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Intermolecular Additions of α-Boryl Radicals.[1]

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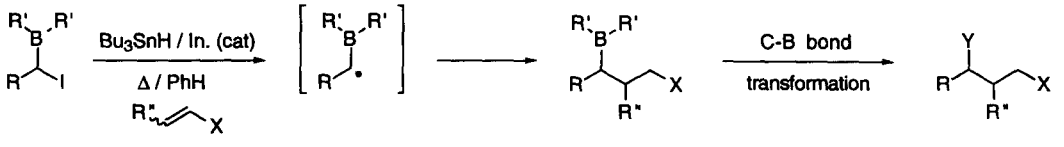
Abstract: The utility of α-boryl radicals **1** in intermolecular addition processes is described. Boronic ester substituted radicals are shown to add to both electron deficient and electron rich radical traps, and give high yields of homoallylboronic esters in radical allylation reactions.

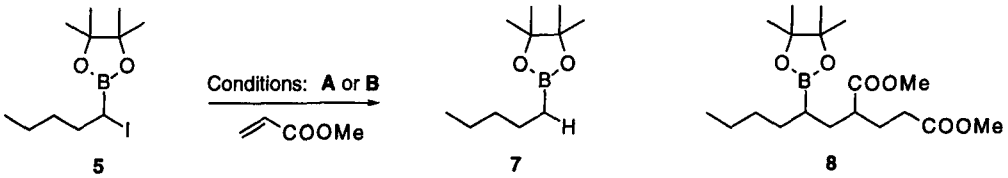
The formation of C-C bonds using free-radical methodology is an increasingly common strategy for the construction of complex molecules,[3] because of the relatively mild, non-polar conditions required, and the high reactivity and selectivity of carbon-centered radicals.[4] As part of a program aimed at developing free-radical and organoboron based methodologies,[5] we were interested in the possibility of conducting preparatively useful C-C bond forming reactions of α-boryl radicals. Surprisingly, little work has been described involving radical reactions of organoboron compounds. Radical attack at the boron atom of trialkylboranes has been demonstrated in conjugate addition reactions,[6] and the use of triethylborane/O_2 to initiate radical reactions at low temperatures is now a standard procedure.[7] Alkenylboranes are efficient radical traps in intermolecular addition reactions,[8,9] and in impressive recent work, Carboni and co-workers have reported their utility in intramolecular radical cyclizations.[9]

In this paper, we present our initial results in the intermolecular additions of boronic ester substituted radicals. Carbon, oxygen, nitrogen, sulfur and phosphorus substituted radicals have all been used in intermolecular addition reactions,[10] but to date there have been no direct methods for the controlled use of α-boryl radicals **1**. The general strategy we envisaged involves treatment of a radical precursor such as an iodide or pseudohalide **2**, with tributylstannane and an appropriate radical trap, in an intermolecular addition process, to yield the functionalized organoboranes **3** (Scheme 1). The advantage of this approach is that the reactivity and selectivity of the radical should be controllable through modification of the substituents R' on boron. Moreover, further transformation of the organoboron adducts **3**, through standard organoboron methodology gives adducts **4**, utilizing the boron substituent as a "dummy" substituent, providing a general route to a wide variety of valuable target molecules.

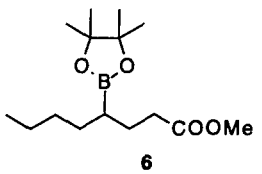


Scheme 1

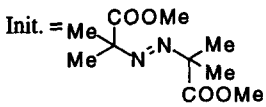
The α-iodoboronic pinacol ester **5** was chosen as an appropriate radical precursor for the initial studies, because boronic esters and acids are valuable synthetic intermediates[11] and are useful biomolecular analogs.[12] Moreover, the oxidative and hydrolytic stability of pinacol boronates, would allow for ready purification and analysis of the products. During the course of our work, Carboni reported a single example of an intramolecular radical cyclization using an α-iodoboronic ester.[9] α-Iodoboronic esters such as **5** are readily prepared in high overall yields, using the protocol developed by Matteson,[13] involving one-carbon homologation of boronic esters with dichloromethyllithium and subsequent Finkelstein reaction. Our initial choice of conditions to achieve the desired intermolecular addition reactions of the α-boronic ester radicals, was to use a catalytic amount of tributylstannane with sodium cyanoborohydride as a co-reductant, since this has been demonstrated to maintain a low concentration of H-atom donor, resulting in more efficient intermolecular addition, as well as minimizing the amount of toxic organostannane residues.[14] A variety of conditions were screened to optimize the yield of monoadduct **6**[15] over the unwanted reduced product **7** and telomer **8** (di-addition)[16] (Scheme 2).

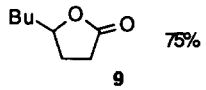


Conditions:
A: Bu_3SnH (0.03 eq.) / $NaCNBH_3$ (2.0 eq.) / Init. (0.15 eq.)
methyl acrylate (2 eq.) / t-BuOH (0.1 M solution)
B: Bu_3SnH (1.05 eq.) / Init. (0.15 eq.) / slow addition
methyl acrylate (3 eq.) / benzene (0.1 M solution)



Method	Temp.	6	7	8
A	85 °C	44%	30%	17%
A	60 °C	0%	quant.	0%
B	80 °C	40%	20%	25%





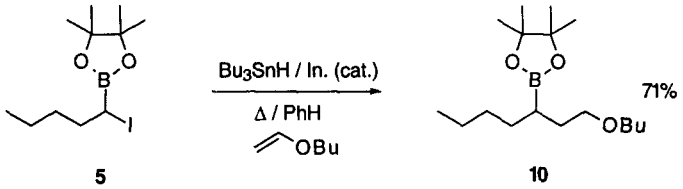
75%

Scheme 2

A modest yield of the desired product **6** (44%) was formed using the catalytic tributylstannane method **A** (See table: entry 1, Scheme 2). Dimethyl 2,2'-azobisisobutyrate was used as the radical initiator, which has an almost identical half-life profile to AIBN.[17] Varying the amount of methyl acrylate under these conditions led to a change in the relative formation of reduced to telomerized side-products **7** : **8**, but did not result in higher overall yields of **6**. Addition using acrylonitrile gave similar results, resulting in a 38% yield of the corresponding nitrile monoadduct. Decreasing the temperature of the reaction with methyl acrylate led to increasing yields of reduced product **7**, and at 60 °C this was the only product formed in the reaction (entry 2). Thus, unusually, ionic reduction of the substrate by the co-reductant was a competing side-reaction under the reaction conditions. Hydride delivery to the boron followed by a 1,2-migration may account for the facile reduction of this compound. However, ionic reduction was not expected to be a side-reaction using the stoichiometric tributylstannane method. Treatment of **5** under standard stoichiometric tributylstannane

conditions **B**, resulted in a 40% isolated yield of the monoadduct **6**, without an overall improvement in selectivity. As a simple demonstration of the utility of the organoborane adducts, oxidation of **6** and lactonization led smoothly to the γ-lactone **9**.

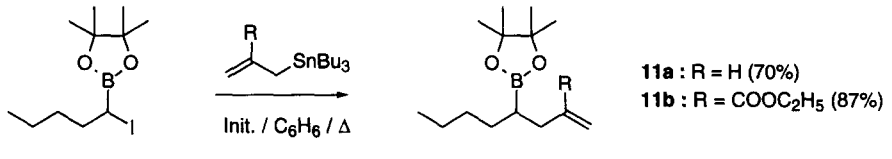
The difficulty in obtaining high yields of mono-adducts from the α-haloboronic esters implies that there is only a small difference in the selectivity of the substrate and adduct radicals in their addition to electron deficient alkenes. A similar finding has been noted for instance, in the reactions of α-phosphorylalkyl radicals.[18] Addition to electron-rich alkenes such as butylvinyl ether should avoid this problem, since the adduct radicals are relatively unreactive toward telomerization. This was confirmed by treatment of **5** with stoichiometric tributylstannane under slow-addition conditions, providing the monoadduct **10** in high yield (Scheme 3). α-Boronic ester radicals are thus ambiphilic in nature, resulting in facile addition to both electron-rich and electron-deficient radical traps. However in a competition experiment between methyl acrylate (2.0 equiv) and butylvinyl ether (2.0 equiv), addition to the electron-deficient alkene occurred preferentially, with formation of **6** in 43% yield, without any of the adduct **10** being detected.



5 **10**

Scheme 3

The so-called "fragmentation method" using allyl stannanes,[19] does not suffer from the problems of reduction and telomerization of traditional intermolecular radical additions, since the lifetimes of the intermediate radicals are not limited by the rate of hydrogen atom abstraction. Thus, treatment of **5** with allyl stannanes using standard conditions resulted in radical allylation to provide high yields of the corresponding homoallylic boronic esters **11a** and **11b**,[20] in 70% and 87% yields respectively (Scheme 4).



5

Scheme 4

In summary, we have demonstrated the utility of α-boryl radicals in intermolecular additions with alkenes and allyl stannanes. The boronic ester substituted radicals are readily generated from the corresponding α-iodoboronic esters, and are ambiphilic, with ready addition to electron deficient and electron-rich alkenes occurring under standard tributylstannane conditions. This methodology provides a new synthesis of functionalized boronic ester derivatives, important synthetic intermediates and valuable targets in their own right. Efforts are currently underway in these laboratories to explore further the factors which control the reactivity of α-boryl radicals, and to investigate their synthetic utility in diastereoselective and auxiliary controlled intermolecular radical additions.[21]

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References and Notes:

(1) This work was presented in part at the 79th Canadian Society for Chemistry Conference, Memorial University of Newfoundland, June 1996 (Abstract 559), and at the 11th International Conference on Organic Synthesis, Amsterdam, July 1996 (Abstract PO-203).

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(15) Selected spectral data for compound **6**: IR (neat) υ 2980, 2959, 2931, 2860, 1743 (s) (C=O), 1462, 1384, 1321, 1244, 1145, 1026, 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, J = 7.0 Hz, 3H), 0.92 (p, J = 5.5 Hz, 1H), 1.22 (s, 12H), 1.24 (m, 4H), 1.27 (m, 2H), 1.68 (q, J = 5.0 Hz, 2H), 2.29 (m, 2H), 3.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.02, 22.89, 24.73, 24.80, 26.27, 30.62, 31.16, 33.64, 51.38, 82.97, 174.32; HRMS (EI) calcd. for $C_{15}H_{29}BO_4$ 284.2159, found 284.2155.

(16) Smaller amounts of higher telomers were sometimes isolated from these reactions, but their low solubility generally excluded their isolation.

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(20) Selected spectral data for compound **11b**: IR (neat) υ 2980, 2924, 2861, 1722 (s) (C=O), 1630, 1461, 1448, 1384, 1370, 1321, 1145, 1026, 970, 864 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83-0.87 (t, J = 7.0 Hz, 3H), 0.83-0.88 (m, 1H), 1.20 (s, 12H), 1.27 (t, J = 7.0 Hz, 3H), 1.22-1.32 (m, 4H), 1.32-1.42 (m, 2H), 2.30-2.42 (m, 2H), 4.16 (q, J = 7.0 Hz, 2H), 5.52 (d, J = 1.5 Hz, 1H), 6.09 (d, J = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.09, 14.25, 22.93, 24.83, 24.87, 30.95, 31.25, 33.27, 60.46, 82.95, 124.39, 140.80, 167.27; HRMS (EI) calcd. for $C_{17}H_{31}BO_4$ 310.2315, found 310.2309.

(21) The development of stereocontrolled intermolecular free-radical addition reactions has been the focus of considerable attention recently. See references 4a and 10.

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