -78°C .⁸ The data are summarized in Table I. We found it possible to use PMR to determine directly the $[Z]/[E]$ ratio of enol borinate formed from propiophenone and phenyl benzyl ketone. We were pleasantly surprised to find dicyclohexylboron chloride gave exclusively the $[E]$ -enol borinate from propiophenone. Moreover, the *syn/anti* ratio of aldols obtained from these two enol borinates corresponds closely to the $[Z]/[E]$ ratio of the enol borinates formed in the enolization stage as determined by the PMR analysis of the products. In addition, the conversion of a number of cyclic ketones to pure $[E]$ -enol borinates, required by their cyclic structures, provided aldols

which analyzed predominantly or exclusively for the *anti* aldol products: cyclopentanone, ~100%; cyclohexanone, 98%; cycloheptanone, 97%; cyclooctanone, ~100%. Previous workers in this area have also relied on this method to establish the [Z]/[E] ratio of their enol borinates.^{1,2} Consequently, with the additional data now available, it appears safe to conclude that under our conditions, the [Z]/[E] ratio of the enol borinate formed in the enolization can be safely deduced from the *syn* to *anti* ratio of the aldol products for cases where the [Z]/[E] ratio cannot be measured directly.⁹

Our experimental data for the enolization of propiophenone and diethyl ketone by two different R₂B groups, Chx₂B- and 9-BBN, two different leaving groups, Cl and OTf, and two different amines, Et₃N and *i*-Pr₂EtN, are summarized in Table I. It is seen that the stereochemical outcome of the reaction varies not only with the steric requirements of R₂B and the steric requirements of the amine,^{1,2} but also with the nature of the leaving group, Cl or OTf.

The effect of varying the amine and the alkyl groups on boron are considerably more significant in the case of R₂BCl than in the case of R₂BOTf. It is observed that triflates lead to *syn* aldol ([Z]-enol borinate) predominantly, irrespective of the amine used or the steric requirements of the alkyl groups on the boron reagent. On the other hand, Chx₂BCl and Et₃N provide the *anti* aldol ([E]-enol borinate) preferentially. Encouraged by these results, the R₂BCl reagents were applied to several other representative ketones. The results established that the synthesis of either [Z]- or [E]-enol borinate can be achieved with high stereochemical purity (~80-90%) by proper choice of reagent and amine (Table II) (eq 5).



This appears to be the first successful conversion of ketones into enol borinates that are largely or entirely the [*E*]-isomer. This discovery, combined with the fact that the dialkylboron chlorides are readily synthesized and are very stable, makes the methodology here described a valuable procedure for applying the aldol reaction to synthesis. The preferred formation of the [*E*]-enolate over the [*Z*]- is favored by the following: a) use of R_2BCl instead of R_2BOTf ; b) use of Et_3N instead of $i-Pr_2EtN$; c) use of Chx_2B (larger steric requirements) instead of 9-BBN (smaller steric requirements).

The R_2BOTf reagents achieve the conversion of representative ketones into pure [*Z*]-enol borinates (leading to the *syn* aldol). However, the R_2BCl reagents now make possible the conversion of representative ketones into either the essentially pure [*Z*]-enol borinates or the essentially pure or predominant [*E*]-enol borinates, the latter being a transformation not previously available.

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References and Notes

- (1) (a) Von Horn, D. E.; Masamune, S. *Tetrahedron Lett.* **1979**, *24*, 2229. (b) Hirama, M.; Masamune, S. *Ibid*, 2225.

(2) (a) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120. (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *Ibid.* **1981**, *103*, 3099.

(3) (a) Reetz, M. T.; Kunish, F.; Heitmann, P. *Tetrahedron Lett.* **1986**, *27*, 4721. (b) Paterson, I.; Lister, M. A.; McClure, C. K. *Ibid.* 4787.

(4) (a) Hooz, J.; Unke, S. *J. Am. Chem. Soc.* **1968**, *90*, 5936. (b) Hooz, J.; Gunn, D. M. *Ibid.* **1969**, *91*, 6195. (c) Kabalka, G. W.; Brown, H. C.; Suzuki, A.; Honma, S.; Arase, A.; Itoh, M. *Ibid.* **1970**, *92*, 712.

(5) (a) Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559. (b) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174.

(6) Fenzl, W.; Köster, R. *Justus Liebigs Ann. Chem.* **1975**, 1322.

(7) Brown, H. C.; Ravindran, N.; Kulkarni, S. U. *J. Org. Chem.* **1979**, *44*, 2417. (b) Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1974**, *73*, 1.

(8) To a 0.5M ether solution of the R_2BX (5 mmol) and the amine (5 mmol) at 0°C, ketone (5 mmol) was added slowly with stirring. The reaction mixture was then cooled to -78°C, benzaldehyde (5 mmol) was added, and stirring was continued for 2 h. The reaction mixture was warmed to 25°C, the organic phase was separated following addition of water (10 mL) and the solvent was evaporated (25°C, 20 torr). The residue was dissolved in methanol (10 mL) and oxidized with 30% H_2O_2 (3 mL, 25°C, 12 h). It was then extracted with ether, dried over anhydrous magnesium sulfate and the solvent evaporated to give the crude aldol product. The diastereomeric ratio was observed by PMR (470 MHz) analysis of the crude product. The crude aldol product can be further purified by column chromatography over silica gel (~70-80% yield).

(9) It has been reported recently that the stereochemistry of aldol products derived from amide enolates can be influenced by dissolved ammonium salts (ref. 10). In our studies, the ammonium salts separate from the reaction medium essentially quantitatively and have no observable effect on the stereochemistry of the aldol products.

(10) Baker, R.; Castro, J. L.; Swain, C. J. *Tetrahedron Lett.* **1988**, *29*, 2247.

Table I. Enolization of Propiophenone and Diethyl Ketone with R₂BX and Amines^a

reagent R ₂ BX	amine R ₃ N	propiophenone		diethyl ketone
		<i>Z:E</i> ^c	<i>syn:anti</i> ^d	<i>syn:anti</i> ^d
B-Cl-9-BBN	Et ₃ N	52:48 65:35 ^b	60:40	>99:1
	<i>i</i> -Pr ₂ EtN	>99:1	95:5	>99:1
B-OTf-9-BBN	Et ₃ N	>99:1	93:7	>99:1
	<i>i</i> -Pr ₂ EtN	>99:1	95:5	>99:1
Chx ₂ BCl	Et ₃ N	<1:99	5:95	21:79
	<i>i</i> -Pr ₂ EtN	51:49		72:28
Chx ₂ BOTf	Et ₃ N	67:33		80:20
	<i>i</i> -Pr ₂ EtN	>99:1	98:2	93:7

^aEnolization at 0°C, except where otherwise noted. ^bEnolization at 25°C. ^cDirect measurement of *Z:E* ratios of enol borinates by PMR. ^dMeasurement of the diastereoselection achieved in the benzaldehyde aldol product.

Table II. Stereoselective Enolization of Representative Ketones with R₂BCl and Amines

ketone	B-Cl-9-BBN ^a	Chx ₂ BCl ^b	yield of [<i>E</i>]-isomer, %		ref.
	<i>Z</i> : <i>E</i>	<i>Z</i> : <i>E</i>	present ^c	literature ^d	
propiophenone	>99:1	<1:99	>99	3	2b
phenyl benzyl ketone	>99:1	15:85	85		
isopropyl ethyl ketone	65:35 (98):(2) ^e	<1:99	>99	81	2b
cyclohexyl ethyl ketone	60:40 (96):(4) ^e	<1:99	>99	86	1a
diethyl ketone	>99:1	21:79	79	31	2b

^aEnolization carried out at 25°C using *i*-Pr₂EtN. ^bEnolization carried out at 0°C using Et₃N. ^cHighest conversion to [*E*]-enolate achieved with Chx₂BCl. ^dHighest conversion to [*E*]-enolate achieved for triflates. ^e*E*/*Z* ratio obtained after equilibration at 25°C of the corresponding enol borinate. For the first two ketones, direct measurement of the *Z*/*E* ratio of enol borinates by PMR; for the other ketones, indirect measurement of *Z*/*E* ratio based upon analysis of the benzaldehyde aldol product.