Enolboration. 4. An Examination of the Effect of the Leaving Group (X) on the Stereoselective Enolboration of Ketones with Various R_2BX/Et_3N. New Reagents for the Selective Generation of either *Z* or *E* Enol Borinates from Representative Ketones

Herbert C. Brown,* Kumaraperumal Ganesan,[1] and Raj K. Dhar[1]

H. C. Brown and R. B. Wetherill Laboratories of Chemistry, Purdue University, West Lafayette, Indiana 47907-3699

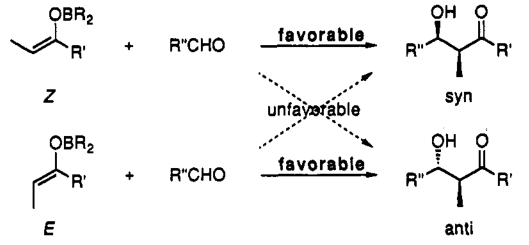
Received June 19, 1992

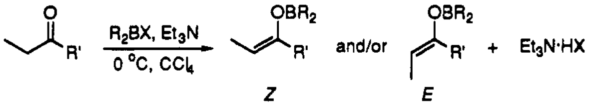
A smooth, rapid, quantitative and stereoselective enolboration of representative ketones to either *Z* or *E* enol borinates is achieved with many new R_2BX/Et_3N reagents. Representative B-X-9-BBN and Chx_2BX reagents with various leaving groups, such as triflate, mesylate, iodide, bromide, and chloride, have been examined with representative ethyl ketones, such as diethyl ketone, ethyl isopropyl ketone, ethyl *tert*-butyl ketone, and propiophenone, as model ketones, in order to attain an understanding of the effect of the leaving group in controlling the enolate geometry. R_2BX reagents with better leaving groups, such as triflate, mesylate, and iodide, favor the formation of *Z* enol borinates, whereas those with relatively poorer leaving groups, such as bromide and chloride, favor the formation of *E* enol borinates. The steric requirements of R in R_2BX and R′ in C_2H_5COR' also contribute substantially to the control of enolate geometry. An unusual behavior of the iodide reagents, favoring the exclusive formation of the *Z* enol borinates, has been observed in the enolboration of EtCO*t*-Bu and EtCOPh. The achievement of an understanding of this important effect of the leaving group in R_2BX, as well as the effects of steric requirements of the substituents on boron and ketone in controlling the enolate geometry, and also the discovery of new R_2BX reagents for the stereoselective generation of either *Z* or *E* enol borinates from representative ethyl ketones, are emphasized in this exploratory study.

Enol borinates are highly versatile intermediates in organic synthesis.[2] Their high reactivity and stereospecificity are very useful for stereocontrolled aldol reactions.[3-7] Evans has systematically studied the aldol stereoselection of enol borinates and established that *Z* enol borinates give syn aldols and *E* enol borinates give anti aldols stereoselectively[4b] (Scheme I). Similar stereoselection has also been realized by Mukaiyama[3b,c] and Masamune.[5] It is highly desirable, therefore, to achieve selective generation of either *Z* or *E* enol borinates at will.

Developing simple and efficient methodologies for the generation of enol borinates has received considerable attention in the past decade. One of the best methodologies, developed by Mukaiyama,[3] involves the reaction of ketones with R_2BX reagents containing a powerful leaving group (X = triflate, OTf) in the presence of a suitable tertiary amine, such as triethylamine (eq 1).

Scheme I





(1)

Based on this methodology, many R_2BOTf reagents have been designed and used for the enolboration of ketones in the presence of various tertiary amines of different steric requirements.[3,4] Both triethylamine and *N*,*N*-diisopropylethylamine are quite efficient for such enolboration.[3] However, these R_2BOTf reagents could not achieve the synthesis of *E* enol borinates selectively. They convert various ketones either to *Z* enol borinates exclusively or to a mixture of *Z* and *E* enol borinates. The development of new reagents and methodologies to achieve selective generation of *E* enol borinates has been an unanswered challenge in this field.

Our preliminary study indicated that the effect of the leaving group on boron plays a significant role in enolboration. For example, R_2BOTf reagents favor the formation of *Z* enol borinates, whereas the corresponding R_2BCl reagents favor the formation of *E* enol borinates.[6a]

---

[1] Postdoctoral research associates on a grant from the United States Office of Naval Research.

[2] (a) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 1. (b) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 2. (c) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.

[3] (a) Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559. (b) Inoue, T.; Uchimaru, T.; Mukaiyama, T. *Chem. Lett.* **1977**, 153. (c) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174.

[4] (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. *J. Am. Chem. Soc.* **1981**, *103*, 3099.

[5] (a) Masamune, S.; Mori, S.; Van Horn, D.; Brooks, D. W. *Tetrahedron Lett.* **1979**, *19*, 1665. (b) Hirama, M.; Masamune, S. *Tetrahedron Lett.* **1979**, *24*, 2225. (c) Van Horn, D. E.; Masamune, S. *Tetrahedron Lett.* **1979**, *24*, 2229. (d) Hirama, M.; Garvey, D. S.; Lu, L. D. L.; Masamune, S. *Tetrahedron Lett.* **1979**, *41*, 3937.

[6] (a) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441. (b) d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979.

[7] (a) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 499. (b) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 2716. (c) Brown, H. C.; Ganesan, K.; Dhar, R. K. *J. Org. Chem.* **1992**, *57*, 3767.

0022-3263/93/1958-0147$04.00/0

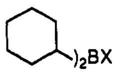
Dialkylboron triflates could not enolize aldehydes, but Chx_2BCl achieves such enolboration.[7a] The enolization of both esters and tertiary amides could not be achieved with either R_2BOTf or R_2BCl reagents. But Chx_2BI proved highly efficient for the enolization of such classes of less reactive carbonyl compounds.[8] The high reactivity of this reagent must be attributed to the influence of the iodide leaving group.

Evans and his co-workers have examined the effects of the steric requirements of alkyl groups on boron, the ketone, and the amine on the enolate and aldol stereoselections in the enolboration of various ethyl alkyl ketones using representative R_2BOTf reagents and amines.[4b] We have also systematically investigated the effect of the steric requirements of R in various R_2BCl reagents in controlling the enolate geometry.[7c] Even though many organoboron reagents with different leaving groups, such as triflate,[3-5] chloride,[9] and bromide,[10] have been used for enolboration, no systematic study has been attempted to achieve an understanding of this influence of the leaving group on the enolate geometry. Therefore, we decided to undertake such a systematic study by examining various R_2BX reagents with different leaving groups, such as OTf, OMs, I, Br, and Cl, of variable steric and electronic requirements, in the hope of achieving an understanding of the importance of this leaving group effect in controlling the enolate geometry, as well as to establish new organoboron reagents that are especially favorable for such stereoselective enolborations.

Results and Discussion

Careful attention was paid to the selection and examination of appropriate leaving groups. Since it has been realized that the R_2BX reagents with the very powerful leaving group, triflate, favor the formation of *Z* enol borinates, while those with the relatively poorer leaving group, chloride, favor the formation of *E* enol borinates,[6a] we decided to select representative leaving groups of intermediate nature, such as mesylate, iodide, and bromide, in addition to the two extremes, triflate and chloride, for the proposed stereochemical study. The availability, the ease of preparation, and the stability of the corresponding R_2BX reagents were also considered in the choice of the leaving groups to be included. The effect of the leaving group in the present study is expected to be in the order: OTf > OMs > I > Br > Cl.

Based on these essential requirements, the following R_2BX reagents were selected for the present study: (1) *B*-triflato-9-borabicyclo[3.3.1]nonane (B-OTf-9-BBN); (2) *B*-mesylato-9-borabicyclo[3.3.1]nonane (B-OMs-9-BBN); (3) *B*-iodo-9-borabicyclo[3.3.1]nonane (B-I-9-BBN); (4) *B*-bromo-9-borabicyclo[3.3.1]nonane (B-Br-9-BBN); (5) *B*-chloro-9-borabicyclo[3.3.1]nonane (B-Cl-9-BBN); (6) dicyclohexyltriflatoborane (Chx_2BOTf); (7) dicyclohexylmesylatoborane (Chx_2BOMs); (8) dicyclohexyliodoborane (Chx_2BI); (9) dicyclohexylbromoborane (Chx_2BBr); and (10) dicyclohexylchloroborane (Chx_2BCl).



	X		X
1	OTf	6	OTf
2	OMs	7	OMs
3	I	8	I
4	Br	9	Br
5	Cl	10	Cl

Representative ethyl ketones, such as diethyl ketone, ethyl isopropyl ketone, ethyl *tert*-butyl ketone, and propiophenone, were selected as model ketones to permit an examination of the combined effects of the steric requirements of R′ in the ketone, EtCOR′, and the leaving group (X) in the R_2BX reagents (**1–10**) on the enolate geometry.

Preparation of Various R_2BX Reagents. The various R_2BX reagents (**1–10**) selected for the present study are readily prepared from the corresponding dialkylboranes, R_2BH, using well established methods. The commercially available 9-BBN (Aldrich) was used for the preparation of the various B-X-9-BBN reagents (**1–5**), while Chx_2BH, readily synthesized[7a] by hydroboration of cyclohexene (2 equiv) with borane–methyl sulfide (BMS, 1 equiv), was used for the preparation of the various Chx_2BX reagents (**6–10**). Direct hydroboration of the suitable alkenes (2 equiv) with $XH_2B{\cdot}SMe_2$ (X = Br or Cl, 1 equiv) also yields the corresponding R_2BX.[11] This method is especially useful when the hydroboration with BMS fails to give a clean dialkylborane intermediate. Detailed procedures for the syntheses of the various R_2BX reagents (**1–10**) are given in the Experimental Section.

Characterization of R_2BX Reagents. In the present study, all the various R_2BX reagents (**1–10**) have been prepared using well-established methods. The R_2BH intermediates have been purified, well characterized, and then used for the syntheses of various R_2BX reagents. All the reactions (except for the direct hydroboration of alkenes with $XH_2B{\cdot}SMe_2$, where X = Br or Cl) liberate equimolar quantities of hydrogen gas, and therefore, the reactions could be easily followed by measuring H_2 with a gasimeter. All these reactions are rapid and quantitative. The various R_2BX reagents prepared in the present study were purified either by recrystallization or by distillation, and the purity was confirmed by ^{11}B NMR. The purity of these reagents was further confirmed by treating them with methanol to produce the corresponding methyl borinates, R_2BOMe (^{11}B NMR, broad, δ 50–56 ppm).

Enolboration. The enolboration experiments were carried out in carbon tetrachloride in cases where direct analysis of the reaction mixture by ^1H NMR was desirable. The ^1H NMR spectrum (olefinic proton) was examined with benzene as an internal standard to determine the extent of enolboration and the ^{11}B NMR spectrum (borinate region, usually broad, around δ 50–56 ppm) was also used to confirm the formation of enol borinates. This is a well-established technique which we have been using for the quantification of the formation of the enol borinates.[6a,7] Enolization could also be carried out successfully in other organic solvents, such as diethyl ether (except for R_2BI), CH_2Cl_2, $CHCl_3$, and hexane. Wherever

---

(8) Brown, H. C.; Ganesan, K. *Tetrahedron Lett.* **1992**, *33*, 3421.

(9) (a) Gennari, C.; Colombo, L.; Poli, G. *Tetrahedron Lett.* **1984**, *25*, 2279. (b) Gennari, C.; Gardani, S.; Colombo, L.; Scolastico, C. *Tetrahedron Lett.* **1984**, *25*, 2283. (c) Hamana, H.; Saskura, K.; Sugasawa, T. *Chem. Lett.* **1984**, 1729. (d) Chow, H.-F.; Seeback, D. *Helv. Chim. Acta* **1986**, *69*, 604. (e) Reetz, M. T.; Kunisch, F.; Heitmann, P. *Tetrahedron Lett.* **1986**, *27*, 4721.

(10) (a) Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976. (b) Corey, E. J.; Choi, S. *Tetrahedron Lett.* **1991**, *32*, 2857.

(11) (a) Brown, H. C.; Kulkarni, S. U. *J. Organomet. Chem.* **1979**, *168*, 281. (b) Brown, H. C.; Ravindran, N.; Kulkarni, S. U. *J. Org. Chem.* **1979**, *44*, 2417. (c) Brown, H. C.; Ravindran, N. *J. Am. Chem. Soc.* **1976**, *98*, 1785.

Table I. Effect of the Leaving Group on Enolate Geometry in the Enolboration of Ethyl Isopropyl Ketone with Various R_2BX/Et_3N[a,b]

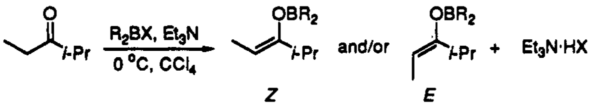
	B-X-9-BBN[c] (%)			Chx_2BX[c] (%)		
X	*Z*	*E*	yield[d,e]	*Z*	*E*	yield[d,e]
OTf	88	12	96	25	75	95
OMs	82	18	94	23	77	93
I	73	27	97	32	68	98
Br	57	43	96	11	89	95
Cl	46	54	95	<3	>97	97

[a] Enolizations and the subsequent aldolizations with PhCHO were carried out in hexane at 0 and at −78 °C, respectively, unless otherwise stated. [b] In cases where the spectrum shows only one major isomer, we have indicated the minor isomer to be <3% since such small peaks may be lost in the background. [c] *Z*/*E* ratio was determined on the basis of the syn/anti ratio of their corresponding benzaldehyde aldol products [benzylic proton, syn at δ 4.97 ppm (d, *J* = 6.0 Hz) and anti at δ 4.74 ppm (d, *J* = 7.7 Hz)]. [d] Determined by ^1H NMR. [e] The yields were also confirmed by collecting and weighing the precipitated $Et_3N{\cdot}HX$ (where X = I, Br, and Cl).

aldolization was to be performed on the enol borinate, the corresponding enolization was carried out in hexane. In representative cases, the yields were also determined by isolating and weighing the byproduct, $Et_3N{\cdot}HX$ (X = I, Br, and Cl). In these cases, the yields were quantitative and comparable with that determined directly by ^1H NMR.

Effect of the Leaving Group (X) in R_2BX on Enolate Geometry. The present study has been primarily designed to understand the important effect of the leaving group on the enolate geometry as well as to achieve competitive control of the enolate geometry from other effects, such as the steric requirements of R and R′, by carefully selecting suitable R_2BX and C_2H_5COR' reactants. In order that these objectives of the present study may be understood clearly, every case is discussed individually in the following sections.

Stereoselective Enolboration of Ethyl Isopropyl Ketone. In the present study also, this moderately hindered EtCO*i*-Pr serves as the best model ketone to understand the effect of the leaving group in controlling the enolate geometry. It yields a mixture of *Z* and *E* enol borinates with the various R_2BX reagents, and therefore, the effects of the different leaving groups are clearly revealed. The regiochemistry of the enolboration is always on the less hindered ethyl side irrespective of the R_2BX reagents used. The results of the enolboration of EtCO*i*-Pr with the various R_2BX reagents (1–10) in the presence of Et_3N (eq 2) are summarized in Table I.



(2)

From the results in Table I, it is evident that the nature of the leaving group in R_2BX exerts a major influence in controlling the enolate geometry. A comparison of the results obtained in the enolboration of EtCO*i*-Pr with the various B-X-9-BBN reagents (1–5) reveals that the reagent 1, with a powerful leaving group (OTf), favors the formation of the *Z* enol borinate, while the reagent 5, with a weaker leaving group (Cl), favors the formation of the *E* enol borinate. As the leaving power of the group X decreases from OTf to Cl, the formation of the *E* enol borinate increases and that of the *Z* enol borinate decreases. A similar conclusion as to the effect of the leaving group in controlling the enolate geometry is also drawn from the results obtained in the enolboration of EtCO*i*-Pr with the various Chx_2BX reagents. It is now possible to achieve the synthesis of either *Z* or *E* enol borinate either predominantly or exclusively from EtCO*i*-Pr merely by a careful selection of the boron reagent.

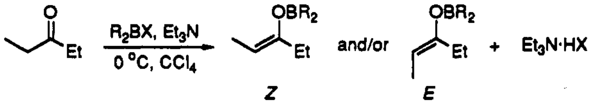
Table II. Effect of the Leaving Group on Enolate Geometry in the Enolboration of Diethyl Ketone with Various R_2BX/Et_3N[a,b]

	B-X-9-BBN[c] (%)			Chx_2BX[c] (%)		
X	*Z*	*E*	yield[d,e]	*Z*	*E*	yield[d,e]
OTf	>97	<3	97	80	20	96
OMs	>97	<3	95	80	20	93
I	>97	<3	97	56	44	98
Br	>97	<3	97	30	70	96
Cl	>97	<3	95	21	79	97

[a] Enolizations and the subsequent aldolizations with PhCHO were carried out in hexane at 0 and at −78 °C, respectively, unless otherwise stated. [b] Refer to footnote *b* of Table I. [c] *Z*/*E* ratio was determined on the basis of the syn/anti ratio of their corresponding benzaldehyde aldol products [benzylic proton, syn at δ 5.02 ppm (d, *J* = 4.4 Hz) and anti at δ 4.74 ppm (d, *J* = 8.4 Hz)]. [d] Determined by ^1H NMR. [e] Refer to footnote *e* of Table I.

A comparison of the results obtained with the various B-X-9-BBN reagents (1–5) with those obtained for the corresponding Chx_2BX reagents (6–10) suggests that the steric requirements of R in R_2BX also contribute substantially to the enolate geometry of the product. We have already established the effect of steric requirements of R in the various R_2BCl in controlling the enolate geometry.[7c] From this study, it can be safely concluded that the R_2BX reagents with lower steric requirements of R and stronger leaving effects of X favor the formation of *Z* enolates, while those with relatively bulkier R groups and poorer leaving groups favor the formation of *E* enolates.

Stereoselective Enolboration of Diethyl Ketone. Essentially all the known R_2BOTf reagents give either selective *Z* enol borinate or a mixture of *Z* and *E* enol borinates from diethyl ketone.[3,4] The selective generation of the kinetic *E* enolate has been a great challenge in this field. In our efforts to understand the leaving group effect on the enolate geometry using diethyl ketone, we were pleasantly surprized to note that all the B-X-9-BBN reagents studied achieve formation of the *Z* enol borinate essentially exclusively. The results of the enolboration of EtCOEt (eq 3) with the various R_2BX reagents (1–10) are given in Table II.



(3)

From the results in Table II, it is clear that in the case of B-X-9-BBN reagents, the smaller steric requirements of the 9-BBN moiety on boron control the stereochemistry of the enolboration process more than the corresponding leaving group. Therefore, irrespective of the nature of the leaving groups, all the B-X-9-BBN reagents studied give *Z* enol borinate selectively from diethyl ketone.

However, the effect of the leaving group is much larger in the enolization of diethyl ketone with the relatively bulkier Chx_2BX reagents. The stronger Lewis acid, Chx_2BOTf, with a better leaving group, favors the formation of *Z* enolate, while the relatively weaker Lewis acid, Chx_2BCl, with a poorer leaving group, favors the formation of *E* enolate. It is interesting to note that the reagent couples

Table III. Effect of the Leaving Group on Enolate Geometry in the Enolboration of Ethyl *tert*-Butyl Ketone with Various $R_2BX/Et_3N^{a,b}$

	B-X-9-BBN[c] (%)			Chx_2BX^c (%)		
X	*Z*	*E*	yield[d,e]	*Z*	*E*	yield[d,e]
OTf	10	90	90	<3	>97	85
OMs	<3	>97	87[f]	<3	>97	66[f]
I	>97	<3	95	>97	<3	96
Br	<3	>97	94	10	90	82[g]
Cl[f]	<3	>97	94	<3	>97	60[h]

[a] Enolizations and the subsequent aldolizations with PhCHO were carried out in hexane at 0 and at −78 °C, respectively, unless otherwise stated. [b] Refer to footnote *b* of Table I. [c] *Z*/*E* ratio was determined on the basis of the syn/anti ratio of their corresponding benzaldehyde aldol products [benzylic proton, syn at δ 4.88 ppm (d, J = 4.4 Hz) and anti at δ 4.65 ppm (d, J = 8.0 Hz)]. [d] Determined by ^1H NMR. [e] Refer to footnote *e* of Table I. [f] Enolization at 25 °C for 48 h. [g] Enolization at 25 °C for 24 h. [h] Enolization at 25 °C for 48 h.

Table IV. Effect of the Leaving Group on Enolate Geometry in the Enolboration of Propiophenone with Various $R_2BX/Et_3N^{a,b}$

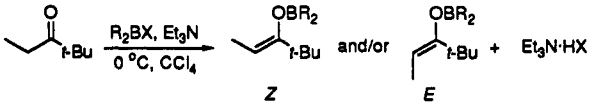
	B-X-9-BBN[c] (%)			Chx_2BX^c (%)		
X	*Z*	*E*	yield[d,e]	*Z*	*E*	yield[d,e]
OTf	>97	<3	97	67	33	96
OMs	>97	<3	96	62	38	95
I	>97	<3	98	>97	<3	97
Br	83	17	96	5	95	97
Cl	52	48	97	<3	>97	97

[a] Enolizations and the subsequent aldolizations with PhCHO were carried out in hexane at 0 and at −78 °C, respectively, unless otherwise stated. [b] Refer to footnote *b* of Table I. [c] *Z*/*E* ratio was determined on the basis of the syn/anti ratio of their corresponding benzaldehyde aldol products [benzylic proton, syn at δ 5.23 ppm (d, J = 3.0 Hz) and anti at δ 4.98 ppm (d, J = 8.1 Hz)]. [d] Determined by ^1H NMR. [e] Refer to footnote *e* of Table I.

triflate and mesylate, 1 and 2, and 6 and 7, give essentially individual identical mixture of *Z* and *E* enol borinates from this ketone.

Even though half of the reagents studied give the *Z* enol borinate selectively from diethyl ketone, neither of them gives the corresponding *E* enol borinate exclusively. Only Chx_2BCl achieves a maximum selectivity of 79% *E* enolate from this ketone. The corresponding bromide derivative, Chx_2BBr, also achieves a good selectivity as compared to all the other reagents examined. Bco_2BCl, with greater steric requirements, is the only organoboron reagent available for the predominant generation of *E* enolate from this ketone.[7c]

Stereoselective Enolboration of Ethyl *tert*-Butyl Ketone. The effect of the larger steric requirements of the carbonyl substituents (R′ in EtCOR′, EtCOOR′, and EtCOSR′) in controlling the enolate geometry has been utilized to achieve the formation of *E* enol borinates selectively in enolboration.[4,5,7,10] The essentially exclusive formation of *E* enolate is achieved where R′ = *t*-Bu. For the present study also, we selected EtCO*t*-Bu as one of the model ketones to examine the combined effects of the leaving group on boron and the bulky substituent in the ketone in controlling the geometry of the enolate produced. The results of the enolboration of EtCO*t*-Bu with the various R_2BX reagents in the presence of Et_3N (eq 4) are summarized in Table III.

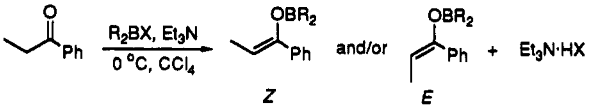


(4)

From the results in Table III, it is well understood that all the R_2BX reagents studied, with the exception of R_2BI, favor the formation of *E* enol borinate, either exclusively or predominantly, from ethyl *tert*-butyl ketone. Apparently, the large steric requirements of the bulkier *tert*-butyl group contribute more effectively to this *E* selectivity. *It is a major surprize to note that the R_2BI reagents* (**3** and **8**) *give the isomeric Z enolate essentially exclusively.* They are also more reactive than the other R_2BX reagents. The high reactivity of Chx_2BI has been exploited for the enolboration of the relatively less reactive carbonyl compounds, such as esters and tertiary amides.[8]

The enolization of this sterically more hindered EtCO*t*-Bu is also essentially instantaneous and quantitative at 0 °C with most of the reagents studied except for Chx_2BX (where X = OMs, Br, and Cl). However, faster reactions with better yields have been achieved with these reagents by carrying out the enolizations at 25 °C.

Stereoselective Enolboration of Propiophenone. After studying the important leaving group effect on the enolate geometry with the various aliphatic ethyl ketones, we decided to examine this effect in the enolboration of propiophenone, a widely studied aromatic ethyl ketone. R_2BOTf reagents have been shown to give *Z* enol borinate essentially exclusively from this ketone.[4b] The selective generation of the *E* enol borinate from propiophenone could not be achieved until we reported the successful generation of the *E* enol borinate with Chx_2BCl/Et_3N.[6a] The results of the enolboration of propiophenone (eq 5) with the various R_2BX reagents in the present study are presented in Table IV.



(5)

The results obtained in the case of propiophenone also corroborate our earlier conclusion on the influence of the nature of leaving group in controlling the enolate geometry. In the case of B-X-9-BBN, the reagents with better leaving groups (X = OTf, OMs, and I) give essentially exclusive *Z* enol borinate, while those with relatively poorer leaving groups (X = Br and Cl) give a mixture of *Z* and *E* enol borinates. Similar results have also been obtained in the enolboration of propiophenone with the various Chx_2BX reagents. Chx_2BI behaves unusually, in this case also, favoring the formation of *Z* enolate. A careful comparison of the results obtained in the enolboration of EtCOEt and EtCOPh with the various Chx_2BX reagents suggests that the phenyl group plays a significant role in favoring the formation of *E* enol borinate as observed earlier with the various R_2BCl reagents.[7c]

Unusual Behavior of the R_2BI Reagents. In the case of EtCO*t*-Bu, as mentioned earlier, the larger steric requirements of the bulky ketone substituent, *t*-Bu, overcome the combined effects of R and X in R_2BX, resulting in the formation of *E* enol borinates with all the reagents except in the case of the R_2BI reagents. Unexpectedly, these R_2BI reagents (**3** and **8**) give the isomeric *Z* enol borinate essentially exclusively. Similar results have also been obtained in the enolboration of propiophenone. A comparison of the enolboration of EtCO*t*-Bu and EtCOPh using Chx_2BCl and Chx_2BI is worth pointing out at this place. These are the outstanding examples in which the effect of the leaving group is so important. A change in the leaving group has a tremendous influence on the enolate geometry. The reagent with a poor leaving group, chloride, favors the formation of *E* enolates, while that with a considerably better leaving group, iodide, favors the formation of *Z* enolates.

In the present study, the *Z*/*E* ratio of the enol borinates was determined on the basis of the syn/anti ratio of the corresponding benzaldehyde aldol products (refer to the following section on Enolate Geometry). However, in the case of aromatic ketones, it is possible to determine the *Z*/*E* ratio directly by ^{1}H NMR at the enol borinate stage itself. Therefore, it was decided to test with propiophenone, an aromatic ethyl ketone, whether the effect of the leaving group occurs at the enolization stage or at the subsequent aldolization stage. A careful study was carried out with propiophenone using Chx_2BCl and Chx_2BI. The enolboration with Chx_2BCl/Et_3N gives 8% *Z* and 92% *E* enolates (corresponding closely to the 12% syn and 88% anti aldols achieved in the reaction with benzaldehyde in CCl_4 at 0 °C), while the enolboration with Chx_2BI/Et_3N gives 92% *Z* and 8% *E* enolates (providing 91% syn and 9% anti aldols in aldolization with benzaldehyde under the identical experimental conditions). This clearly demonstrates that the leaving group effect is controlling in the enolization process itself.

The enolboration with these R_2BI reagents is very rapid, even in the case of the highly hindered EtCO*t*-Bu. Apparently, the higher reactivity of the R_2BI reagents may be responsible for their unusual control of stereochemistry favoring the *Z* enolates. Further research is in progress to understand the reversal of the enolate geometry with these R_2BI reagents and also to explore this significant selectivity for various reactions.

Enolate Geometry. The olefinic protons of both *Z* and *E* enol borinates exhibit essentially identical chemical shifts, and therefore, the *Z*/*E* ratio cannot be determined directly by ^{1}H NMR. As mentioned earlier, the reactions of enol borinates with benzaldehyde are highly stereospecific (Scheme I), providing an indirect method to determine this ratio from the syn/anti ratio of the corresponding aldol products obtained from the reaction of enol borinates with benzaldehyde. This is a well-established technique which we have been using to determine the *Z*/*E* ratio of the enol borinates when direct determination by ^{1}H NMR is very difficult.[6a,7]

Conclusions

This is the first systematic and detailed study of the effect of the leaving group (X) in R_2BX in controlling the enolate geometry. The present stereochemical study with representative R_2BX reagents containing a variety leaving groups, such as triflate, mesylate, iodide, bromide, and chloride, using representative model ketones, provides significant conclusions about the factors that contribute to the enolate geometry. The moderately hindered ethyl isopropyl ketone serves as a favorable model ketone, yielding a mixture of *Z* and *E* enol borinates, to reflect the effect of the leaving group on the enolate geometry. The R_2BX reagents with better leaving groups, in general, favor the formation of *Z* enol borinates, whereas those with relatively poorer leaving groups favor the formation of *E* enol borinates. A comparison of the results obtained with the selected B-X-9-BBN and Chx_2BX reagents reveals that the smaller steric requirements of the alkyl group(s) in the B-X-9-BBN reagents (**1–5**) contribute substantially to *Z* selectivity, whereas the relatively bulkier steric requirements of the alkyl groups in the Chx_2BX reagents (**6–10**) contribute to *E* selectivity. The steric requirements of the ketone substituent R′ in EtCOR′ also play a significant role in the control of enolate geometry. The smaller R′ groups favor the formation of *Z* enolates, while the bulkier R′ groups favor the formation of *E* enolates. The R_2BI reagents are highly reactive and they behave in an unusual manner, yielding the *Z* enolates exclusively from EtCO*t*-Bu and EtCOPh. Their high reactivities may contribute substantially to the observed reversal of stereochemistry. Further research is in progress to understand what is going on with these reagents. A major effect of the phenyl group in contributing strongly to the formation of the *E* enol borinate is also observed in the enolboration of propiophenone. This study has established several new R_2BX reagents to achieve the preferential formation of either *Z* or *E* enol borinates from the model ketones studied. The discovery of the new reagents, B-I-9-BBN and Chx_2BI for the selective generation of *Z* enol borinates and Chx_2BBr for the generation of *E* enol borinates, either exclusively or predominantly, is an especially valuable result from this study. This systematic study also provides valuable informations that can be very helpful in designing new reagents for stereoselective enolboration.

Experimental Section

Materials. All glassware was thoroughly dried in an air oven, cooled, and assembled under nitrogen for the experiments. Degassed, anhyd solvents, CH_2Cl_2, CCl_4, and hexane, were used. THF was freshly distilled from sodium benzophenone ketyl. Et_3N was distilled over CaH_2. Methanesulfonic acid, trifluoromethanesulfonic acid, cyclohexene, and ketones, except for ethyl *tert*-butyl ketone, were commercial products of the highest purity available. 9-BBN, borane–methyl sulfide (BMS), monobromoborane–methyl sulfide (MBBS) and monochloroborane–methyl sulfide (MCBS) reagents were purchased from Aldrich and used as such for the reaction. The special experimental techniques used in handling air- and moisture-sensitive compounds have been described elsewhere.[12] All of the following experiments were conducted under a nitrogen atmosphere.

Synthesis of R_2BOTf reagents. Controlled addition of trifluoromethanesulfonic acid (1 equiv) to R_2BH (1 equiv) in hexane or in CH_2Cl_2 at 0 °C gives the corresponding R_2BOTf.[13] This well-established procedure has been used in the present study for the preparation of both B-OTf-9-BBN and Chx_2BOTf. The synthesis of Chx_2BOTf (**6**) is described here as a general procedure. A 250-mL round-bottom flask capped with a rubber septum, a magnetic stirring bar, and a connecting tube attached to a mercury bubbler was kept at 0 °C and charged with hexane (100 mL) and Chx_2BH (26.7 g, 150.0 mmol). Trifluoromethanesulfonic acid (13.3 mL, 150.0 mmol) was added dropwise using a syringe with constant stirring. Hydrogen is rapidly evolved and should be safely vented. The stirring was continued at 0 °C for 2–3 h. All the suspended solid Chx_2BH dissolved, and the homogeneous reaction mixture was left at 0 °C for 1–2 h without stirring. Two layers were obtained and the top layer was transferred into a dry 250-mL round-bottom flask leaving the small yellow layer (about 2 mL) behind. Solid Chx_2BOTf was obtained by removing the solvent using a water aspirator (15–20 mm). It was then recrystallized in hexane. ^{11}B NMR (hexane) δ 59.6 ppm, mp 88 °C, yield 80%. Stock solutions (1.00 M) in CCl_4 and in hexane were prepared and kept at 0 °C for the use of enolboration.

---

(12) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*; Wiley-Interscience: New York, 1975.

(13) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663.

Reagent 1, B-OTf-9-BBN [^{11}B NMR (hexane) δ 67.8 ppm, bp 67–68 °C (0.3 mm), yield 85%] was prepared by treating the commercially available 9-BBN (Aldrich) with CF_3SO_3H.

Synthesis of R_2BOMs reagents. Based on the above method used for the preparation of R_2BOTf reagents,[13] a controlled addition of methanesulfonic acid (1 equiv) to R_2BH (1 equiv) is expected to give the corresponding R_2BOMs. This method has been optimized in the present study and used for the syntheses of both B-OMs-9-BBN and Chx_2BOMs. The synthesis of Chx_2BOMs (7) is described here as a general procedure. A 250-mL round-bottom flask capped with a rubber septum, a magnetic stirring bar, and a connecting tube attached to a mercury bubbler was kept at 0 °C and charged with $CHCl_3$ (100 mL) and Chx_2BH (26.7 g, 150.0 mmol). Methanesulfonic acid (9.7 mL, 150.0 mmol) was added dropwise using a syringe with constant stirring. Hydrogen is rapidly evolved and should be safety vented. The stirring was continued at 0 °C for 2 h and at 25 °C for 2 h. The reaction mixture was concentrated using a water aspirator (15–20 mm) and then kept at 0 °C for crystallization. The supernatant liquid was removed by a double-ended needle by keeping the flask in an ice bath (the solid Chx_2BOMs melts if allowed to warm to room temperature). It was again recrystallized using $CHCl_3$. The colorless, solid Chx_2BOMs was dried under vacuum by keeping the flask in an ice bath. ^{11}B NMR (hexane) δ 58.5 ppm, mp 22–23 °C, yield 80%. Stock solutions (1.00 M) in CCl_4 and in hexane were prepared and kept at 0 °C for the use of enolboration.

Reagent 2, B-OMs-9-BBN [^{11}B NMR (hexane) δ 58.2 ppm, mp 106–107 °C, yield 82%] was prepared from 9-BBN and CH_3SO_3H.

Synthesis of R_2BI reagents. The synthesis of Chx_2BI (8) is described as a general procedure. A 250-mL round-bottom flask with a side arm capped with rubber septums, a magnetic stirring bar, and a connecting tube attached to a mercury bubbler was kept at 0 °C and charged with hexane (100 mL) and Chx_2BH (26.7 g, 150.0 mmol). Powdered iodine (19.1 g, 75.2 mmol) was added through the side arm in small installments with constant stirring. Hydrogen is evolved and should be safely vented. After adding all the iodine, the stirring was continued at 0 °C for 2 h and at 25 °C for 1 h. A pale pink color (due to the small excess of I_2) persists which shows the completion of the reaction. Then the solvent was removed using a water aspirator (15–20 mm). Distillation of the concentrated mixture under vacuum yields pure, colorless Chx_2BI. ^{11}B NMR (hexane) δ 84.0 ppm, bp 198–200 °C (1.25 mm), yield 80%.

Reagent 3, B-I-9-BBN [^{11}B NMR (hexane) δ 84.8 ppm, bp 85 °C (0.3 mm), yield 75%] was obtained by treating 9-BBN with iodine.

Synthesis of R_2BBr reagents. The reagent, Chx_2BBr (9), is prepared by the direct hydroboration of cyclohexene with monobromoborane–methyl sulfide (MBBS). A 250-mL round-bottom flask capped with a rubber septum, a magnetic stirring bar, and a connecting tube attached to a mercury bubbler was kept at 0 °C and charged with CH_2Cl_2 (100 mL) and cyclohexene (30.0 mL, 296.0 mmol). Then MBBS (15.0 mL, 9.0 M, 135.0 mmol) was added dropwise using a syringe with constant stirring. The stirring was continued at 0 °C for 3 h. The homogeneous mixture was left overnight at 25 °C without stirring. Solid $Chx_2BBr{\cdot}SMe_2$ (^{11}B NMR, δ 37.6 ppm in CH_2Cl_2) was obtained by removing the solvent using a water aspirator (15–20 mm). It was then recrystallized in hexane (mp 70 °C). Pure, colorless Chx_2BBr was obtained by vacuum distillation of the crystalline solid (which melts during distillation). ^{11}B NMR (hexane) δ 81.3 ppm, bp 120 °C (1.5 mm), yield 86%.

Reagent 4, B-Br-9-BBN [^{11}B NMR (hexane) δ 83.3 ppm, bp 58–60 °C (1.0 mm), yield 85%] was prepared by treating 9-BBN and HBr gas using the reported procedure.[12a]

Synthesis of R_2BCl reagents. The detailed procedure for the synthesis of both Chx_2BCl (10) [^{11}B NMR (hexane) δ 76.0 ppm, bp 95–96 °C (0.35 mm), yield 75%] and B-Cl-9-BBN (5) [^{11}B NMR (hexane) δ 79.0 ppm, bp 65 °C (0.3 mm), yield 75%] from the corresponding dialkylborane and anhyd HCl in ether has been described in our earlier paper.[7a]

Synthesis of Ketones. Ethyl *tert*-butyl ketone was prepared directly by the chromic acid two phase (ether–water) oxidation[14] of the corresponding alcohol (commercially available). Distillation provided >99% GC pure ketone (bp 121 °C) and the ^1H NMR spectrum confirmed the structure.

Spectra. The ^1H NMR spectra were recorded on both T-60 and 300-MHz instruments. The ^{11}B NMR spectra were recorded on FT-80A and 300-MHz instruments. The chemical shift values are in δ (ppm) relative to $BF_3{\cdot}OEt_2$. The melting points were determined using a sealed tube (under N_2).

General Procedure for the Enolboration of Ketones with R_2BX/Et_3N (Where X = OTf and OMs). A simple and general procedure for the enolization of ketones with the various R_2BX reagents (X = OTf and OMs) is described as follows. To a stirred solution of R_2BX (5.15 mL, 1.00 M in CCl_4, 5.15 mmol) and Et_3N (0.72 mL, 5.16 mmol) in CCl_4 (17.0 mL) [$CHCl_3$ is preferable for the mesylate reagents], kept at the required temperature (0 °C or 25 °C) under a N_2 atmosphere, was added the ketone (5.00 mmol) dropwise. An internal standard, benzene (0.50 mL, 1.00 M in CCl_4, 0.50 mmol), was added for quantification of the enol borinate by ^1H NMR analysis, except in the case of propiophenone, where the aromatic ring was used as the internal standard. The reaction mixture was stirred for 2 h. The enol borinate solution was then transferred into an NMR tube using a double-ended needle. The ^1H NMR analysis gave the extent of enolboration and the ^{11}B NMR spectra (borinate region, usually broad, around 50–56 ppm) also confirmed the formation of enol borinates. The ^1H NMR data of the olefinic protons of the enol borinates are given in our earlier papers.[7a,b]

General Procedure for the Enolboration of Ketones with R_2BX/Et_3N (Where X = I, Br, and Cl). A simple and general procedure for the enolboration of ketones with the various R_2BX reagents (X = I, Br, and C) is described as follows. To a stirred solution of R_2BX (5.15 mmol) and Et_3N (0.72 mL, 5.16 mmol) in CCl_4 (17.0 mL), kept at the required temperature (0 or 25 °C) under a N_2 temperature, was added the ketone (5.00 mmol) dropwise. The enol borinate was generated rapidly with concurrent formation and precipitation of $Et_3N{\cdot}HX$. An internal standard, benzene (0.50 mL, 1.00 M in CCl_4, 0.50 mmol), was added for quantification of the enol borinate by ^1H NMR analysis, except in the case of propiophenone, where the aromatic ring was used as the internal standard. The reaction mixture was stirred for 2 h and then transferred into a centrifuge vial using a double-ended needle (18 gauge). Centrifugation resulted in the separation of the enol borinate solution from the precipitated $Et_3N{\cdot}HX$. In representative cases, the solid $Et_3N{\cdot}HX$ has been collected, washed, dried, and weighed. Essentially quantitative yields were obtained. The enol borinate solution was then transferred into an NMR tube using a double-ended needle. The ^1H NMR analysis gave the extent of enolboration and the ^{11}B NMR spectra (borinate region, usually broad, around 50–56 ppm) also confirmed the formation of enol borinates.

General Procedure for the Aldolization of the Enol Borinates, Generated with the Various R_2BX/Et_3N (Except for X = I), with Benzaldehyde. To a solution of enol borinate in hexane generated under a N_2 atmosphere from 5.00 mmol of the ketone using R_2BX/Et_3N (except for X = I) as described above, benzaldehyde (5.00 mmol) was added dropwise at −78 °C. The reaction mixture was stirred for 2–3 h and then allowed to warm up overnight slowly to attain room temperature. The absence of residual benzaldehyde confirmed the essentially quantitative formation of enol borinate, as indicated by ^1H NMR analysis. Then 10 mL of methanol was added and 1.70 mL of H_2O_2 (30%) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and then at 25 °C for 3–4 h. The solvent and methanol were then removed by a water aspirator (15–20 mm), and the reaction mixture was extracted with ether, washed with dilute HCl and water, and then dried over anhyd Na_2SO_4. The solvent was removed and the products were analyzed as such by ^1H NMR (in $CDCl_3$) to determine the syn/anti ratio.

General Procedure for the Aldolization of the Enol Borinates, Generated with R_2BI/Et_3N, with Benzaldehyde. To a solution of enol borinate in hexane generated under a N_2 atmosphere from 5.00 mmol of the ketone and R_2BI/Et_3N, as described above, was added benzaldehyde (5.00 mmol) dropwise

---

(14) Brown, H. C.; Garg, C. P.; Liu, K.-T. *J. Org. Chem.* **1971**, *36*, 387.

at −78 °C. The reaction mixture was stirred for 2–3 h and then allowed to warm up overnight slowly to attain room temperature. The absence of residual benzaldehyde confirmed the essentially quantitative formation of enol borinate, as indicated by ^{1}H NMR analysis. Then 10 mL of methanol was added, and 2.50 mL of H_2O_2 (30%) was added dropwise at 0 °C. [Oxidation of the reaction mixtures containing the boron aldolates produced from the R_2BI reagents requires excess H_2O_2 (2.50 mL in place of the 1.70 mL used for other R_2BX reagents). The excess hydrogen peroxide is necessary because the iodide, present as $Et_3N{\cdot}HI$, is also oxidized to iodine]. The resulting mixture was stirred at 0 °C for 30 min and then at 25 °C for 3–4 h. The solvent and methanol were then removed under vacuum, 15–20 mm (water aspirator), and the reaction mixture was extracted with ether. The dark-colored ether solution containing iodine was washed with dilute sodium thiosulfate solution, dilute HCl, and then with water. The colorless ether solution was dried over anhyd Na_2SO_4, the solvent was evaporated, and the products were analyzed as such by ^{1}H NMR (in $CDCl_3$) to determine the syn/anti ratio.

Acknowledgment. We gratefully acknowledge financial support from the United States Office of Naval Research, which made this research possible.

Supplementary Material Available: ^{1}H NMR spectra of the enol borinates from propiophenone and the benzaldehyde aldols of the various ethyl ketones, EtCOR′, with R′ = *i*-Pr (anti and mixture), Et (syn and mixture), *t*-Bu (syn and anti), and Ph (syn, anti, and mixture) (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.