Enolboration. 1. Dicyclohexylchloroborane/Triethylamine as a Convenient Reagent for Enolboration of Ketones and Other Carbonyl Derivatives

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A facile enolization of ketones and other carbonyl derivatives is achieved with dicyclohexylchloroborane in the presence of triethylamine in simple solvents such as methylene chloride, ethyl ether, carbon tetrachloride, and hexane. A number of R_2BCl reagents have been examined using 2-butanone and 3-pentanone as model ketones to explore their effect on the regioselectivity and reactivity of enolization: (1) *B*-chloro-9-borabicyclo[3.3.1]nonane (B-Cl-9-BBN); (2) bis(*exo*-norbornyl)chloroborane (*exo*-Nrb_2BCl); (3) dicyclooctylchloroborane (Coc_2BCl); (4) dicyclohexylchloroborane (Chx_2BCl); (5) disiamylchloroborane (Sia_2BCl); and (6) bis(2,5-dimethylcyclohexyl)-chloroborane (2,5-Me_2Chx_2BCl). Reagents 2–6 achieve rapid, regioselective, and quantitative enolization for the unhindered methyl ketone, 2-butanone. Reagent 1 achieves enolization but fails to give a regioselective product. On the other hand, reagents 1–4 achieve quantitative enolization for the more hindered diethyl ketone. However, the more hindered reagents, 5 and 6, achieve only very slow enolization of this ketone. Consequently, the moderately sterically hindered reagent 4, Chx_2BCl, was screened for the enolization of both simple ketones and many other carbonyl derivatives, such as aldehydes, carboxylic acids, anhydrides, acid chlorides, esters, tertiary amides, and thioesters. Finally, a bifunctional derivative, a keto ester, was also examined. It was observed that with the exception of acid chlorides, esters, and amides, all of these classes of carbonyl compounds were easily and rapidly converted into enolborinates in ≥94% conversion with concurrent formation and precipitation of Et_3NHCl. The visual observation of the formation of Et_3NHCl as a white precipitate as the enolization progresses is an added advantage for this new reagent providing a convenient guide to the course of the reaction, in contrast to the behavior of Et_3NHOTf, which does not precipitate. These enolborinates react readily with aldehydes at temperatures as low as −78 °C, comparable to the reaction with aldehydes of the enolborinates produced by the organoboron triflates previously introduced and used in organic synthesis. The impressive regioselectivity and reactivity of Chx_2BCl, together with its greater stability and ease of formation and handling, indicate it to be the reagent of choice for enolboration. Consequently, this reagent was emphasized in this exploratory study.

Enolborinates are highly useful intermediates in organic synthesis.[4-8] Considerable attention has been paid in the past decade to developing simple methodologies for generating enolborinates by the reaction of ketones with suitable organoboron derivatives, R_2BX, containing a good leaving group in the presence of a suitable tertiary amine. The reagents employed previously are R_2BOTf,[8] ethylene chloroboronate,[9] $ROBCl_2$,[10] BCl_3,[10] and $PhBCl_2$.[11] However, these reagents are either difficult to prepare in the pure form or give only moderate conversion to the desired enolborinates. The limitations of the available reagents suggested a search for boron reagents which possess better selectivity and reactivity while being easily accessible.

Dialkylhaloboranes are easy to prepare and show remarkable stability.[12] Moreover, R_2BX reagents have been utilized in our laboratory for asymmetric reduction,[13] asymmetric opening of *meso*-epoxides,[14] and synthesis of secondary amines.[15] Therefore, we undertook to explore the applicability of such reagents for enolboration. An unexpected bonus from these studies was the discovery of a valuable control of enolate geometry for ethyl ketones.[16] In this paper we are reporting the examination of representative R_2BCl reagents and our results on the enolization of representative types of carbonyl compounds using the preferred reagent, Chx_2BCl/Et_3N.

Results and Discussion

For the present study, we selected the following R_2BCl reagents: (1) *B*-chloro-9-borabicyclo[3.3.1]nonane (B-Cl-9-BBN); (2) bis(*exo*-norbornyl)chloroborane (*exo*-Nrb_2BCl); (3) dicyclooctylchloroborane (Coc_2BCl); (4) dicyclohexylchloroborane (Chx_2BCl); (5) disiamylchloroborane (Sia_2BCl); and (6) bis(2,5-dimethylcyclohexyl)-chloroborane (2,5-Me_2Chx_2BCl).

Preparation of R_2BCl Reagents. The R_2BCl reagents are readily prepared by hydroboration of selected olefins (2 equiv) to R_2BH with borane–methyl sulfide (BMS, 1 equiv), followed by addition of hydrochloric acid[12a] (anhyd

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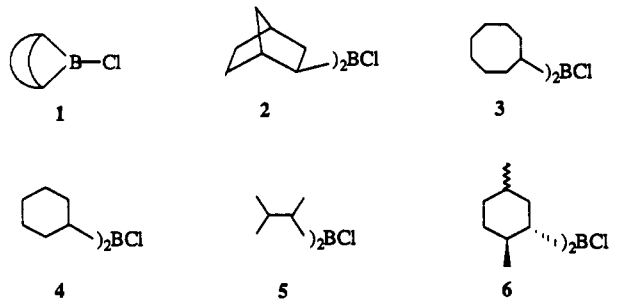

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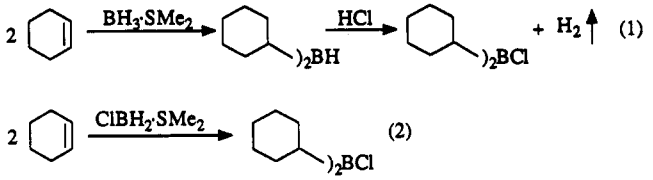
HCl in ether). Alternately, these can also be prepared directly from the olefins by hydroboration with monochloroborane.[12b-d] The latter method is especially useful for cases where the hydroboration reaction fails to stop cleanly at the dialkylborane stage. A typical example of the preparation of a dialkylchloroborane, Chx_2BCl, by both methods is shown (eqs 1 and 2).



Since the hydroboration of norbornene and cyclooctene with BMS proceeds rapidly past the desired R_2BH intermediates to the trialkylboranes, these alkenes were hydroborated with monochloroborane to obtain the desired dialkylchloroboranes.

Selection of Amine. Mukaiyama introduced the use of dialkylboron triflates, R_2BOTf, for enolboration.[8] He examined a number of tertiary amines for the enolization of ketones with the dialkylboron triflates, 9-bicyclo[3.3.1]nonylboron triflate and di-*n*-butylboron triflate. He reported that less hindered amines, such as pyridine, gave very poor enolization, whereas, more sterically hindered amines, such as triethylamine, Et_3N, diisopropylethylamine, *i*-Pr_2EtN, and tri-*n*-butylamine, *n*-Bu_3N, gave moderate to good enolization.[8d] The poor enolization was explained on the basis that the less sterically hindered amines coordinate very strongly with R_2BOTf, resisting the reaction of the boron moiety with the ketones.[17] These literature results prompted us to utilize both Et_3N and *i*-Pr_2EtN for the initial experiments. However, we subsequently selected Et_3N as preferable, since during the enolization process it forms a solid amine hydrochloride, insoluble in the common organic solvents, providing both a simple method for following the course of the reaction and an easy process for removing this byproduct from the reaction mixture.

Selection of Solvent. The enolization experiments were often carried out in carbon tetrachloride since the ^1H NMR spectra can be directly recorded for such reaction mixtures. Enolization was also successfully carried out in other organic solvents, such as diethyl ether, methylene chloride, tetrahydrofuran, and hexane. Further, it was established that these enolborinate solutions in the above-mentioned organic solvents are stable and can be stored for several days under an inert atmosphere without any observable change.

(17) "Dabco, DBU, and tetramethyleneguanidine are totally ineffective in the enolization process when R_2BOTf reagents are used. The ineffectiveness of these amines is attributed to the irreversible amine-borane complexation" (ref 4b). Et_3N and *i*-Pr_2EtN were found to be the most suitable tertiary amines for enolization of ketones by R_2BOTf (refs 4b, 8a, 8b).

Table I. Regioselective Enolboration of 2-Butanone with Various R_2BCl/Et_3N[a]

			% regioisomer[c]	
R_2BCl	time (min)	% enolborinate[b]	terminal	internal
1	30	95	67	33
2	30	97	99	1
3	30	97	99	1
4	30	98	99	1
5	30	95	99	1
6[d]	45	92	99	1

[a] Reactions were carried out in CCl_4 at 0 °C unless otherwise stated. [b] Determined by ^1H NMR using benzene as an internal standard and ^{11}B NMR. [c] Determined by ^1H NMR. [d] Reaction at 25 °C.

Table II. Enolization of 3-Pentanone with Various R_2BCl/Et_3N[a]

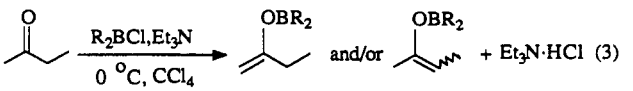
R_2BCl	time (min)	% enolborinate[b]
1	30	95
2	30	96
3	30	97
4	30	96
5	90	32
6[c]	45	25

[a] Reactions were carried out in CCl_4 at 0 °C unless otherwise stated. [b] Determined by ^1H NMR using benzene as an internal standard and ^{11}B NMR. [c] Reaction at 0 °C.

Reaction with Benzaldehyde. We examined the reaction of representative enolborinates with benzaldehyde. The reaction proceeds readily at −78 °C and gives essentially quantitative conversion, comparable to the behavior of the previously known enolborinates prepared with the boron triflates. ^1H NMR examination of these aldol products established the geometry of the enolborinates produced.[16]

Steric Effect of R_2BCl on the Enolization of Model Ketones. Regioselective Enolization of 2-Butanone. We undertook to examine R_2BCl reagents 1–6 for the enolization of two model ketones, the unsymmetrical ketone, 2-butanone, and the symmetrical ketone, 3-pentanone.

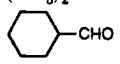
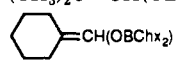
The enolization experiments were carried out in carbon tetrachloride, using benzene as the internal standard. Both ^1H NMR (olefinic proton) and ^{11}B NMR (borinate region) were used to determine the extent of enolization. Examination of the reaction product mixture (olefinic proton) by ^1H NMR also revealed the regioselectivity of the enolization. The two olefinic protons of the terminal enolate (on the methyl side) appear as two singlets at δ 4.2 and 4.4 ppm, and the olefinic proton of the internal enolate (on the ethyl side) appears as a quartet at δ 4.7–5.0 ppm. The results of the enolization of 2-butanone (eq 3) with the various R_2BCl reagents examined (1–6) are summarized in Table I.



From the results, it is clear that all of the reagents, with the exception of the least hindered derivative 1, cause enolization exclusively on the methyl side within the precision of the T-60 NMR instrument. Essentially quantitative enolization was achieved for 2-butanone with all reagents.

Enolization of 3-Pentanone. After establishing the regioselectivity and reactivity of various R_2BCl reagents toward 2-butanone, their reactivities were examined toward 3-pentanone as a model ketone. These results for 3-pentanone (yield) are summarized in Table II. A rapid

Table III. Enolization of Simple Ketones and Aldehydes with Chx_2BCl/Et_3N[a]

carbonyl compound	time (min)	enolborinate	^{11}B NMR[b] (δ ppm)	^1H NMR[c] (δ ppm)	% enolborinate[d]
ketones					
CH_3COCH_3	30	$CH_2{=}C(OBChx_2)CH_3$	51	4.18 (s, 1 H), 4.30 (s, 1 H)	100
$CH_3COCH_2CH_3$	30	$CH_2{=}C(OBChx_2)CH_2CH_3$	51	4.12 (s, 1 H), 4.25 (s, 1 H)	97
$CH_3CH_2COCH_2CH_3$	30	$CH_3CH{=}C(OBChx_2)CH_2CH_3$	53	4.12 (q, J = 6.3 Hz)	97
$PhCOCH_2CH_3$	60	$CH_3CH{=}C(OBChx_2)Ph$	52	5.10 (q, J = 7.4 Hz)	90
aldehydes					
$CH_3CH_2CH_2CHO$	30	$CH_3CH_2CH{=}CH(OBChx_2)$	53	4.5–4.78 (m) and 6.58 (d, J = 6.8 Hz)	95
$PhCH_2CHO$	30	$PhCH{=}CH(OBChx_2)$	52	5.45 (d, J = 6.8 Hz) and 6.70 (d, J = 6.8 Hz)	95
$(CH_3)_2CHCHO$	45	$(CH_3)_2C{=}CH(OBChx_2)$	53	6.38 (s, 1 H)	94
	45		54	6.38 (s, 1 H)	94

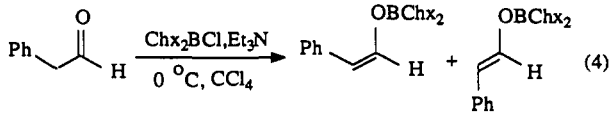
[a] Reactions were carried out in CCl_4 at 0 °C unless otherwise stated. [b] ^{11}B NMR observed as broad singlet. [c] Olefinic proton(s). [d] Determined by ^1H and ^{11}B NMR.

quantitative enolization of 3-pentanone by reagents **1–4** was also achieved. However, the more sterically hindered reagents, **5** and **6**, result in a much slower enolization of 3-pentanone.

Choice of Chx_2BCl for Enolization. Based on the above results, it was concluded that reagents **2–4** give both regioselective and quantitative enolization of the model ketones. Further consideration of which reagent would be the best among **2–4** was based on the ease of preparation, the availability of starting material, the reagent stability, and the ease of handling. Chx_2BCl was then selected as the preferred choice for our further study. Control of enolate geometry was not further considered as a factor to select the best reagent, since all the five reagents were far inferior to Chx_2BCl in other considerations. It is important to mention here once again that Chx_2BCl is the best reagent known to give the E enolate predominately for diethyl ketone and exclusively for propiophenone.[16]

Enolboration of Selected Ketones. Simple ketones, such as acetone, methyl ethyl ketone, diethyl ketone, and propiophenone, were enolized quantitatively by Chx_2BCl and Et_3N. These reactions were carried out at 0 °C in CCl_4 to permit direct examination of the enolborinates by ^1H NMR. The results are given in Tables III and V. The regioselective, rapid, and quantitative enolization of simple ketones encouraged us to investigate the application of Chx_2BCl/Et_3N to other types of carbonyl derivatives. The achievement in control of enolate geometry has already been discussed in our earlier communication.[16]

Enolization of Aldehydes. Hoffmann[18] has reported an indirect method for generating enolborates from aldehydes via the corresponding silyl enol ethers or lithium enolates. However, to the best of our knowledge, there is no report available where boron reagents have been utilized to enolize aldehydes directly. For aldehydes, it was necessary to add aldehydes, preferably as a dilute solution, extremely slowly to a stirred solution of R_2BCl and Et_3N in order to prevent any condensation of the enolborinates formed in the initial stages of the reaction with the free aldehydes. Utilizing this reverse addition technique, *n*-butyraldehyde, phenylacetaldehyde (eq 4), cyclohexanecarboxaldehyde, and isobutyraldehyde were successfully enolized in >94% yield. The ^1H NMR of the enolborinate suggests that phenylacetaldehyde gives a mixture of the Z and E enolates.



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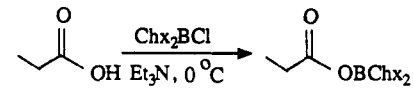
(18) Hoffmann, R. W.; Ditrich, K.; Fröch, S. *Liebigs Ann. Chem.* 1987, 977.

The olefinic protons of both Z and E enolborinates obtained from aromatic ketones differ in chemical shift and so the direct determination of the Z/E ratio is possible by ^1H NMR.[16] It was also possible to determine the Z/E ratio for phenylacetaldehyde directly by ^1H NMR. The Z enolate olefinic protons appeared as two doublets at δ 5.45 ppm (J = 6.8 Hz) and at δ 6.7 ppm (J = 6.8 Hz). One of the olefinic protons of the E enolate appeared as a doublet at δ 6.2 ppm (J = 12 Hz) and the other merged with aromatic protons. The results of the enolboration of aldehydes are given in Tables III and V.

Enolboration of Carboxylic Acids, Anhydrides, and Chlorides. Evans[4b] and Masamune[5b] have described the successful application of R_2BOTf for the enolization of carboxylic acids. Two equivalents of reagents are required for this enolization. Chx_2BCl/Et_3N also successfully enolizes carboxylic acids. Propionic acid (eqs 5 and 6), caproic acid, and phenylacetic acid were successfully enolized using this reagent.



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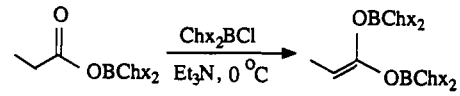

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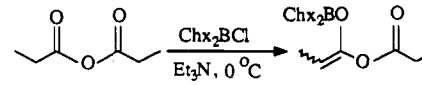
While propionic acid gave a mixture of the Z and E enolates, phenylacetic acid gave exclusively the E enolate.

Anhydrides are also readily enolizable with Chx_2BCl/Et_3N. Propionic anhydride was enolized quantitatively (eq 7) and 71% of the E enolate was achieved.



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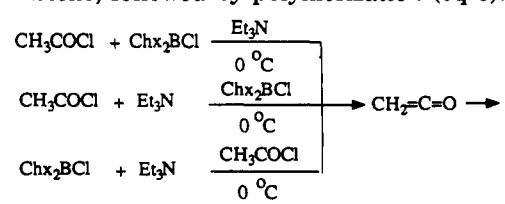
In the case of acid chlorides, enolization was not possible. Apparently, rapid conversion of the acid chlorides by the tertiary amine to ketene interfered with the enolboration process. The reaction resulted largely in the formation of ketene, followed by polymerization (eq 8). The use of



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different modes of addition of reagents also failed to help. The results are summarized in Tables IV and V.

Enolboration of Carboxylic Esters, Tertiary Amides, and Thioesters. We next examined some repre-

Table IV. Enolization of Carboxylic Acids and Derivatives with Chx_2BCl/Et_3N[a]

carbonyl compound	time (min)	enolborinate	^{11}B NMR[b] (δ ppm)	^1H NMR[c] (δ ppm)	% enolborinate[d]
acids[e]					
CH_3CH_2COOH	60	$CH_3CH{=}C(OBChx_2)_2$	50	4.18 (q, J = 6.8 Hz)	97
$CH_3(CH_2)_4COOH$	60	$CH_3(CH_2)_3CH{=}C(OBChx_2)_2$	51	4.10 (t, J = 7.1 Hz)	95
$PhCH_2COOH$	60	$PhCH{=}C(OBChx_2)_2$	50	5.40 (s)	98
anhydrides					
$(CH_3CH_2CO)_2O$	60	$CH_3CH{=}C(OBChx_2)OCOC_2H_5$	50	4.9 (q)	90
acid chlorides[f]		no enolization			
esters[f]		no enolization			
amides[f]		no enolization			
thioesters[g]					
$CH_3COSC(CH_3)_3$	60	$CH_2{=}C(OBChx_2)SC(CH_3)_3$	52	4.85 (s, 1 H), 4.95 (s, 1 H)	95
CH_3COSPh	30	$CH_2{=}C(OBChx_2)SPh$	50	4.62 (s, 1 H), 4.73 (s, 1 H)	90
β-keto ester					
$CH_3COCH_2CO_2C_2H_5$	60	$CH_3C(OBChx_2){=}CHCO_2C_2H_5$	15	4.68 (s, 1 H)	94

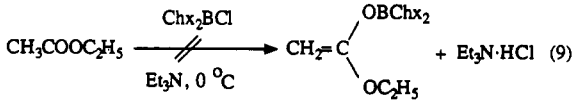
[a] Reactions were carried out in CCl_4 at 0 °C unless otherwise stated. [b] ^{11}B NMR observed as broad singlet. [c] Olefinic proton(s). [d] Determined by ^1H and ^{11}B NMR. [e] Enolization with 2 equiv of reagents. [f] See text for individual compounds examined. [g] Enolization at 25 °C.

Table V. Enolate Geometry of the Enolborinates from Representative Carbonyl Compounds

carbonyl compound	^1H NMR[a] (δ ppm) syn	^1H NMR[a] (δ ppm) anti	% enolate[b] Z	% enolate[b] E	% yield[c]
$CH_3CH_2COCH_2CH_3$	5.01 (d, J = 4.4 Hz)	4.72 (d, J = 8.4 Hz)	21	79	95
$PhCOCH_2CH_3$	5.08 (d, J = 4.0 Hz)	4.88 (d, J = 8.0 Hz)	<1	>99	87
$PhCH_2CHO$[d]	-	-	67	33	95
CH_3CH_2COOH	5.17 (d, J = 3.8 Hz)	4.73 (d, J = 9.1 Hz)	18	82	95
$PhCH_2COOH$	-	5.20 (d, J = 10.0 Hz)[e]	<1	>99	95
	-	3.90 (d, J = 10.0 Hz)[f]			
$(CH_3CH_2CO)_2O$	5.14 (d, J = 3.9 Hz)	4.71 (d, J = 8.7 Hz)	29	71	85

[a] Corresponds to the benzylic proton of the aldol products with benzaldehyde. [b] Based on the syn/anti ratio. [c] Determined by ^1H NMR analysis (not isolated yield). [d] Directly determined from the enolborinate; see text for ^1H NMR data. [e] Corresponds to the benzylic proton α to OH of the aldol. [f] Corresponds to the benzylic proton α to COOH of the aldol.

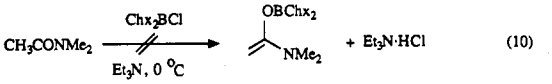
sentative derivatives of carboxylic acid, such as esters, tertiary amides, and thioesters. It is surprising that simple esters, such as ethyl acetate and phenyl acetate, failed to undergo enolization with Chx_2BCl/Et_3N (eq 9).



(9)

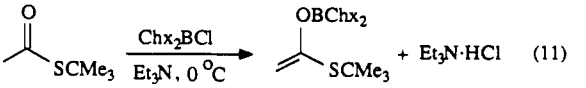
A similar failure was also observed by Evans when he attempted to enolize methyl propionate with R_2BOTf and tertiary amine.[4b]

N,N-Disubstituted amides, such as *N,N*-dimethylacetamide and *N,N*-dimethylpropionamide, also proved to be resistant to enolization by Chx_2BCl/Et_3N (eq 10).



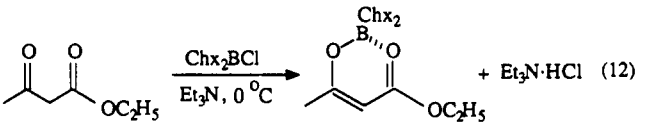
(10)

However, thioesters, such as *S-tert*-butyl thioacetate and *S*-phenyl thioacetate, underwent rapid and quantitative enolization with Chx_2BCl/Et_3N. The enolization of thioesters has also been achieved previously by Masamune[5] with R_2BOTf and *i*-Pr_2EtN. The ^{11}B NMR analysis of both of these enolized thioesters (δ 52 and 50 ppm, respectively) suggests that sulfur does not coordinate with boron of the corresponding enolborinate (eq 11). These results are summarized in Table IV.



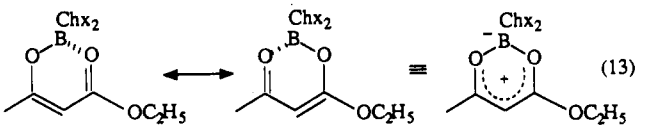
(11)

Enolboration of Bifunctional Derivatives. Finally, a bifunctional derivative, a keto ester, was also examined. Enolization of ethyl acetoacetate was achieved smoothly with Chx_2BCl/Et_3N. The olefinic proton appeared at δ 4.68 ppm (s, 1 H). Its enolate geometry is presumed to be *Z* since the ^{11}B NMR absorption shows considerable upfield shift, δ 15 ppm, suggesting that the oxygen atom of the carbonyl group in the ester moiety must be coordinated to the boron atom of its enolborinate (eq 12).



(12)

The ^{11}B NMR value also suggests resonating structures for the enolborinate (eq 13).



(13)

The results on the enolization of different carbonyl derivatives with Chx_2BCl/Et_3N are summarized in Tables IV and V.

Enolate Geometry. The *Z*/*E* ratio of the enolborinates could not be directly determined by ^1H NMR since, unfortunately, the olefinic protons of both *Z* and *E* enolates exhibit essentially identical chemical shifts. Therefore an indirect method was used to find this ratio from the syn/anti ratio of their aldol products with benzaldehyde.[16] The benzylic protons of the syn and anti aldols have a different chemical shift and coupling constant,[19] and so the crude reaction mixture (after the necessary workup) was analyzed as such by ^1H NMR, which gave this ratio precisely (Table V).

(19) House, H. O.; Crumrine, D. S.; Teranishi, A. V.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.

Conclusions

Various R_2BCl reagents have been prepared and analyzed for the regioselective and quantitative enolization of model ketones. The dicyclohexylchloroborane was selected as the preferred reagent. It was then explored for the enolization of simple ketones and various other carbonyl derivatives in the presence of triethylamine. Except for esters, tertiary amides, and acid chlorides, all other classes of carbonyl compounds, such as aldehydes, acids, anhydrides, thioesters, and β-keto esters, were easily and rapidly converted into enolborinates in almost quantitative yield. The Z/E ratio has been determined for the representative enolates. Further research is in progress to achieve selectivity in enolate geometry. The impressive regioselectivity and reactivity observed in the enolboration of ketones and various carbonyl compounds, combined with the ease of preparation and handling, make Chx_2BCl/Et_3N a valuable reagent for enolboration.

Experimental Section

Materials. All glassware used for the experiments were thoroughly dried in an oven and cooled and assembled under a stream of nitrogen. Degassed and anhydrous solvents, CCl_4, CH_2Cl_2, benzene, and hexane, were used. THF was freshly distilled from sodium benzophenone ketyl. Et_3N was used after distilling over CaH_2. All alkenes, ketones, aldehydes, carboxylic acids, anhydrides, acid chlorides, esters, amides, thioesters, and β-keto ester were commercial products of the highest purity available. Whenever necessary, the commercial samples of liquid olefins were purified by distillation over $LiAlH_4$ and ketones over CaH_2. Borane–methyl sulfide (BMS) and monochloroborane–methyl sulfide (MCBS) reagents were purchased from Aldrich and used for the reaction. The special experimental techniques used in handling air- and moisture-sensitive materials are described elsewhere.[20] All of the following experiments were conducted under N_2.

Spectra. ^1H NMR spectra were recorded on T-60, 200- and 300-MHz instruments.[21] ^{11}B NMR spectra were recorded on FT-80A and 300-MHz instruments. The chemical shift values are in δ (ppm) relative to $BF_3{\cdot}OEt_2$.

Synthesis of Dialkylchloroborane via Hydroboration of Alkenes with Borane–Methyl Sulfide (Procedure A). The synthesis of dicyclohexylchloroborane, Chx_2BCl, is described as a typical procedure. A 500-mL round-bottom flask capped with a rubber septum, a magnetic stirring bar, and a connecting tube attached to a mercury bubbler was charged with diethyl ether (150 mL) and cyclohexene (41 mL, 400 mmol). The flask was cooled in an ice bath, borane–methyl sulfide, BMS (20 mL, 10 M, 200 mmol), was added slowly, and stirring was continued for 3 h at 0 °C. Dicyclohexylborane, Chx_2BH, precipitated as a white solid. The supernatant liquid was removed by a double-ended needle, the solid was washed with ether, and the liquid was removed. Then the solid was suspended in 100 mL of diethyl ether, and anhydrous HCl in ether (66.7 mL, 3 M, 200 mmol) was added slowly to the suspension at 0 °C. Hydrogen is rapidly evolved and should be safely vented. Stirring was continued at 0 °C for an additional 4 h. A clear solution was obtained. The ^{11}B NMR analysis of the resulting solution showed formation of $Chx_2BCl{\cdot}SMe_2$ (δ 66 ppm in diethyl ether). Distillation provided pure Chx_2BCl (δ 76 ppm in hexane), 31.6 g, 75% yield, bp 95–96 °C (0.35 mm).

Reagent 1[12c] [75% yield, ^{11}B NMR δ 79 ppm in hexane, bp 65 °C (0.3 mm)] was prepared by treating the commercially available 9-BBN (Aldrich) with anhyd HCl in ether. Reagent 5[12b,d] (75% yield and >98% pure based on ^{11}B NMR, δ 78 ppm in hexane) and reagent 6 (70% yield and >98% pure based on ^{11}B NMR, δ 74 ppm in ether) were prepared using the above procedure. Both decomposed on attempted distillation and so were used as such.

Synthesis of Dialkylchloroborane via Hydroboration of Alkenes with Monochloroborane–Methyl Sulfide (Procedure B). The synthesis of dicyclohexylchloroborane, Chx_2BCl, is described as a typical procedure. A 250-mL round-bottom flask fitted with a rubber septum, a magnetic stirring bar, and a connecting tube attached to a mercury bubbler was cooled in an ice bath and charged with diethyl ether (90 mL) under inert atmosphere. Cyclohexene (21.2 mL, 210 mmol) was added, followed by monochloroborane–methyl sulfide (11.6 mL, 8.62 M, 100 mmol) slowly. The mixture was stirred at 0 °C for 2 h. The solvent was removed under reduced pressure (25 °C, 12 Torr). Distillation provided pure Chx_2BCl (δ 76 ppm in hexane), 16.85 g, 80% yield, bp 104–105 °C (0.5 mm). Synthesis of Chx_2BCl can be carried out on a molar scale without any difficulty.

Reagent 2[12b,d] (72% yield and ~90% pure based on ^{11}B NMR, δ 71 ppm in ether) and reagent 3 (76% yield and ~90% pure based on ^{11}B NMR, δ 72 ppm in ether) were prepared using the above procedure and could not be distilled. About 10% $RBCl_2$ corresponding to the amount of $Cl_2BH{\cdot}SMe_2$ in the commercial MCBS (Aldrich) was present. This $RBCl_2$ impurity was readily deactivated by complexation with a small excess of amine and did not influence the reaction.

General Procedure for the Enolization of Ketones by R_2BCl/Et_3N. A general procedure for the enolization of ketones is described here. To a stirred solution of R_2BCl (5.2 mmol) and Et_3N (0.73 mL, 5.2 mmol) in CCl_4 (20 mL) cooled at 0 °C was added dropwise ketone (5 mmol). Enolborinate was generated instantaneously with concurrent formation and precipitation of $Et_3N{\cdot}HCl$. An internal standard, benzene (0.5 mmol), was added for quantification of the enolborinate by ^1H NMR analysis. Molarity was adjusted around 0.2–0.3 M. The reaction mixture was stirred for the desired length of time and transferred into a centrifuge vial through a double-ended needle (18 gauge). Centrifugation resulted in the separation of the enolborinate solution from $Et_3N{\cdot}HCl$, which was transferred into an NMR tube by double-ended needle. ^1H NMR and ^{11}B NMR analyses showed the extent of enolization.

Enolization of Aldehydes by Chx_2BCl/Et_3N. A representative example of enolization of phenylacetaldehyde is described here. To a stirred solution of Chx_2BCl (1.2 mL, 5.5 mmol) and Et_3N (0.77 mL, 5.5 mmol) in CCl_4 (15 mL) cooled at 0 °C was added dropwise phenylacetaldehyde in CCl_4 (5 mL, 1 M, 5 mmol) over a period of 20–30 min. An immediate precipitation of $Et_3N{\cdot}HCl$ occurred along with the addition of aldehyde, suggesting that enolization is very fast. (It is important to mention that the aldehyde, preferably in dilute solution, should be added very slowly, drop by drop, to the well-stirred solution of Chx_2BCl and Et_3N in order to prevent any condensation of the enolborinate formed with the aldehyde.) An internal standard is not necessary since the aromatic protons of the reagent can be used for quantification. The reaction mixture was stirred for about 30 min and worked up as described earlier for ketones. Both ^1H NMR and ^{11}B NMR analyses suggested >95% enolization.

Enolization of Carboxylic Acids by Chx_2BCl/Et_3N. A representative example of enolization of propionic acid is described here. To a stirred solution of Chx_2BCl (2.4 mL, 11 mmol, 2.1 equiv) and Et_3N (1.54 mL, 11 mmol, 2.1 equiv) in CCl_4 (50 mL) cooled at 0 °C was added an internal standard, benzene (0.5 mmol). The molarity of the solution was adjusted to 0.2 M with respect to R_2BCl. Then propionic acid (0.38 mL, 5 mmol, 1 equiv) was added dropwise. An immediate precipitation of $Et_3N{\cdot}HCl$ occurred, suggesting a fast reaction. The reaction mixture was stirred at 0 °C for 1 h and worked up as described previously for ketones. Analysis of the olefinic protons by ^1H NMR suggests >95% enolization of the acid.

Enolization of Anhydrides by Chx_2BCl/Et_3N. The enolization of propionic anhydride is described as follows as an example. To a stirred solution of Chx_2BCl (1.2 mL, 5.5 mmol) and Et_3N (0.77 mL, 5.5 mmol) in CCl_4 (15 mL) cooled at 0 °C was added an internal standard, benzene (0.5 mmol), followed by the dropwise addition of propionic anhydride (0.64 mL, 5 mmol). The molarity of the solution was adjusted to 0.3 M. The reaction mixture was stirred for 1 h and worked up as described previously for ketones. Analysis of ^1H NMR showed >90% enolization.

(20) For handling of air- and moisture-sensitive compounds, see: Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*; Wiley-Interscience: New York, 1975; p 191.

(21) These experiments extended over a considerable period during which our NMR instruments changed. Much of the early work was done with T-60, with the later work carried out on 200- and currently with 300-MHz instruments.

Enolization of Thioesters by Chx_2BCl/Et_3N. A representative example of enolization of *S-tert*-butyl thioacetate is described as follows. To a stirred solution of Chx_2BCl (1.2 mL, 5.5 mmol) and Et_3N (0.77 mL, 5.5 mmol) in CCl_4 (15 mL) cooled at 0 °C was added an internal standard, benzene (0.5 mmol), followed by the slow addition of *S-tert*-butyl thioacetate (0.78 mL, 5 mmol). The molarity of the solution was adjusted to 0.3 M. The reaction mixture was stirred for 1 h and worked up as described for ketones. Analysis of the olefinic proton by ^1H NMR suggests >95% enolization.

Enolization of β-Keto Ester by Chx_2BCl/Et_3N. The enolization of ethyl acetoacetate is described as follows. To a stirred solution of Chx_2BCl (1.2 mL, 5.5 mmol) and Et_3N (0.77 mL, 5.5 mmol) in CCl_4 (15 mL) cooled at 0 °C was added an internal standard, benzene (0.5 mmol), followed by the slow addition of ethyl acetoacetate (0.64 mL, 5 mmol). The molarity of the solution was adjusted to 0.3 M. The reaction mixture was stirred for 1 h and worked up as described previously for ketones. Analysis by ^1H NMR showed 94% enolization.

General Procedure for the Aldolization with Benzaldehyde. To a solution of enolborinate in diethyl ether generated from 5 mmol of the carbonyl compound using Chx_2BCl/Et_3N as described above was added benzaldehyde (0.51 mL, 5 mmol) dropwise at -78 °C, and the mixture was stirred for 2-3 h. Then the reaction mixture was allowed to warm up overnight slowly to attain the room temperature. (Later we discovered that the reaction is essentially complete in 2-3 h at -78 °C, so that the slow warmup to 25 °C is unneccessary. Both procedures give the same results.) Then 10 mL of methanol was added to dissolve the precipitate (Et_3NHCl), 1.7 mL of H_2O_2 (30%) was added at 0 °C, and the mixture was stirred for 5-6 h at 25 °C. The solvent was then removed by water aspirator and the reaction mixture was extracted with ether, washed with dilute HCl and water, and dried over anhyd Na_2SO_4. The solvent was removed and the products were analyzed as such by ^1H NMR to determine the syn/anti ratio.

In the case of carboxylic acids, after the aldolization, 5 mL of H_2O was added to the reaction mixture at 25 °C, and the resulting mixture was stirred for 30 min. The products were then extracted with aqueous $NaHCO_3$, neutralized with 20% HCl, extracted with ether, dried over anhyd Na_2SO_4, concentrated, and analyzed by ^1H NMR.

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

Registry No. 1, 22086-34-6; 2, 137495-66-0; 3, 137495-67-1; 4, 36140-19-9; 5, 58335-30-1; 6, 137495-68-2; BMS, 13292-87-0; 9-BBN, 280-64-8; CH_3COCH_3, 67-64-1; $CH_3COCH_2CH_3$, 78-93-3; $CH_3CH_2COCH_2CH_3$, 96-22-0; $PhCOCH_2CH_3$, 93-55-0; $CH_3CH_2CH_2CHO$, 123-72-8; $PhCH_2CHO$, 122-78-1; $(CH_3)_2CHCHO$, 78-84-2; c-$C_6H_{11}CHO$, 2043-61-0; CH_2=$C(OBChx_2)CH_3$, 137495-69-3; CH_2=$C(OBChx_2)CH_2CH_3$, 137495-70-6; (*E*)-CH_3CH=$C(OBChx_2)CH_2CH_3$, 120312-96-1; (*E*)-CH_3CH=$C(OBChx_2)Ph$, 120312-92-7; CH_3CH_2CH=$CH(OBChx_2)$, 137495-71-7; (*Z*)-$PhCH$=$CH(OBChx_2)$, 137495-72-8; $(CH_3)_2C$=$CH(OBChx_2)$, 137495-73-9; c-C_6H_{10}=$CH(OBChx_2)$, 137495-74-0; $ClBH_2{\cdot}SMe_2$, 63348-81-2; CH_3CH_2COOH, 79-09-4; $CH_3(CH_2)_4COOH$, 142-62-1; $PhCH_2COOH$, 103-82-2; $(CH_3CH_2CO)_2O$, 123-62-6; $CH_3COSC(CH_3)_3$, 999-90-6; CH_3COSPh, 934-87-2; $CH_3COCH_2CO_2C_2H_5$, 141-97-9; CH_3CH=$C(OBChx_2)_2$, 137495-75-1; $CH_3(CH_2)_3CH$=$C(OBChx_2)_2$, 137495-76-2; $PhCH$=$C(OBChx_2)_2$, 137495-77-3; CH_3CH=$C(OBChx_2)OCOC_2H_5$, 137495-78-4; CH_2=$C(OBChx_2)SC(CH_3)_3$, 137495-79-5; CH_2=$C(OBChx_2)SPh$, 137495-80-8; (*Z*)-$CH_3C(OBChx_2)$=$CHCO_2C_2H_5$, 137495-81-9; PhCHO, 100-52-7; (*E*)-$PhCH$=$CH(OBChx_2)$, 137495-82-0; cyclohexene, 110-83-8.

Chiral Synthesis via Organoboranes. 33. The Controlled Reaction of *B*-Alkyldiisopinocampheylboranes with Aldehydes Providing a Convenient Procedure for the Enantiomeric Enrichment of the Boronic Ester Products through Kinetic Resolution

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Controlled treatment of *B*-alkyldiisopinocampheylborane (**3a**), Ipc_2BR*, obtained by asymmetric hydroboration of appropriate olefin, with aldehydes produces chiral boronate esters (**5**) having enantiomeric purities markedly higher than those of the substrate. A systematic study of the reaction revealed that the intermediate borinic esters (**4**) are being kinetically resolved. Since asymmetric hydroboration of alkenes with diisopinocampheylborane (**1**) provides predominantly the diastereomer that reacts faster with aldehydes, the reaction furnishes in situ enantiomeric enrichment of the products. Thus, *B*-alkyldiisopinocampheylboranes (**3a**) possessing 81-96% ee are readily converted into borinic esters (**5**) including 2-butyl, 3-hexyl, and *exo*-norbornyl derivatives of ≥99% ee. Successful efforts were also made to extend the scope of asymmetric hydroboration-kinetic resolution to representative cyclic dienes making available pure enantiomers of *exo*-5-norbornenyl- and 3-cyclohexenylboronic esters.

Hydroboration is one of the fundamentally novel reactions in organic chemistry. In recent times a variety of procedures have become available for the enantioselective version of this reaction. They include chiral organoboranes derived from terpenes,[2] Masamune's reagent,[3] and a modestly successful catalytic procedure involving chiral transition metal complexes.[4] All of these routes transform prochiral alkenes to the corresponding chiral alcohols. However, the reagents derived from (+)- and (-)-α-pinene

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(2) Brown, H. C.; Vara Prasad, J. V. N.; Zaidlewicz, M. *J. Org. Chem.* **1988**, *53*, 2911 and references cited therein.

(3) Masamune, S.; Kim, B. M.; Peterson, J. S.; Sato, T.; Veenstra, S. J. *J. Am. Chem. Soc.* **1985**, *107*, 4549.

(4) Brown, J. M.; Lloyd-Jones, G. C. *Tetrahedron Asymmetry* **1990**, *1*, 869 and references cited therein.

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