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Communication

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Radical Instability in Aid of Efficiency: A Powerful Route to Highly Functional MIDA Boronates

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Supporting Information

ABSTRACT: The inability of the sp^3 boron in MIDA boronates to stabilize an adjacent radical makes possible the efficient addition of a wide array of xanthates to vinyl MIDA boronate, leading to highly functionalized and diverse aliphatic organoboron structures. The lack of radical stabilization also allows the exchange of the xanthate in the adducts with a bromine. In one case, the bromine was substituted to generate a cyclopropyl MIDA derivative.

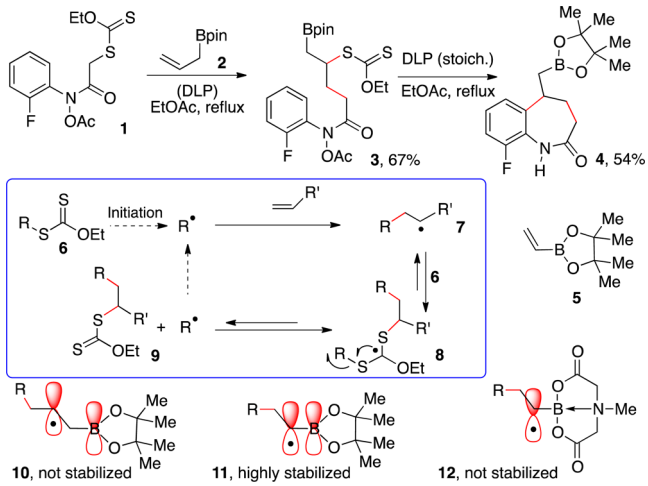
The chemistry of boron has all but revolutionized organic synthesis, from the total synthesis of natural products to medicinal chemistry to material sciences.[1] Indeed, the subtle and often intricate mechanistic beauty underlying organoboron chemistry has allowed the design of exceedingly powerful reactions.[2] In addition to facilitating so many transformations, boron is increasingly appearing in natural products and in synthetic drugs with important biological activities.[3] As for material sciences, applications range from self-healing polymers to hydrogels to lithium batteries to carbohydrate sensors and to controlled drug release.[4]

Paradoxically, despite the wide-ranging applications of organic boron compounds, the main limitation has been the restricted number of routes to functional organoboron derivatives, especially in the aliphatic series. Most of the established synthetic methods are not compatible with the presence of polar groups, and circuitous approaches are often necessary. Radical processes are known to be particularly tolerant of polar functionality, yet they have hardly been applied in this context.[5] In the present communication we describe a flexible, convergent approach that leads to unique, highly functional organoboron compounds.

As part of our work on the radical addition of xanthates,[6] we have examined the addition to allyl and vinyl pinacolato boronates.[7] While the addition to allyl pinacolato boronate **2** did not present any special difficulties (the conversion of **1** into **3** and then **4** in Scheme 1 is one example; DLP = lauroyl peroxide),[7c] reactions with the vinyl congener **5** gave modest yields and proved despairingly capricious.[7a,b]

The cause of this variance could be traced to the profoundly different nature of the intermediate adduct radicals. In the simplified mechanism in the box in Scheme 1, the addition of xanthates requires that adduct radical **7** be *less stable* than initial radical R• (neglecting polar effects in a first approximation). This ensures that radical **8** will preferentially collapse in favor of product **9** and sustain the chain by concomitantly regenerating

Scheme 1. Mechanism and Radical Stabilities



R•. This condition is particularly stringent for *intermolecular* additions.[8]

In the case of the allyl boronate, adduct radical **10** is comparable in stability to an ordinary secondary radical, with the influence of the boronate being only marginal. In additions to vinyl boronate **5**, in contrast, the unpaired electron in adduct **11** is stabilized by delocalization onto the empty p-orbital of the adjacent boron atom. Calculations give a radical stabilization energy (RSE) value of 10−11 kcal/mol for borylmethyl radical H_2BCH_2•, a value only slightly lower than that of a benzyl radical (RSE = 14−15 kcal/mol).[9a−c] Oxygen substituents decrease the RSE to about 6−7 kcal/mol.[9d] Nevertheless, this remains a rather strong stabilization, and the condition for success enunciated above regarding the relative stabilities of starting and adduct radicals is seldom met in additions to vinyl boronate **5**. Another limitation arises from the electrophilic nature of this alkene, caused by the empty p-orbital of the boron acting as an internal Lewis acid. This results in a polarity mismatch with radicals bearing useful electron-withdrawing groups such as ketones, esters, etc.

In principle, these limitations should disappear by using vinyl *N*-methyl imidodiacetic acid (MIDA) boronate **13** (Scheme 2), where the vacant orbital of the boron is filled by the lone electron pair from the amine and the boron hybridization changes from sp^2 to sp^3.[10] This neutralizes any stabilizing effect of the boron, so

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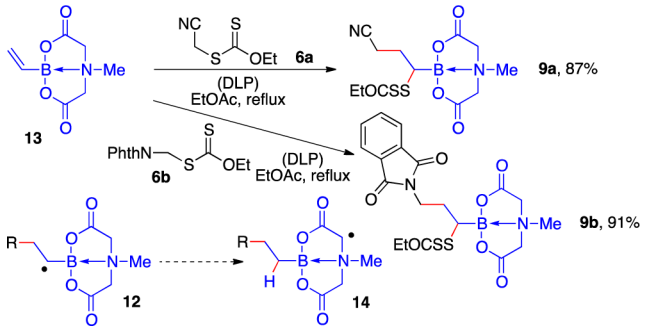
Scheme 2. First Additions to Vinyl MIDA Boronate



that adduct radical **12** (Scheme 1) becomes *less stable* than most incoming radicals R●.

These expectations were borne out in practice, as demonstrated by the additions in Scheme 2 involving two radicals with different electronic characteristics. The cyanomethyl radical derived from xanthate **6a** is electrophilic in nature, whereas the phthalimidomethyl radical from **6b** has a slight nucleophilic character.[11] Both additions proceeded smoothly to give the respective addition products **9a** and **9b** in high yield. Interestingly, in olefin **13**, the amine counteracts the stabilizing effect of the boron, and the boron in turn blocks the basicity of the amine and prevents it from ionically decomposing the xanthate and generating chain-breaking sulfur side-products. Another potential difficulty we were happy to avoid is the 1,5-hydrogen abstraction of one of the iminoacetyl hydrogen atoms in the MIDA part of the molecule.[12] This translocation would have led to stabilized capto-dative radical **14** (Scheme 2). Presumably (and fortunately), unfavorable geometrical constraints prevent radical **12** from adopting the correct conformation for a 1,5-hydrogen shift.

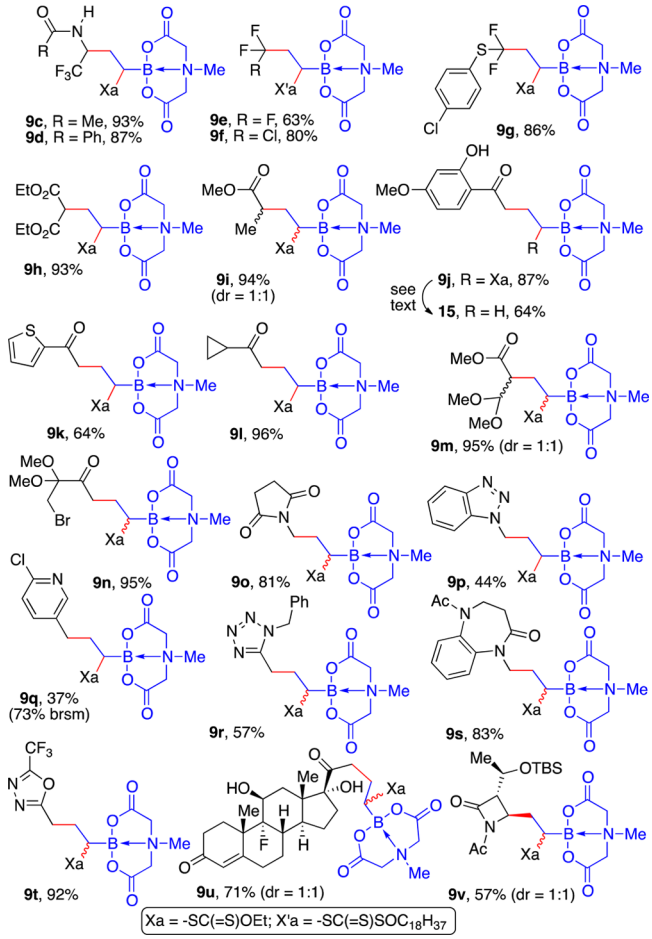
In both transformations shown in Scheme 2 and in most of the following examples, the products were isolated by mere filtration. The high crystallinity, stability to air, and compatibility with chromatography, as well as a tolerance for a broad range of commonly used reagents, are highly attractive practical features of MIDA boronates, which justify their rapidly increasing popularity in synthesis.[13,14]

The success of the preliminary experiments in Scheme 2 augured well for the possibility of accessing a vast array of densely functionalized MIDA boronates. Indeed, over the years, more than 200 xanthates bearing diverse functional groups have been examined. Each addition, therefore, can associate a MIDA boronate with a different combination of functionalities, as in the examples in Scheme 3.

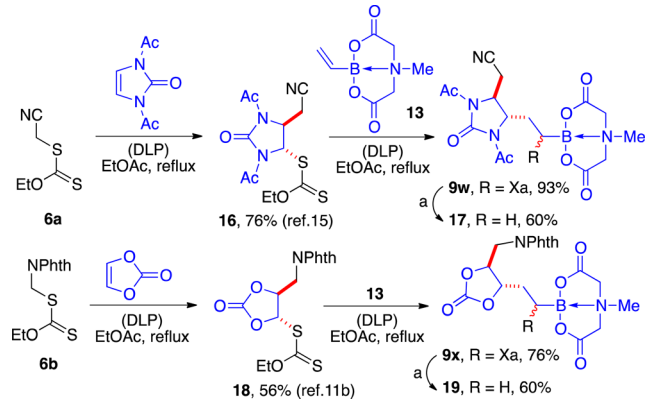
Addition products **9c**−**g** illustrate the introduction of various organofluorine groupings. Heterocyclic and heteroaromatic motifs can be incorporated, including benzotriazole **9p**, pyridine **9q**, tetrazole **9r**, and oxadiazole **9t**. Also noteworthy are adducts **9m** and **9n** featuring a masked aldehyde and an α-bromoketone, respectively. Finally, the obtention of steroid **9u** and β-lactam **9v** confirms the mildness of the experimental conditions. The yields are not only generally high, *they correspond on average to some of the best yields we have ever observed for intermolecular radical additions to any olefin*.

The complexity of the products can be considerably increased by performing a radical addition to an alkene prior to reaction with vinyl MIDA boronate **13** (Scheme 4). Thus, xanthates **16** and **18**, generated by addition to *N*,*N*-diacetyl imidazolone[15] and vinylidene carbonate, respectively, furnished the corresponding

Scheme 3. Additions to Vinyl MIDA Boronate



Scheme 4. Access to Complex MIDA Boronates



MIDA boronates **9w** and **9x** in high yield. In both cases, the xanthate group was reductively removed (**17** and **19**, respectively) to simplify the spectra. In these sequences, the adduct radical in one addition becomes the starting radical in the next. Hence, the relative stabilities of the radicals must follow the condition stated above. It is precisely *because the MIDA boronate group does not particularly stabilize an adjacent radical that the addition to vinyl MIDA boronate* **13** *can be placed last in the sequence of additions*. This would not be feasible with vinyl pinacolato boronate **5** where stabilization of the adduct radical by the vacant p-orbital of the boron would make it *more stable* than the starting radical.

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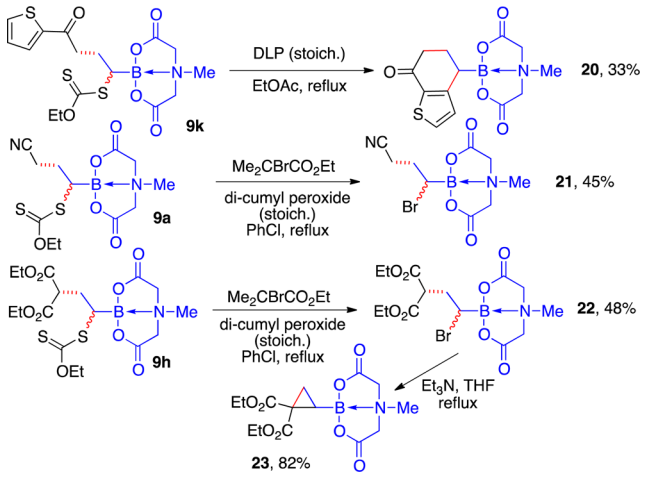
Attempts to exploit the presence of the xanthate to accomplish ring fusion to aromatic cycles were met with limited success. Thus, treatment of adduct **9k** with stoichiometric lauroyl peroxide furnished dihydrobenzothiophene **20** in only 33% yield (Scheme 5).[16a] A similar experiment on adduct **9j** failed to provide the corresponding tetralone; only the reduced compound **15** was isolated.[16b]

Scheme 5. Further Synthetic Variations



More interesting is the replacement of the xanthate in the adducts by a bromine using ethyl 2-bromoisobutyrate as the bromine atom transfer agent,[17] illustrated by the conversion of adducts **9a** and **9h** into bromo MIDA boronates **21** and **22**, respectively. Success again hinges on the fact that a MIDA boronate does not stabilize the adjacent radical center making the exchange of bromine exothermic and irreversible. This is yet another process that would not work well or not at all with the pinacolato boronates.

α-Halo organoboron compounds are precursors to α-amino-boronic acids, a few of which have useful biological properties,[3] and are substrates to powerful rearrangements developed by Matteson (the Matteson reaction).[18] Despite the moderate yield due to the concomitant formation of unidentified polar side-products, the present approach constitutes a simple two-step route to the rare α-bromo MIDA boronates. Furthermore, in the case of malonyl bromide **22**, treatment with Et_3N resulted in the formation of cyclopropyl MIDA boronate **23** in high yield. Cyclopropyl boronates readily undergo typical organometallic couplings and are rapidly emerging as an important subclass of organoboranes.[19]

Following the pioneering studies of Burke,[13a] and because of the strategic importance of the Suzuki–Miyaura and related couplings, most of the work on MIDA boronates has involved (hetero)aromatic and vinylic derivatives. Routes to aliphatic members have remained limited, despite recent results from the group of Yudin indicating the ability of primary aliphatic MIDA boronates to undergo sp^3–sp^2 couplings.[13c] The present radical approach is convergent and flexible and provides a unique access to a myriad of densely functionalized MIDA derivatives.[20] Moreover, the xanthate motif provides a direct entry into the rich chemistry of sulfur and can be directly exchanged for numerous other groups by a number of radical processes: not only hydrogen or bromine but also, in principle, arylsulfide,[21] azide,[22] oximinocarbinyl,[23] and functional allyl and vinyl groups.[24] From a broader perspective, the ability to bring into close proximity unusual combinations of functional groups should allow the discovery of new reaction pathways not hitherto observed.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures as well as a compilation of spectral and analytical data of all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b03893.

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Notes

The authors declare no competing financial interest.

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This article is dedicated with respect to the memory of Professor Yves Chauvin (Institut Français du Pétrole).

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