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Investigation of the factors controlling the regioselectivity of the hydroboration of fluoroolefins

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Either Markovnikov or anti-Markovnikov regioselectivity can be achieved at will during the hydroboration–oxidation of perfluoroalkyl(aryl)ethylenes by varying the hydroborating agent.

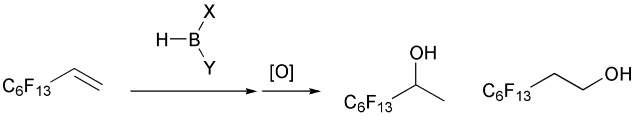
Dihaloboranes (Br_2BH and Cl_2BH) are unique hydroborating agents. For example, dibromoborane preferentially hydroborates 2-substituted-1-alkenes in the presence of unsubstituted terminal olefins.[1] In comparison, diisoamylborane, (Sia_2BH) furnishes the complementary product from the latter alkenes.[1] Again, Br_2BH chemoselectively hydroborates an internal acetylene in the presence of a terminal alkene, whereas a dialkylborane, 9-borabicyclo[3.3.1]nonane (9-BBN), provides the complementary product from the hydroboration of the olefin moiety.[2]

Recently we reported the reaction of dihaloboranes with fluorinated olefins, followed by oxidation providing Markovnikov hydration products, whereas the lone dialkylborane tested, 9-BBN, is inert to such alkenes.[3] We had surmised that this is entirely due to the effect of the fluorine atoms. Herein we have demonstrated that the reagent also plays an important role in determining the regioselectivity for the hydroboration of fluoroolefins.

A careful examination of the kinetics and mechanism of hydroboration suggested that 9-BBN might have been an improper reagent to hydroborate perfluoroalkylethylenes. Brown and coworkers have shown that the kinetic rate expressions and thus the mechanistic pathways of hydroboration with dialkylboranes depend on the reagent and substrate used. For example, with less nucleophilic olefins, the reaction sequence with $(9\text{-BBN})_2$ expressed a three-halves order kinetic rate ($-d[(9\text{-BBN})_2]/dt = K_{3/2}[(9\text{-BBN})_2]^{1/2}[\text{alkene}]$) in which the rate-determining step is the olefin hydroboration and *not the dimer dissociation*. However, it has been confirmed that $(Sia_2BH)_2$ reacts by means of a second order kinetic rate ($-d[(Sia_2BH)_2]/dt = K_1[(Sia_2BH)_2][\text{alkene}]$) regardless of alkene reactivity.[4] Contrary to that of 9-BBN, the kinetic evidence supported a direct attack of the substrate on the dimer, and *not* a prior dissociation followed by hydroboration.[4]

On the basis of the above rate expressions, we envisaged that $(Sia_2BH)_2$ might reveal different reactivity toward perfluoroalkylethylenes. Indeed, the reaction of 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-1-octene (**1a**) with $(Sia_2BH)_2$ proceeded to completion within 14 h at rt, as revealed by ^{11}B NMR spectroscopy. Alkaline H_2O_2 oxidation provided a 3 : 2 regioisomeric mixture favoring the anti-Markovnikov alcohol. In all probability, the lack of regioselectivity might be due to the disproportionation of the borane as it is unstable at rt for long periods of time (*vide infra* for regioselectivities with monoalkylboranes).[5] This prompted us to examine the relatively stable dicyclohexylborane (Chx_2BH).[6] As anticipated, the hydroboration was complete within 16 h at rt and oxidation furnished essentially pure 1°-ol! The generality of the anti-Markovnikov hydration of fluorinated olefins with sterically demanding Chx_2BH was further demonstrated by the reaction with 3,3,3-trifluoropropene (**1b**) and 3,3,4,4,5,5,6,6,6-nonafluoro-1-hexene (**1c**), which resulted in the formation of the 1°-ol in 94 and 95% regioselectivities in 80 and 85% yields, respectively.

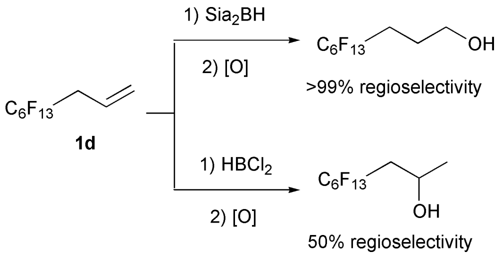
Clearly, the dihaloboranes might be exhibiting a special case of Markovnikov hydroboration–oxidation with fluoroolefins due to a combined electronic effects of the reagent and the subtrate. Interestingly, variants of $HBCl_2$ provided a mixture of regioisomeric products revealing a trend dependent on both the alkyl moiety and the Lewis acidity of the borane reagents. Monochloroborane ($ClBH_2$) provided a majority of the 2°-ol (84%).[3] The exchange of a halogen atom for a cyclohexyl moiety also led to 80% of 2°-ol. The moderately electrophilic and sterically hindered boranes, $ChxBH_2$[7]and thexylborane ($ThxBH_2$), readily hydroborated **1a** within 1 h at rt to afford a 1 : 1 regioisomeric mixture after oxidation [eqn. (1)].



(1)

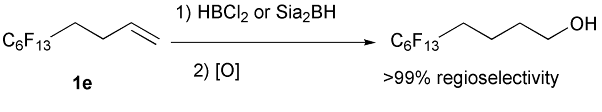
1a	X=Cl, Y=Cl	***98***	2
	X=H, Y=Cl	86	14
	X=Chx, Y=Cl	80	20
	X=Chx, Y=H	51	49
	X=Chx, Y=Chx	5	***95***

Additional support for the above hypothesis that the regioselectivities observed in the hydroboration of perfluoroalkylethylenes with dihaloboranes are due to combined effects of the substrate and the reagent was obtained by probing the hydroboration of fluoroolefins with inserted methylene spacers. Thus, hydroboration of 4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoronon-1-ene[8] (**1d**) with $HBCl_2$, followed by alkaline H_2O_2 oxidation provided a 1 : 1 mixture of 1°- and 2°- regioisomers[9] in 89% yield [eqn. (2)]. However, the dialkylborane provided pure 1°-alcohol. Thus, homologation of **1a** by a methylene entity significantly diminished the electron withdrawing effect of the perfluoroalkyl group when hydroborated with a dihaloborane.



(2)

Introducing a second methylene spacer between the alkene and the perfluoroalkyl entity[10] restored the anti-Markovnikov regioselectivity for hydroboration–oxidation with dichloroborane [eqn. (3)]. Hydroboration–oxidation of both **1d** and **1e** with Sia_2BH furnished essentially regiopure 1°-ol.[11]



(3)

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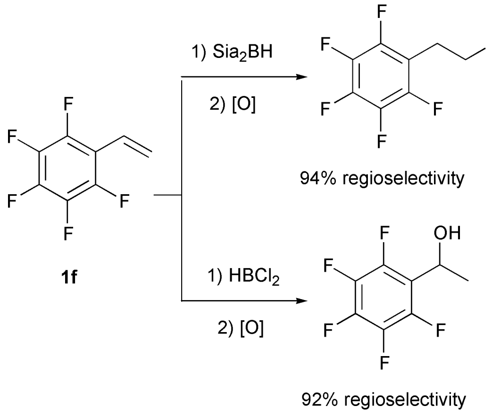
The results from the hydroboration–oxidation of **1a–e** with sterically and electronically diverse borane reagents are summarized in Table 1.

The hydroboration–oxidation of perfluoroarylethylenes is even more fascinating. 2,3,4,5,6-Pentafluorostyrene (**1f**) provided the Markovnikov product exclusively with $HBCl_2$ or $HBBr_2$.[3] In contrast to the inertness of **1a** toward 9-BBN, **1f** reacted within 96 h and furnished 92% of the 1°-ol (anti-Markovnikov product). The hydroboration of **1f** with Chx_2BH readily proceeded within *1 h* at rt and provided 85% of the 1°-regioisomer. By utilizing $(Sia_2BH)_2$, enhanced regioselectivities were observed (94%, 1°-ol) within *0.75 h* at 0 °C under identical conditions [eqn. (4)].



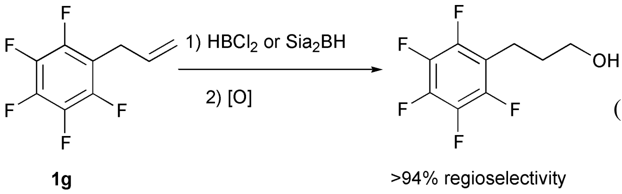
(4)

Table 1 Hydroboration–oxidation of **1a–1g** with representative borane reagents

				Product alcohol		
Olefin	Reagent	Solvent	Time/h	Yield (%)	2°-ol[a]	1°-ol
1a	BCl_2H	Hexane	inst.	90	**99**	**1**[b]
1a	BBr_2H	Hexane	inst.	90	**99**	**1**[b]
1a	$BClH_2$	Et_2O	24	86	84	16
1a	ChxBClH	Hexane	1	82	80	20
1a	$ChxBH_2$	THF	1	78	51	49
1a	$ThxBH_2$	THF	1	81	50	50
1a	Sia_2BH	THF	16	82	40	60
1a	Chx_2BH	THF	16	86	**5**	**95**
1a	9-BBN	THF	96	0	NR	
1b	BCl_2H	Hexane	inst.	82	**99**	**1**[b]
1b	BBr_2H	Hexane	inst.	82	**99**	**1**[b]
1b	Chx_2BH	THF	16	80	**6**	**94**
1c	BCl_2H	Hexane	inst.	84	**99**	**1**[b]
1c	BBr_2H	hexane	inst.	84	**99**	**1**[b]
1c	Chx_2BH	THF	16	85	**5**	**95**
1d	BCl_2H	Hexane	inst.	81	50	50
1d	Chx_2BH	THF	10	83	3	97
1e	BCl_2H	Hexane	inst.	88	**1**	**99**
1e	Chx_2BH	THF	4	79	**1**	**99**
1f	BBr_2H	Hexane	inst.	90	**94**	**6**[b]
1f	BCl_2H	Hexane	inst.	90	**92**	**8**[b]
1f	ChxBClH	Hexane	1	73	70	30
1f	$ThxBH_2$	THF	1	82	50	50
1f	CHx_2BH	THF	1	82	15	85
1f	9-BBN	THF	96	52	**8**	**92**
1f	Sia_2BH	THF	0.75	86	**6**	**94**
1g	BCl_2H	Hexane	inst.	78	**6**	**94**
1g	Sia_2BH	THF	0.75	88	**1**	**99**

[a] Determined by a combination of ^1H NMR, ^{19}F NMR, and GC analysis. [b] From ref. 3.

In order to delineate the effect of the pentafluorophenyl group, as performed previously with the aliphatic olefins, the regioselectivity of 3-(2′,3′,4′,5′,6′-pentafluorophenyl)-1-propene (**1g**) was examined under the standard $HBCl_2$and Sia_2BH conditions. Hydroboration of **1g** with $HBCl_2$, followed by alkaline peroxide oxidation provided an 86% yield of a regioisomeric mixture of 94:6 favoring the 1°-ol.[12] As expected, Sia_2BH also furnished the 1°-ol exclusively [eqn. (5)]. Obviously the effect of the pentafluorophenyl group is dependent on the conjugation of the olefin to the aromatic ring in that just by removing the perfluoroaryl group by one carbon the effect ceased almost entirely. The results for the hydroboration of **1f** and **1g** are also summarized in Table 1.



(5)

In summary, we have observed a rare example of complete regioselective control for a series of fluorinated *terminal* olefins by a judicious choice of borane reagent. By investigating the hydroboration of these olefins, a dramatic difference in reactivity between similar dialkylboranes, 9-BBN, Chx_2BH, and Sia_2BH has been observed. With Chx_2BH the hydroboration–oxidation of perfluoroalkyl(aryl)ethylenes *readily* proceeds to provide predominantly the anti-Markovnikov isomer, in contrast to the procedure involving $HBCl_2$. Consequently, it is now possible to conveniently synthesize either regioisomer of fluoroalkylboranes from the corresponding olefins by selecting the appropriate borane reagent. We are testing the limits of this selectivity and utilizing these intermediates in fluoroorganic syntheses.

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