it to be a suitable basis for consideration of our further studies of structural effects on reactivity in alkoxide dehalogenations, soon to be reported.

**Acknowledgment.** We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society (Grant 10705-AC1), for funding this research. We are grateful for this support.

**Registry No.** *m*-Chloroiodobenzene, 625-99-0; sodium methoxide, 124-41-4; potassium methoxide, 865-33-8; azobisisobutyronitrile, 78-67-1; nitrobenzene, 98-95-3.

# Enolboration. 2. Dicyclohexylchloroborane/Triethylamine as a Convenient Reagent for Regio- and Stereoselective Enolboration of Representative Classes of Ketones

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A smooth, rapid, regio- and stereoselective enolboration of representative classes of ketones is achieved with dicyclohexylchloroborane in the presence of triethylamine in simple solvents such as methylene chloride, diethyl ether, carbon tetrachloride, and hexane. All classes of ketones, methyl, ethyl, $\alpha,\beta$-unsaturated, cyclic, bicyclic, heterocyclic, and aromatic, except the sterically hindered isopropyl ketones and related ketones containing two sec-alkyl groups attached to the carbonyl group, undergo enolboration successfully. The enol borinates, generated instantaneously with concurrent formation and precipitation of triethylammonium chloride, react readily with aldehydes at temperatures as low as −78 °C, comparable to the behavior of the organoboron triflates previously utilized for such enolboration. The remarkable reactivity, regioselectivity, stereoselectivity, ease of preparation and handling, and the greater stability of dicyclohexylchloroborane all make it a preferred reagent for enolboration.

Enol borinates are highly reactive and are used as important intermediates in organic synthesis.[3-7] Developing simple methodologies for generating enol borinates has been a challenge to organic chemists. One of the methodologies involves the reaction of ketone with a suitable organoboron derivative, $R_2BX$, having a good leaving group, in the presence of a suitable tertiary amine. Various reagents employed previously are $R_2BOTf$,[7] ethylene chloroboronate,[8] $ROBCl_2$,[9] $BCl_3$,[9] and $PhBCl_2$.[10] However, these reagents are either difficult to prepare in the pure form or give only a moderate yield of the desired enolates. These limitations of the available reagents together with the lack of availability of boron reagents to achieve selective formation of *E* enol borinates suggested a search for new boron reagents possessing better selectivity and reactivity while being easily accessible.

Dialkylboron triflates have been widely used for enolboration. However, these reagents must be freshly prepared each time prior to their use. On standing for 3-4 weeks, the original colorless reagent becomes colored and the $^{11}B$ NMR shows many peaks. On the other hand, the $R_2BCl$ reagents show the same single $^{11}B$ NMR peak even after 1 year. The preparation of $R_2BCl$ reagents is also easy.[11] We have prepared and used various $R_2BX$ reagents in our laboratory for asymmetric reduction,[12] asymmetric opening of *meso*-epoxides,[13] and synthesis of secondary amines.[14] Our examination of various $R_2BCl$ reagents for the enolboration of representative classes of carbonyl compounds suggested dicyclohexylchloroborane, $Chx_2BCl$, as the preferred reagent in the presence of triethylamine.[15] A pleasant bonus from this exploration was the unexpected achievement of a considerable control of enolate geometry.[16] Therefore, it appeared appropriate to explore the applicability of $Chx_2BCl/Et_3N$ for the enolboration of various classes of ketones. This paper reports the successful regio- and stereoselective enolboration of a wide variety of ketones with $Chx_2BCl/Et_3N$.

## Results and Discussion

The present study explores the following classes of ketones for the enolboration using $Chx_2BCl$ and $Et_3N$: (i) methyl ketones; (ii) ethyl ketones; (iii) isopropyl ketones; (iv) $\alpha,\beta$-unsaturated ketones; (v) cyclic ketones; (vi) bicyclic ketones; (vii) heterocyclic ketones, and (viii) aromatic ketones. The detailed study which led to the selection of

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(2) Present address: Department of Chemistry, University of California, Santa Cruz, CA 95064.
(3) (a) Hirama, M.; Masamune, S. *Tetrahedron Lett.* **1979**, *24*, 2225. (b) Van Horn, D. E.; Masamune, S. *Tetrahedron Lett.* **1979**, *24*, 2229.
(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) Fenzl, W.; Köster, R. *Liebigs Ann. Chem.* **1975**, 1322. (b) Reetz, M. T.; Kunisch, F.; Heitmann, P. *Tetrahedron Lett.* **1986**, *27*, 4721.
(6) (a) Hooz, J.; Linke, S. *J. Am. Chem. Soc.* **1968**, *90*, 5936. (b) Hooz, J.; Gunn, D. M. *J. Am. Chem. Soc.* **1969**, *91*, 6195.
(7) (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.
(8) (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.
(9) Chow, H.-F.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 604.
(10) Hamana, H.; Sasakura, K.; Sugasawa, T. *Chem. Lett.* **1984**, 1729.
(11) (a) Chandrasekharan, J.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1985**, *50*, 5446. (b) Brown, H. C.; Ravindran, N. *J. Am. Chem. Soc.* **1976**, *98*, 1785. (c) Brown, H. C.; Kulkarni, S. U. *J. Organomet. Chem.* **1979**, *168*, 281. (d) Brown, H. C.; Ravindran, N.; Kulkarni, S. U. *J. Org. Chem.* **1979**, *44*, 2417.
(12) Brown, H. C.; Park, W. S.; Cho, B. T.; Ramachandran, P. V. *J. Org. Chem.* **1987**, *52*, 5406.
(13) Joshi, N. N.; Srebnik, M.; Brown, H. C. *J. Am. Chem. Soc.* **1988**, *110*, 6246.
(14) Brown, H. C.; Midland, M. M.; Levy, A. B.; Suzuki, A.; Sono, S.; Itoh, M. *Tetrahedron* **1987**, *43*, 4079.
(15) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 499.
(16) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441.

0022-3263/92/1957-2716$03.00/0 

**Table I. Enolization of Methyl and Ethyl Ketones with $Chx_2BCl/Et_3N$[a]**

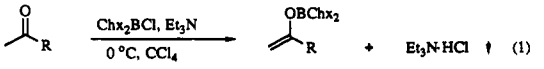
| R'COR R' | R | time (h) | enolate[b] | $^{11}B$ NMR[c] ($\delta$ ppm) | $^1H$ NMR[d] ($\delta$ ppm) | yield[e] (%) |
|---|---|---|---|---|---|---|
| | | | Methyl Ketones[f] | | | |
| Me | Me | 0.5 | 1 | 51 | 4.18, 4.30 | >97 |
| Me | Et | 0.5 | 2 | 51 | 4.12, 4.25 | 97 |
| Me | *n*-Pr | 0.5 | 3 | 52 | 4.18, 4.28 | 97 |
| Me | *i*-Pr | 0.5 | 4 | 53 | 4.10, 4.30 | 96 |
| Me | *i*-Bu | 0.5 | 5 | 51 | 4.20, 4.29 | 95 |
| Me | *neo*-Pen | 0.5 | 6 | 53 | 4.20 (s)[g] | 95 |
| Me | Ph | 0.7 | 7 | 50 | 4.55, 5.12 | 95 |
| | | | Ethyl Ketones[h] | | | |
| Et | Et | 0.5 | 8 | 53 | 4.65 (6.3) | 97 |
| Et | *i*-Pr | 0.5 | 9 | 54 | 4.67 (6.5) | 95 |
| Et | *i*-Bu | 0.5 | 10 | 54 | 4.64 (6.3) | 93 |
| Et | *t*-Bu[i] | 46 | 11 | 54 | 4.65 (6.4) | 60 |
| Et | Chx | 0.5 | 12 | 54 | 4.60 (6.6) | 94 |
| Et | Ph | 1.0 | 13 | 52 | 5.10 (7.4)[j] | 90 |

[a] The reactions were carried out in $CCl_4$ at 0 °C unless otherwise stated. [b] Refer to text for the individual structure. [c] $^{11}B$ NMR observed as a broad singlet. [d] Olefinic proton(s). [e] Determined by $^1H$ NMR using benzene as an internal standard (in representative cases, the yields were also confirmed by collecting and weighing the precipitated $Et_3N{\cdot}HCl$). [f] In the case of aliphatic methyl ketones, the olefinic protons appear as two merged doublets (unless otherwise stated) instead of the expected quartet with AA' or AB pattern. [g] Appears as a singlet. [h] The olefinic proton appears as a quartet (the value in parentheses corresponds to the coupling constant (Hz)). [i] Enolization at 25 °C. [j] Corresponds to *E* enolate (its *Z* enolate, obtained after isomerization, appeared at $\delta$ 5.5 ppm (q, $J$ = 7.4 Hz)).

$Chx_2BCl/Et_3N$ as the preferred reagent for regioselective and quantitative enolboration has been previously presented.[15]

The enolization was successfully carried out in simple solvents such as $CCl_4$, $CH_2Cl_2$, ether, THF, and hexane. However, $CCl_4$ was preferred for the present study since the $^1H$ NMR spectra can be directly recorded for the reaction mixture using benzene as an internal standard for quantification.[15] In the case of aromatic ketones, the external standard, benzene, is not necessary since the aromatic peak can be used for quantification. $^1H$ NMR (olefinic proton) was mainly used to establish the extent of enolboration, and $^{11}B$ NMR (borinate region) was also used to confirm the formation of enol borinates.

**Methyl Ketones.** Formation of regioselective enolates is one of the main problems in enolate chemistry. Usually kinetic enolates are generated by the abstraction of a less hindered proton by a strong, hindered base in an aprotic medium at very low temperature.[17] Mukaiyama has shown that the steric requirements on both $R_2BOTf$ and amine affect the regioselectivity in the enolization of methyl alkyl ketones.[7] Regioselective enolboration has also been realized in the Hooz reaction.[6] In the present study, simple methyl ketones, such as acetone, methyl ethyl ketone, methyl *n*-propyl ketone, methyl isopropyl ketone, methyl isobutyl ketone, methyl neopentyl ketone, and acetophenone, were successfully enolized. In all cases, regioselective and quantitative enolization was achieved exclusively on the methyl side, irrespective of the organic group (R) present on the other side of the ketone (eq 1).



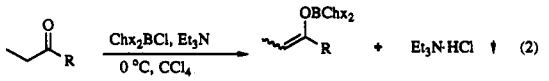

(1)

R = Me (1), Et (2), *n*-Pr (3), *i*-Pr (4), *i*-Bu (5), *neo*-Pen (6), Ph (7)

The results are presented in Table I.

(17) d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979.

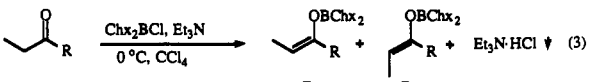
**Ethyl Ketones.** Diethyl ketone, ethyl isopropyl ketone, ethyl isobutyl ketone, ethyl *tert*-butyl ketone, ethyl cyclohexyl ketone, and propiophenone were chosen to represent this class of ketones. Except for ethyl *tert*-butyl ketone, all other ketones gave the corresponding enolborinates in >90% at 0 °C. Though the enolization of the sterically hindered ethyl *tert*-butyl ketone was very slow at 0 °C, about 60% enolization was achieved in 46 h at 25 °C. A similar slow enolboration has been reported in the literature[4b] for $n\text{-}Bu_2BOTf/i\text{-}Pr_2EtN$ which gave only 65% enolization at 35 °C in 30 min. In all cases other than R = Me, wherever a mixture of regioenolates is theoretically possible, >97% regioselectivity was achieved on the ethyl side (eq 2).




(2)

R = Et (8), *i*-Pr (9), *i*-Bu (10), *t*-Bu (11), Chx (12), Ph (13)

Evans has studied the enolboration of various ethyl ketones using different $R_2BOTf$ in the presence of $i\text{-}Pr_2EtN$ under various conditions.[4] In all the cases, he was able to get either *Z* enolates or a mixture of *Z* and *E* enolates. Corey has achieved the controlled generation of either *Z* or *E* enol borinates from propionate derivatives with $R^*_2BBr$.[18] However, not much is known for the controlled generation of *E* enol borinates from ketones. It is an achievement that our reagent, $Chx_2BCl/Et_3N$, gives predominantly or exclusively *E* enolates for most of the representative ethyl ketones. Indeed, except for diethyl and ethyl isobutyl ketones, all other ethyl ketones examined gave only *E* enolates (eq 3).



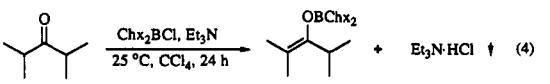

(3)

| | *Z* | *E* |
|---|---|---|
| (i) R = Et (8) | 21% | 79% |
| (ii) R = *i*-Bu (10) | 12% | 88% |
| (iii) R = *i*-Pr (9), *t*-Bu (11), Chx (12), Ph (13) | <3% | >97% |

Consequently, it appears that the steric requirements of R in $C_2H_5COR$ must contribute substantially to the control of enolate geometry. When R is bulky, the *E* enolate predominates. The results are summarized in Tables I and V.

The importance of our reagent, $Chx_2BCl/Et_3N$, has been well demonstrated by Paterson for the anti selective and quantitative aldolization of $\alpha$ chiral ethyl and methyl ketones with various aldehydes, such as aliphatic, $\alpha,\beta$-unsaturated, and aromatic aldehydes.[19]

**Isopropyl Ketones.** Enolization of more sterically hindered ketones, such as diisopropyl ketone, was extremely sluggish with $Chx_2BCl/Et_3N$. Only 10% enolization was realized for diisopropyl ketone, even after 24 h at room temperature (eq 4)




(4)

14 (10%)

The other sterically hindered ketones, such as isopropyl phenyl ketone, isopropyl cyclopentyl ketone, 2,5-dimethylcyclopentanone, and 2,6-dimethylcyclohexanone, also failed to undergo enolization at 0 °C with this reagent. To our knowledge, no study on the enolboration of such ketones with boron reagents has been described in the

(18) (a) Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976. (b) Corey, E. J.; Lee, D.-H. *J. Am. Chem. Soc.* **1991**, *113*, 4026.

(19) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121.

Table II. Enolization of α,β-Unsaturated Ketones with $Chx_2BCl/Et_3N$[a]

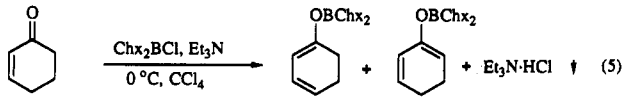
| ketone | time (h) | enolate[b] | $^{11}B$ NMR[c] (δ ppm) | $^1H$ NMR[d] (δ ppm) | yield[e] (%) |
|---|---|---|---|---|---|
| 2-cyclohexenone | 1.0 | 16 | 52 | 5.1 (t) | 85 |
| methyl vinyl ketone | 1.0 | 17 | 53 | 4.4 (s), 4.5 (s) | 65 |
| 4-phenyl-3-butyn-2-one | 0.5 | 18 | 51 | 4.9 (s), 5.0 (s) | 90 |

[a] The reactions were carried out in $CCl_4$ at 0 °C unless otherwise stated. [b] Refer to text for the individual structure. [c] $^{11}B$ NMR observed as a broad singlet. [d] Olefinic proton(s) of the enolate double bond. [e] Refer to footnote e in Table I.

literature. New organoboron reagents are being explored for the enolization of this class of ketones, and we appear to have overcome this difficulty.

**α,β-Unsaturated Ketones.** 1,4-Hydroboration of acyclic *E* α,β-unsaturated ketones with $R_2BH$ to give the corresponding *Z* enol borinates is now known.[20,21] Conjugate reduction of α,β-unsaturated carbonyl compounds by catecholborane also gives the corresponding *Z* enol borates.[22] Hydroboration of alkynes with $(RO)_2BH$ to give the corresponding alkenyl boronates followed by the oxidation with $Me_3NO$ to give the corresponding enol borates is also known.[23] But our aim was to test the enolization of α,β-unsaturated ketones to dienolates or ynenolates with $Chx_2BCl/Et_3N$.

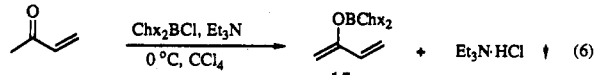
In the case of 2-cyclohexenone, the kinetic enolate **16** was obtained exclusively (eq 5). Enolization of this ketone




**15** (<3%) **16** (>97%)

with LDA is also known to give the less conjugated kinetic enolate.[17]

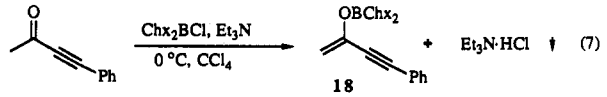
In the case of methyl vinyl ketone, only about 65% dienol borinate was detected (eq 6).




**17**

The moderate yield may be due to partial polymerization of the reactive product. Enolization of β-chlorovinyl ketones has also been achieved by *n*-$Bu_2BOTF$/*i*-$Pr_2EtN$.[24]

The acetylenic ketone, 4-phenyl-3-butyn-2-one, also yielded a clean ynenol borinate without any difficulty (eq 7). The results are summarized in Table II.




**18**

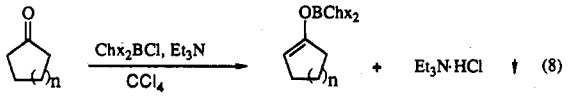
1,4-Addition of *B*-Br-9-BBN to α,β-unsaturated ketones to give the corresponding enol borinates has been reported in the literature.[25] However, a similar 1,4-addition reaction has not been observed in the present study.

**Cyclic Ketones.** In the case of unsubstituted cyclic ketones, the six-, seven-, and eight-membered ketones give the corresponding enol borinates in quantitative yield at 0 °C. But cyclopentanone requires a moderately higher temperature (25 °C) to give a quantitative yield (eq 8).

Table III. Enolization of Cyclic, Bicyclic, and Heterocyclic Ketones with $Chx_2BCl/Et_3N$[a]

| ketone | time (h) | enolate[b] | $^{11}B$ NMR[c] (δ ppm) | $^1H$ NMR[d] (δ ppm) | yield[e] (%) |
|---|---|---|---|---|---|
| cyclopentanone | 0.60[f] | 19 | 53 | 4.80 (s, br) | 97 |
| cyclohexanone | 0.75 | 20 | 53 | 4.92 (t, br) | 97 |
| cycloheptanone | 0.50 | 21 | 54 | 4.95 (t)[g] | 96 |
| cyclooctanone | 0.50 | 22 | 54 | 4.85 (t)[g] | 96 |
| 2-methylcyclohexanone | 0.75 | 23 | 52 | 4.87 (t, br) | 95 |
| 3-methylcyclohexanone | 0.75 | 25 | 50 | 4.80 (t, br) | 95 |
| norcamphor | 0.50[f] | 27 | 53 | 4.85 (d)[h] | 92 |
| camphor | 0.50[f] | 28 | 53 | 4.82 (d)[h] | 96 |
| tetralone | 0.75 | 29 | 52 | 5.22 (t)[i] | 95 |
| tetrahydrothiophen-3-one | 0.50[j] | 30<br>31 | 54 | 5.10 (s, br)<br>5.28 (s, br) | 90 |
| *N*-methylpiperidin-4-one | 1.00[k] | 32 | 53 | 4.95 (s, br) | 70 |

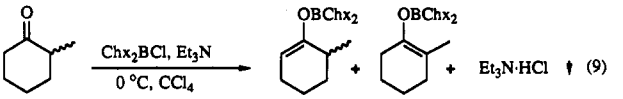
[a] The reactions were carried out in $CCl_4$ at 0 °C unless otherwise stated. [b] Refer to text for the individual structure. [c] $^{11}B$ NMR observed as a broad singlet. [d] Olefinic proton(s). [e] Refer to footnote e in Table I. [f] Enolization at 25 °C. [g] $J$ = 5.8 Hz. [h] $J$ = 3.4 Hz. [i] $J$ = 4.0 Hz. [j] Regioisomer 30:31 = 60:40. [k] Enolization without $Et_3N$.




n = 1 (**19**), 2 (**20**), 3 (**21**), 4 (**22**)

Only *E* enolates are formed from these cyclic ketones due to the geometrical requirements of the ring systems which would cause enormous strain in the *Z* enolates. The study of Evans on the influence of the metal center on the kinetic aldol reaction of the enolate derived from cyclohexanone reveals that essentially an equal mixture of syn and anti aldols was obtained with M = Li and $Al(Et)_2$, while 96% of the anti aldol was obtained with M = B-(Cpn)(Thx).[4b] Excellent stereoselection has also been observed with our reagent in the present study. Exclusively *E* enol borinates were realized from all these cyclic ketones, confirmed by the essentially exclusive formation of anti aldols in the reaction of benzaldehyde at −78 °C with the enol borinates from cyclopentanone (100%), cyclohexanone (98%), cycloheptanone (97%), and cyclooctanone (100%).[16]

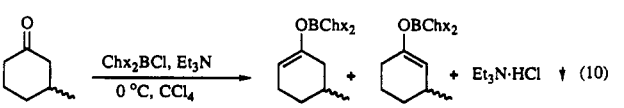
Excellent regioselectivity has been achieved with substituted cyclohexanones. In the case of 2-methylcyclohexanone, the kinetic enolate **23** was obtained exclusively (eq 9).




**23** (>97%) **24** (<3%)

A similar result was also achieved earlier by enolization with LDA.[26]

In the case of 3-methylcyclohexanone also, the enolization occurred exclusively from the least hindered side (eq 10). The results are summarized in Table III.




**25** (>97%) **26** (<3%)

(20) (a) Boldrini, G. P.; Mancini, F.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Chem. Soc., Chem. Commun.* **1990**, 1680. (b) Boldrini, G. P.; Bortolotti, M.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *Tetrahedron Lett.* **1991**, *32*, 1229. (c) Boldrini, G. P.; Bortolotti, M.; Mancini, F.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1991**, *56*, 5820.

(21) Matsumoto, Y.; Hayashi, T. *Synlett* **1991**, 349.

(22) Evans, D. A.; Fu, G. C. *J. Org. Chem.* **1990**, *55*, 5678.

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

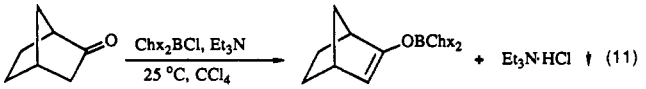
(24) Paterson, I.; Osborne, S. *Tetrahedron Lett.* **1990**, *31*, 2213.

(25) Shimizu, H.; Hara, S.; Suzuki, A. *Synth. Commun.* **1990**, *20*, 549.

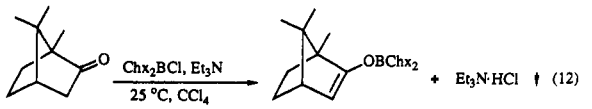
(26) House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1971**, *36*, 2361.

The effect of alkyl substituents at the 3-position in cyclohexanone on regioselectivity had been noted earlier in other reactions.[17]

**Bicyclic Ketones.** Norcamphor, camphor, and tetralone were taken to represent this class of ketones. The enolization of both norcamphor and camphor with $Chx_2BCl/Et_3N$ at 0 °C was slow, but it was essentially complete in 30 min at 25 °C (eqs 11 and 12).

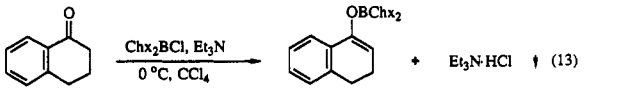



27




28

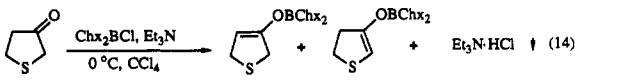
However, tetralone underwent a smooth and essentially instantaneous enolization at 0 °C (eq 13).




29

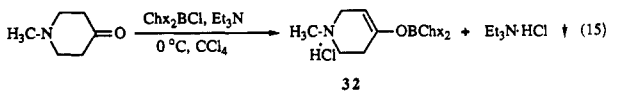
This new reagent is harmless toward strained, bicyclic systems, and no ring cleavage was noticed. The results are included in Table III.

**Heterocyclic Ketones.** A mixture of regioenolates is obtained in the case of tetrahydrothiophen-3-one (eq 14). The olefinic proton of the enolates appears at $\delta$ 5.10 ppm for **30** and at $\delta$ 5.28 ppm for **31**.




30 (60%) 31 (40%)

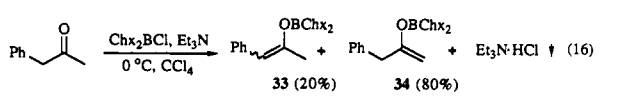
It was also possible to achieve a good enolization in the case of *N*-methylpiperidin-4-one without using an external amine. The intermolecular abstraction of the proton by the basic nitrogen of the starting amino ketone results in the formation of the enol borinate amine hydrochloride as a precipitate (eq 15).




32

No C–S or C–N bond cleavage was observed with this reagent in these ketones. The results are summarized in Table III.

**Aromatic Ketones.** Some representative aromatic ketones were enolized to test for the regio- and stereoselective and quantitative enolboration with $Chx_2BCl/Et_3N$. The conversion was >90% in all cases, and the results are given in Table IV. Only 3% *E* enol borinate has been earlier achieved for propiophenone with other boron reagents,[4] but $Chx_2BCl/Et_3N$ gives essentially exclusive *E* enol borinate.[16] In the case of alkyl benzyl ketones, the steric requirements of the alkyl group decide the regioselectivity. For example, in the case of benzyl methyl ketone, the enolization proceeds mainly from the methyl side (80%) even though the more acidic benzylic protons are available (eq 16).



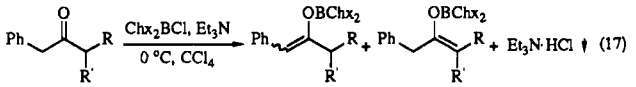

33 (20%) 34 (80%)

However, for benzyl ethyl ketone and benzyl isopropyl ketone, the enolization takes place exclusively on the benzylic side (eq 17). The results are summarized in Table IV.

**Table IV. Enolization of Aromatic Ketones with $Chx_2BCl/Et_3N$[a]**

| R′COR | | | | $^{11}B$ NMR[c] | $^1H$ NMR[d] | yield[e] |
|---|---|---|---|---|---|---|
| R′ | R | time (h) | enolate[b] | ($\delta$ ppm) | ($\delta$ ppm) | (%) |
| Ph | Me | 0.7 | **7** | 50 | 4.55, 5.12 | 95 |
| Ph | Et | 1.0 | **13** | 52 | 5.10 (q)[f] | 90 |
| Bn[g] | Me | 1.0 | **33** | 52 | 4.20, 4.40 | 95 |
| | | | **34** | | 5.68 | |
| Bn | Et | 1.0 | **35** | 52 | 5.73, 5.59 | 94 |
| Bn | Ph | 1.0 | **37** | 53 | 6.40, 6.20 | 92 |
| Bn | *i*-Pr | 1.0 | **38** | 52 | 5.60 | 90 |

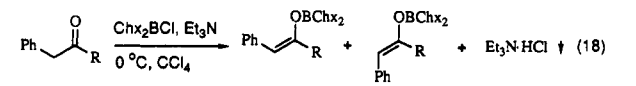
[a] The reactions were carried out in $CCl_4$ at 0 °C unless otherwise stated. [b] Refer to text for the individual structure. [c] $^{11}B$ NMR observed as a broad singlet. [d] Olefinic proton (singlets unless otherwise mentioned). [e] Refer to footnote e in Table I. [f] Refer to footnote i in Table I. [g] Refer to Table V for the individual $^1H$ NMR data of the *Z* and *E* enol borinates of the benzyl ketones.




(i) R = H, R′ = Me 35 (>97%) 36 (<3%)
(ii) R = R′ = Me 38 (>97%) 39 (<3%)

In cases where the enol borinates contain olefinic proton(s), the quantification was done directly from the $^1H$ spectra of enol borinates recorded from the reaction mixture, and the $^{11}B$ NMR spectra also confirmed the formation of enol borinates. In cases where there is no olefinic proton in the enol borinates, for example when R = R′ = Me in the above ketone, the formation of enol borinates was confirmed directly by the $^{11}B$ NMR but the quantification was done indirectly by examining the $^1H$ NMR spectra of their benzylaldehyde aldol products.

Interesting results have also been obtained for the stereochemistry of the enol borinates derived from the various benzyl ketones. As observed earlier for ethyl ketones, in the case of alkyl benzyl ketones also, the steric requirements of R in $PhCH_2COR$ play a vital role in controlling the enolate geometry. When R is bulky, the *E* enolate predominates (eq 18).




(i) R = Me $33^Z$ (>97%) $33^E$ (<3%)
(ii) R = Et $35^Z$ (60%) $35^E$ (40%)
(iii) R = Ph $37^Z$ (20%) $37^E$ (80%)
(iv) R = *i*-Pr $38^Z$ (<3%) $38^E$ (>97%)

By changing R from Me to *i*-Pr, in addition to a better regioselectivity, a complete reversal in enolate geometry is also achieved. The results are summarized in Table V.

**Determination of the Enolate Geometry.** Except in the case of enolates from benzylic ketones, the olefinic protons of both *Z* and *E* enolates exhibit essentially identical chemical shift. Therefore the *Z*/*E* ratio of the enol borinates could not be directly determined by $^1H$ NMR. Aldol reactions of boron enolates are highly stereoselective with the *Z* and *E* enolates giving syn and anti aldols respectively.[4,16] Therefore, an indirect method was used to find this ratio from the syn/anti ratio of the corresponding aldol products formed by the treatment with benzaldehyde.[15,16] The chemical shift and coupling constant of the carbinol protons (in this case benzylic) of these syn and anti aldols are different.[27] Consequently, the

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

Table V. Results of the Enolate Geometry of the Enol Borinates Derived from Various Ethyl and Benzyl Ketones

| R'COR | | $^1$H NMR[a] | ($\delta$ ppm) | % enolate[b,c] | | yield[d] |
|---|---|---|---|---|---|---|
| R' | R | syn/*Z* | anti/*E* | *Z* | *E* | (%) |
| Et | Et | 5.01 (4.4) | 4.72 (8.4) | 21 | 79 | 97 |
| Et | *i*-Pr | 4.63 (6.0) | 4.43 (8.6) | <3 | >97 | 90 |
| Et | *i*-Bu | 5.00 (4.5) | 4.71 (8.2) | 12 | 88 | 90 |
| Et | *t*-Bu | 4.80 (4.0) | 4.68 (8.0) | <3 | >97 | 56 |
| Et | Chx | 4.81 (5.0) | 4.63 (8.0) | <3 | >97 | 90 |
| Et | Ph | 5.08 (4.0) | 4.88 (8.0) | <3 | >97 | 87 |
| Bn | Me | 5.68 | | >97 | <3 | 91 |
| Bn | Et | 5.73 | 5.59 | 60 | 40 | 90 |
| Bn | Ph | 6.40 | 6.20 | 20 | 80 | 88 |
| Bn | *i*-Pr | | 5.60 | <3 | >97 | 87 |

[a] Corresponds to the benzylic proton (doublet) of the benzaldehyde aldol products in the case of ethyl ketones (value in parentheses corresponds to the coupling constant (Hz)) and to the olefinic proton (singlet) of the enol borinate in the case of benzyl ketones. [b] Based on the syn/anti ratio of the benzaldehyde aldols in the case of the ethyl ketones. [c] 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 (see Discussion: Precision of the Analytical Procedure). [d] Determined from the $^1$H NMR spectra (not isolated yield).

crude reaction mixture (after the standardized workup) was analyzed as such by $^1$H NMR to give this ratio precisely.

As reported earlier for aromatic carbonyl compounds,[15,16] in the case of benzyl ketones also, it is possible to determine the *Z*/*E* ratio directly from the reaction mixture by $^1$H NMR since both *Z* and *E* enolates exhibit different chemical shifts. Therefore, for such ketones, the aldol reactions were not usually carried out to determine this ratio. (However, we did establish in a test case that the *Z*/*E* ratio by direct measurement of the $^1$H NMR of the benzylic enolate and that determined after the reaction with benzaldehyde was identical within the limits of the NMR instrument.[16]) The results of the enolate geometry of the enolborinates derived from the various ethyl and benzyl ketones are summarized in Table V.

## Conclusions

A facile enolization of representative classes of ketones with $Chx_2BCl/Et_3N$ has been demonstrated. This systematic study has revealed that enol borinates are generated essentially instantaneously with this reagent from the representative classes of ketones examined. In the case of unsymmetrical ketones, the preference for the deprotonation of the hydrogen $\alpha$- to the carbonyl group by $Et_3N$ is as follows: methyl > methylene > methine. This observed preference of deprotonation, in turn, results in an excellent regioselectivity of enolization of various unsymmetrical ketones. Good selectivity for *E* enolate geometry, which has not been described earlier for other reagents, is achieved for various ethyl ketones by this reagent. Only sterically hindered ketones, R'COR, with both R' and R being *sec*-alkyl, fail to undergo enolization by this reagent and modified organoboron reagents are being explored to achieve the enolization of such ketones. The impressive regio- and stereoselective and quantitative enolboration of various classes of ketones, together with other advantages, make $Chx_2BCl/Et_3N$ a valuable reagent in synthetic organic chemistry for achieving a clean enolboration of the great majority of ketones.

## 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 $CaH_2$. All ketones, except for methyl benzyl, methyl cyclopentyl, and ethyl *tert*-butyl ketones, were commercial products of the highest purity available.

The synthesis and characterization of $Chx_2BCl$ was presented in our earlier paper.[15] The special experimental techniques used in handling air- and moisture-sensitive compounds have been described elsewhere.[28] All of the following experiments were conducted under an inert atmosphere ($N_2$).

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

**Synthesis of Ketones.** The syntheses of methyl benzyl ketone and methyl cyclopentyl ketone were carried via the Grignard reaction on a suitable aldehyde, followed by the (two phase: ether–water) chromic acid oxidation of the corresponding alcohols.[29] Ethyl *tert*-butyl ketone was prepared directly by this oxidation of the corresponding alcohol (commercially available). Distillation provided >99% GC pure ketones, and $^1$H NMR spectra of these ketones confirmed the structures.

**General Procedure for the Enolization of Ketones Using $Chx_2BCl/Et_3N$.** A simple and general procedure for the enolization of all classes of ketones is described as follows. To a stirred solution of $Chx_2BCl$ (1.1 mL, 5.15 mmol) and $Et_3N$ (0.72 mL, 5.16 mmol) in $CCl_4$ (17 mL), cooled at 0 °C under $N_2$ atmosphere, is added the ketone (5.0 mmol) dropwise. The enol borinate is generated instantaneously with concurrent formation and precipitation of $Et_3N{\cdot}HCl$. An internal standard, benzene in $CCl_4$ (0.50–1.00 mL, 1.00 M, 0.50–1.00 mmol), is added (except for aromatic ketones) for quantification of the enol borinate by $^1$H NMR analysis. The molarity is adjusted to 0.2–0.3 M. The reaction mixture is stirred for the desired length of time (given in the tables) and transferred into a centrifuge vial through a double-ended needle (18 gauge). Centrifugation results in the separation of the enol borinate solution from $Et_3N{\cdot}HCl$. In representative cases, we have collected and weighed the precipitated $Et_3N{\cdot}HCl$. Essentially quantitative yields are obtained, in satisfactory agreement with the yields based on $^1$H NMR. The enol borinate solution was transferred into an NMR tube by a double-ended needle. $^1$H NMR analysis shows the extent of enolization. $^{11}$B NMR also confirms the formation of enol borinates.

**General Procedure for the Aldolization with Benzaldehyde.** To a solution of enol borinate in diethyl ether generated from 5.0 mmol of the ketone (only those ketones were studied where the enolate geometry was needed), using $Chx_2BCl/Et_3N$ as described above, is added benzaldehyde (5.0 mmol) dropwise at −78 °C, and the mixture is stirred for 2–3 h. Then the reaction mixture is allowed to warm overnight slowly to attain room temperature. The $^1$H NMR examination of the resulting solution shows the essential absence of residual benzaldehyde. Then 10 mL of methanol is added to dissolve the precipitate ($Et_3N{\cdot}HCl$) and 1.7 mL of $H_2O_2$ (30%) is added at 0 °C and stirred for 5–6 h at 25 °C. The solvent is then removed by a water aspirator (15–20 mm), and the reaction mixture is extracted with ether, washed with dilute HCl then water, and dried over anhyd $Na_2SO_4$. The solvent is removed, and the products are analyzed as such by $^1$H NMR to determine the syn/anti ratio. Providing the experimental procedure is followed precisely, no difficulty was encountered in obtaining reproducible results.

**Precision of the Analytical Procedure.** 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. For quantification, the integration value obtained for the olefinic proton(s) of the enol borinate is compared with that of benzene, the internal standard. In representative cases, we have collected and weighed the precipitated $Et_3N{\cdot}HCl$ and the results (yields) are essentially the same as that determined by the internal standard method. In representative cases, the

(28) 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.
(29) Brown, H. C.; Garg, C. P.; Liu, K.-T. *J. Org. Chem.* **1971**, *36*, 387.

results obtained with the T-60 were also compared with the 300-MHz and the results agree closely. For example, the T-60 analysis of the benzaldehyde aldol products from diethyl ketone showed 21% syn, 79% anti (Table V), as compared to the values of 21% syn, 79% anti and 20% syn, 80% anti obtained in two analyses with the 300-MHz instrument. In the case of ethyl isopropyl ketone, the T-60 analysis showed no peak corresponding to the minor isomer (syn) but a careful analysis with 300-MHz instrument showed 98% for anti and 2% for the syn aldol. In a number of cases, the enolization produced essentially one of a pair of isomeric enolates. Since it is difficult to see very small amounts of the minor component against the background with T-60 instrument, we have indicated the products to be <3% for the minor isomer and >97% for the major isomer, although the spectrum itself shows only the major isomer.

At this stage of our studies, our aim was to explore the generation of enol borinates and not to explore their applications to aldol reactions. However, the quantitative aldolization of chiral ketones with various aldehydes such as aliphatic, $\alpha,\beta$-unsaturated, and aromatic aldehydes with this reagent has already been demonstrated by isolating the products.[19] In the present study, the aldolization with benzaldehyde was used only as a tool to determine the enolate geometry. The $^1$H NMR spectra of the benzaldehyde aldol product mixture give the syn/anti ratio which essentially corresponds to the $Z/E$ ratio of the enol borinates. The syn/anti ratio of the isolated aldol products might be different from that of the crude product mixture since some of the aldol products might be lost during the separation process, and so no attempt was made to determine this ratio by purification.

**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 (**2, 7, 8, 13, 18, 22, 23, 29, 33, 34, 35, 37, 38**) and those of the corresponding benzaldehyde aldol products of the enol borinates (**8, 9, 12**) selected as representatives from each table (15 pages). Ordering information is given on any current masthead page.

# Oxacyclophanes Based on a *m*-Terphenyl Framework

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*Received November 19, 1991*

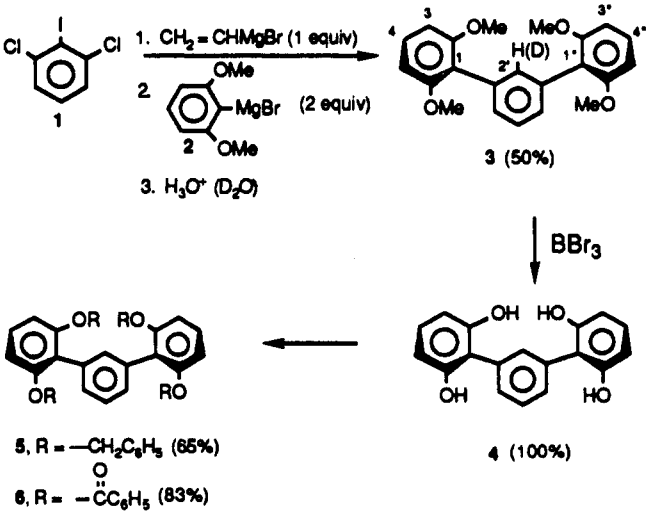
*m*-Terphenyl tetraphenol **4** (Scheme I) and tetrabenzyl alcohol **19** (Scheme IV) were efficiently synthesized from 2,6-dichloroiodobenzene and an appropriate aryl Grignard, using tandem aryne technology. Each tetrol was used to construct bicyclic oxacyclophanes by linking the 3,3″ and 5,5″ substituents with bis-alkylating or acylating agents. Examples are **7, 14, 15,** and **20–24**. Only the meta isomer of xylylene dichloride formed a bicyclic oxacyclophane with **4**; the ortho and para isomers gave polymers. However all three isomers gave oxacyclophanes (i.e., **10–12**) with the diphenol **9** (only one link across the *m*-terphenyl framework) and bicyclic oxacyclophanes with **19** (i.e., **20–22**), where each link contains two additional atoms. Para-linked **12** and **21** show restricted rotation of the *p*-xylylene rings. Two noninterconvertible conformers were obtained when the *m*-xylylene linking group contained a vicinal methoxy substituent (i.e., **15uu** and **15ud**).

*m*-Terphenyls appropriately substituted in the "outer" rings form an excellent base for the construction of novel cyclophanes (cuppedophanes[1a–c] or cappedophanes[1a,b,d]). The required *m*-terphenyls can be assembled in just a few steps, the first one being the tandem aryne addition of an aryl Grignard reagent to a 1,2,3-trihalobenzene.[2] In examples described to date, cyclophanes were prepared in which the links between the "outer" *m*-terphenyl rings contained sulfur[1a,b] or nitrogen[1c] atoms. We describe here the first examples of oxacyclophanes with this design.[3]

## Results and Discussion

The first template to be used as the framework for oxacyclophane construction was tetraphenol **4**. It was synthesized (Scheme I) in two steps from 2,6-dichloroiodobenzene (**1**).[4] Treatment of **1** with 1 equiv of vinylmagnesium bromide at −22 °C gave (2,6-dichlorophenyl)magnesium bromide which, when added to a refluxing THF solution of (2,6-dimethoxyphenyl)magnesium bromide, underwent tandem aryne elimination–nucleophilic addition to give, after aqueous quench, 2,2″,6,6″-tetramethoxy-*m*-terphenyl (**3**) in 50% yield. $^1$H and $^{13}$C NMR spectra confirmed the molecule's $C_{2v}$ symmetry. The proton spectrum showed a singlet for the four methoxyls and a mutually coupled doublet and triplet for the $H_{3,3'',5,5''}$

Scheme I




(1) (a) Vinod, T. K.; Hart, H. *J. Am. Chem. Soc.* **1988**, *110*, 6574–6575. (b) Vinod, T. K.; Hart, H. *J. Org. Chem.* **1990**, *55*, 881–890. (c) Vinod, T. K.; Hart, H. *Ibid.* **1990**, *55*, 5461–5466. (d) Vinod, T. K.; Hart, H. *Ibid.* **1991**, *56*, 5630–5640.

(2) (a) Du, C.-J. F.; Hart, H.; Ng, K.-K. D. *J. Org. Chem.* **1986**, *51*, 3162–3165. (b) Du, C.-J. F.; Hart, H. *Ibid.* **1987**, *52*, 4311–4314.

(3) For a preliminary account, see: Grewal, R. S.; Hart, H. *Tetrahedron Lett.* **1990**, *31*, 4271–4274.

(4) Bolton, R.; Sandall, J. P. B. *J. Chem. Soc., Perkin Trans. 2* **1977**, 278–280.

0022-3263/92/1957-2721$03.00/0 