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

Herbert C. Brown,* Raj K. Dhar, Raman K. Bakshi, Paul K. Pandiarajan, and Bakthan Singaram

H. C. Brown and R. B. Wetherill Laboratories of Chemistry Purdue University, West Lafayette, Indiana 47907

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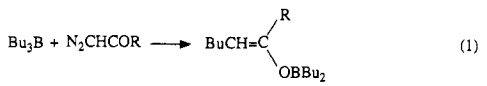
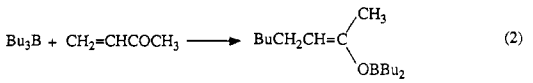
The ready synthesis and ease of handling of dialkylboron chlorides, R_2BCl, compared to triflates, R_2BOTf, give the chlorides a significant advantage as reagents to achieve the conversion of ketones into enol borinates, regiospecifically and quantitatively. This made possible the first study of the 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-BBN vs Chx_2), the amine (Et_3N vs *i*-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.[1-3] A number of published methods have been described for their generation (eq 1 and 2).[4] The introduction of dialkylboron

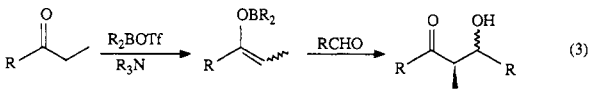


(1)



(2)

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]



(3)

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*:*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.

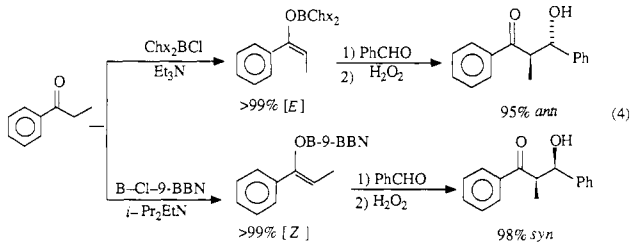
Table I. Enolization of Propiophenone and Diethyl Ketone with R_2BX and Amines[a]

reagent R_2BX	amine R_3N	propiophenone *Z*:*E*[c]	propiophenone syn:anti[d]	diethyl ketone syn:anti[d]
B-Cl-9-BBN	Et_3N	52:48 65:35[b]	60:40	>99:1
	i-Pr_2EtN	>99:1	95:5	>99:1
B-OTf-9-BBN	Et_3N	>99:1	93:7	>99:1
	i-Pr_2EtN	>99:1	95:5	>99:1
Chx_2BCl	Et_3N	>1:99	5:95	21:79
	i-Pr_2EtN	51:49		72:28
Chx_2BOTf	Et_3N	67:33		80:20
	i-Pr_2EtN	>99:1	98:2	93:7

[a] Enolization at 0 °C, except where otherwise noted. [b] Enolization at 25 °C. [c] Direct measurement of *Z*:*E* ratios of enol borinates by PMR. [d] Measurement of the diastereoselection achieved in the benzaldehyde aldol product.

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_2BCl 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).



(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*-Pr_2EtN. 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 (X = OTf and Cl) for the boron reagents, and Et_3N and *i*-Pr_2EtN 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

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(8) To a 0.5 M ether solution of the R_2BX (5 mmol) and the amine (5 mmol) at 0 °C was added ketone (5 mmol) 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 and dried over anhydrous magnesium sulfate, and the solvent was 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).

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Table II. Stereoselective Enolization of Representative Ketones with R_2BCl and Amines

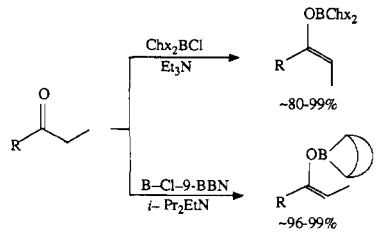
ketone	B-Cl-9-BBN[a] Z:E	Chx_2BCl[b] Z:E	yield of E isomer, % present[c]	literature[d]	ref
propiophenone	>99:1	<1:99	>99	3	2b
phenyl benzyl ketone	>99:1	15:85	85		
isopropyl ethyl ketone	65:35 (98):(2)[e]	<1:99	>99	81	2b
cyclohexyl ethyl ketone	60:40 (96):(4)[e]	<1:99	>99	86	1a
diethyl ketone	>99:1	21:79	79	31	2b

[a] Enolization carried out at 25 °C using *i*-Pr_2EtN. [b] Enolization carried out at 0 °C using Et_3N. [c] Highest conversion to (*E*)-enolate achieved with Chx_2BCl. [d] Highest 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 measurements of *Z*/*E* ratio based upon analysis of the benzaldehyde aldol product.

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 R_2B groups, Chx_2B- and 9-BBN, two different leaving groups, Cl and OTf, and two different amines, Et_3N and *i*-Pr_2EtN, are summarized in Table I. It is seen that the stereochemical outcome of the reaction varies not only with the steric requirements of R_2B 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 R_2BCl than in the case of R_2BOTf. 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, Chx_2BCl and Et_3N provide the anti aldol ((*E*)-enol borinate) preferentially. Encouraged by these results, the R_2BCl 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 (~80–99%) by proper choice of reagent and amine (Table II) (eq 5).



(5)

(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.

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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*)-enolate 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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On the Control of Microenvironment Shape of Functionalized Network Polymers Prepared by Template Polymerization

K. J. Shea* and D. Y. Sasaki

Department of Chemistry, University of California Irvine, California 92717

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The introduction of clusters of functional groups at or near the surface of network polymers may be achieved by template polymerization.[1] The latent functional groups are covalently incorporated into the network by copolymerization of a template assembly with crosslinking monomer. Removal of the template subsequent to polymerization generates a functionalized site.

Molecular recognition has been the principle diagnostic used to evaluate maintenance of the stereochemical integrity of functional groups *after* removal of the template molecule. Crosslinked macromolecules, functionalized by the template synthesis method, have been shown to exhibit an affinity for original template molecules in batch competition rebinding studies[2-4] and when the polymeric materials are used as chromatographic supports.[5,6]

It was earlier shown that rebinding selectivity to template-functionalized polymers could be influenced by changing the initial positioning of the functional groups.[7,8]

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