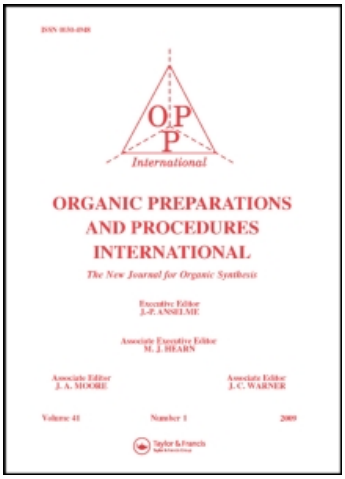

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THEXYL- AND ISOPINOCAMPHEYLHALOBORANES AS STEREOSELECTIVE REDUCING AGENTS

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THEXYL- AND ISOPINOCAMPHEYLHALOBORANES AS STEREOSELECTIVE REDUCING AGENTS

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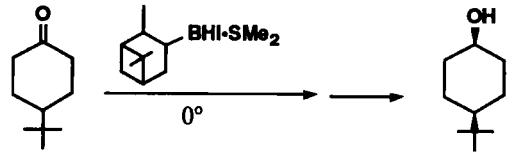
Thexylchloroborane-dimethyl sulfide[1] (ThxBHCl•SMe_2) and thexylbromoborane-dimethyl sulfide[2] (ThxBHBr•SMe_2) have been shown to be attractive selective reducing agents, especially for the conversion of carboxylic acids to the corresponding aldehydes. This important conversion led us to investigate their reducing characteristics in greater detail.[3,4] In the course of the exploration of their selectivity, we found that these reagents reduce cyclic ketones in a much higher degree of stereoselectivity than that realized in reduction with $ThxBH_2$.[5] Furthermore, the stereoselectivity of ThxBBr•SMe_2 is much higher than that of ThxBHCl•SMe_2.[3,4] These results seem to suggest that the steric size of halogen substituent in the monoalkylboranes plays an important role in the stereoselective reduction of cyclic ketones. Accordingly, we have extended this investigation to the reaction of the iodo derivative, and finally to the halo derivatives of monoisopinocampheylborane ($IpcBH_2$), in the hope of providing a new class of stereoselective reducing agents.

As Table 1 shows, the halogen substituent in the monoalkylboranes plays an important role in the stereoselective reduction of typical cyclic ketones as expected. The stereoselectivity increased dramatically with increasing steric size of the substituent. For example, in the reduction of 4-*tert*-

butylcyclohexanone thexylborane affords only 11% *cis*-4-*tert*-butylcyclohexanol, the less stable isomer.[5] However, the substitution of a chlorine atom for hydrogen in thexylborane exerts a tremendous stereoselectivity enhancement (to 66%). Furthermore, the stereoselectivity increases consistently with increasing size of the halogen substituent, approaching 99%. Similarly, the monoisopinocampheylhaloboranes reduce the cyclic ketones examined to the corresponding alcohols in high stereoselectivity. Finally, the iodo derivatives, ThxBHI•SMe_2 and IpcBHI•SMe_2 achieved highly



99.9% *cis*

stereoselective reductions with representative cyclic ketones. Such stereoselectivities are comparable to the results previously achieved at 0° with trialkyl- and alkylalkoxyborohydrides.[6]

TABLE 1. Stereoselective Reduction[a-c] of Cyclic Ketones with Thexylhaloborane-Dimethyl Sulfide (ThxBHX•SMe_2) and Isopinocampheylhaloborane-Dimethyl Sulfide (IpcBHX•SMe_2) in Tetrahydrofuran at 0°

		X in ThxBHX•SMe_2			X in IpcBHX•SMe_2		
Ketone	$ThxBH_2$[d]	Cl	Br	I	Cl	Br	I
cyclohexanone							
-,2-methyl	47-50	94.5	97.5	99	79	91	98
-,3-methyl		68.5	81	93	77	82	96
-,4-methyl		56.5	77	89	69	73	90
-,4-*tert*-butyl	11	65.5	78.5	99	85	95.5	99.9
-,3,3,5-trimethyl		97	98	99	70	92.5	99.5
norcamphor	92	98.5	99	99.9	88	99	99.7
camphor	80	95	97	99	85	94	98

a) A 2:1 ratio for reagent:ketone was utilized. b) The yields of alcohols were more than 95%. c) The figures are percentage of the less stable isomers. d) Data taken from ref 5.

EXPERIMENTAL SECTION

All glassware used was dried thoroughly in an oven, assembled hot, and cooled under a stream of dry nitrogen prior to use. All reactions and manipulations of air- and moisture-sensitive materials were carried out under a dry nitrogen atmosphere. All chemicals were commercial products of the highest available purity, which were further purified by standard methods before use. Tetrahydrofuran (THF) was distilled from benzophenone-sodium ketyl. Monochloroborane-dimethyl sulfide ($BH_2Cl•SMe_2$) and monobromoborane-dimethyl sulfide ($BH_2Br•SMe_2$) were used directly as received from Aldrich. ^{11}B NMR spectra were recorded on a Bruker WP80 SY spectrometer. The chemical shifts are with

reference to BF_3•OEt_2. GC analyses were carried out with a Varian Model 3300 FID chromatograph equipped with a Varian 4400 integrator/plotter. The alcohol products were analyzed with a 15 m capillary column of Carbowax 20 M.

Preparation of Monoiodoborane-Dimethyl Sulfide (BH_2I•SMe_2)[7].- An oven-dried, 2-L, rounded-bottomed flask, equipped with a side arm, a dry ice condenser, and adaptor connected to a mercury bubbler, was cooled to 0° under a stream of nitrogen. In the flask was placed 100 mL of CS_2 and 150 mL of BH_3•SMe_2 (10 M, 1.5 mol). The flask was maintained at 0° by immersion in ice-water bath. To this flask was added a precooled I_2 solution (192 g, 0.75 mol) in CS_2 (750 mL) slowly using a double-ended needle. After hydrogen evolution was completed, the solvent was evaporated under reduced pressure. Fractional distillation yielded 241 g of BH_2I•SMe_2 (80% yield): bp. 56-57° (0.1 mmHg); ^{11}B NMR: δ -20.5 (t, J_{B-H} = 136 Hz).

Preparation of Alkylhaloborane-Dimethyl Sulfide (RBHX· SMe_2).-The following procedure for the preparation of thexyliodoborane-dimethyl sulfide (ThxBHI•SMe_2) is described as representative. An oven-dried, 100-mL, rounded-bottomed flask, equipped with a side arm, a condenser, and an adaptor connected to a mercury bubbler, was cooled to room temperature under a stream of nitrogen. To this flask was added 14 mL of BH_2I•SMe_2 (7.2 M, 100 mol) and 19 mL of CH_2Cl_2; 14.6 g of 2,3-dimethyl-2-butene (105 mmol) was added slowly to the solution with stirring at room temperature. The reaction was complete in 24 hrs, producing ThxBHI•SMe_2 in pure form: ^{11}B NMR δ-1.42 ppm (d, J_{B-H} = 120 Hz).

Stereoselective Reductions.- The following procedure was used to explore the stereoselectivity of these reagents. In a 25-mL, rounded-bottomed flask was placed 1.6 mL of a 2.5 M solution of ThxBHI•SMe_2 in CH_2Cl_2 (4.0 mmol). The flask was maintained at 0° by immersion in an ice-water bath. To this flask was added 0.23 g of 2-methylcyclohexanone (2 mmol) and the mixture was stirred for 24 hrs at 0°. The reaction mixture was then quenched by addition of water. The organoborane was oxidized by treatment with 4 mL of 3 M sodium hydroxide followed by the dropwise addition of 0.5 mL of 30% hydrogen peroxide. The aqueous layer was saturated with anhydrous potassium carbonate, and the organic layer was separated and dried. GC analysis revealed the presence of 98% 2-methylcyclohexanol containing 99% of the *cis* isomer.

In a larger-scale reaction, 5.6 g of 2-methylcyclohexanone (50 mmol) was added dropwise as a neat liquid to 30 mL of a 2.5 M solution of the reagent in THF (75 mmol) at 0°. The reaction mixture was then hydrolyzed with 10 mL of cold water. The mixture was treated with 30 mL of 6 M sodium hydroxide followed by the dropwise addition of 10 mL of 30% hydrogen peroxide. The aqueous layer was saturated with sodium chloride, and the organic layer was separated. Fractional distillation of the solution gave 4.8 g (84% yield) of essentially pure 2-methylcyclohexanol, bp. 167-168° (756 mm). GC examination revealed the presence of 99% *cis*- and 1% *trans*-2-methylcyclohexanol.

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BROMOACETALDEHYDE AND IODOACETALDEHYDE BY OZONOLYSIS OF ALLYL BROMIDE AND ALLYL IODIDE†

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Bromoacetaldehyde (**1a**) and its dimethyl acetal (**2**) are very useful intermediates for the synthesis of various heterocyclic compounds of special biological interest. For example, **1a** is used for the preparation of ethenoguanosine derivatives[2,3] and imidazo[1,2-c]quinazolines,[4] which represent reactions of α-aminopyrimidines with **1a** forming annulated 5-membered rings; **2** is utilized for the synthesis of Tamoxifen derivatives, useful as anticancer agents,[5] as well as for the synthesis of chromone derivatives as allergy inhibitors.[6] Bromoacetaldehyde (**1a**) can be prepared by heating parabromoacetaldehyde[7] or by bromination of acetaldehyde in dioxane followed by purification by preparative gas chromatography.[8] Because of the instability of **1a**, it is often better to use the dimethyl acetal **2**, for which a number of preparations have been reported. The most convenient route has been the addition of bromine to vinyl acetate or alkyl vinyl ethers.[9-15] For the preparation of iodoacetaldehyde (**1b**), only two old references are known, starting from chloroacetaldehyde and potassium