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A Modular Access to 1,2- and 1,3-Disubstituted Cyclobutylboronic Esters by Consecutive Radical Additions.

Jean Michalland,^{*[a]} Nicolas Casaretto^[b] and Samir Z. Zard^{*[a]}

In memory of Professors Duilio Arigoni and Jack Dunitz

- [a] J. Michalland, Prof. Dr. S. Z. Zard
Laboratoire de Synthèse Organique, CNRS UMR 7652, Ecole polytechnique, 91128 Palaiseau Cedex, France
E-mail : samir.zard@polytechnique.edu
- [b] Dr. N. Casaretto
Laboratoire de Chimie Moléculaire, CNRS UMR 9168, Ecole polytechnique, 91128 Palaiseau Cedex, France

Abstract: A modular approach to substituted cyclobutylboronic esters is described. It proceeds by successive intermolecular radical additions of xanthates to pinacolato 1-cyclobutenylboronate and to pinacolato bicyclo[1.1.0]but-1-ylboronate. Success hinges on tuning the stability of the α -boryl radical by exploiting the stabilizing influence of the trivalent boronic ester and the slightly destabilizing cyclobutane, which increases the σ -character of the radical. Reductive removal of the xanthate group finally provides a range of 1,2- and 1,3-disubstituted cyclobutylboronic esters. The contrast with cyclopropylboronic esters is striking, since the strong destabilization by the highly strained cyclopropane ring allows the first radical addition to take place but not the second. Furthermore, the first adducts are geminal xanthyl boronic esters that can be converted into cyclobutanones. This chemistry furnishes cyclobutylboronic esters that would be quite difficult to obtain otherwise and thus complements existing methods.

Introduction

Cyclobutanes have always been popular and challenging synthetic targets. They are key structural units in a variety of natural products,^[1] a number of which are endowed with interesting biological activity, and in a few synthetic pharmaceuticals^[2] (Scheme 1). Their structures possess the rigidity and metabolic stability found in aromatics and, at the same time, allow the exploration of 3-dimensional space. Cyclobutanes are thus extremely appealing non-classical isosteres of arene rings.^[3]

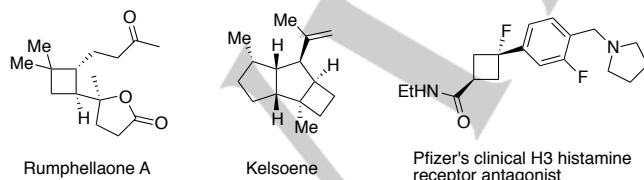
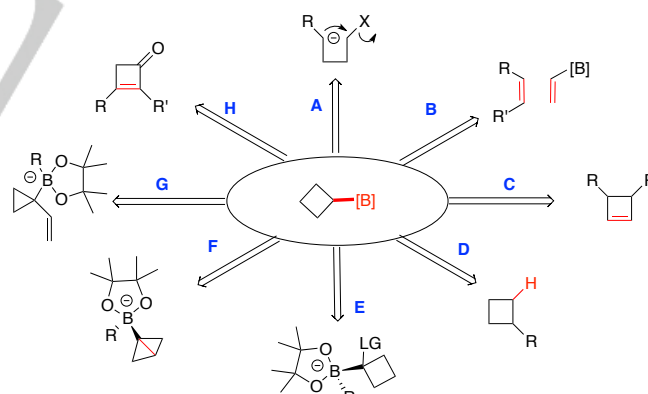


Figure 1. Examples of cyclobutane-containing natural products and pharmaceuticals.

Installing substituents on the cycle in a stereocontrolled fashion represents a serious synthetic challenge in general^[4] and, in the present context, stereodefined cyclobutylboronic esters have been particularly targeted as intermediates of some importance. In fact, the C-B bond is an incredibly versatile synthetic handle that can be turned into C-C, C-O, C-N or C-X bonds, most of the

time in a stereospecific manner^[5]. In a 2018 review,^[6] Tortosa *et al.* described the state of the art in stereoselective approaches to such scaffolds (Scheme 1), including: ring closure (**A**),^[7] [2+2] cycloadditions (**B**),^[8] functionalization of cyclobutenes (**C**),^[9] and C-H activation (**D**).^[10] Interestingly, several new routes were disclosed in just three years following this review, reflecting the vibrancy of this area of research. Thus, Liu *et al.* reported in 2019 an efficient method to access 2-aminocyclobutylboronic esters by photoisomerization of 1,2-azaborine.^[11] The Aggarwal group, another prominent contributor to this field, recently described various new methods: by metalation of a cyclobutane bearing a leaving group (**E**),^[12] by strain release from bicyclobutanes in a radical^[13] and ionic^[14] fashion (**F**), as well as by harnessing the power of 1,2-metallate shifts in a strain increase^[15] and a ring-expansion strategy (**G**).^[16] Finally, Hall *et al.* performed enantioselective conjugate borylation on substituted cyclobutenones and cyclobutene-1-carboxylates to access a wide variety of enantiopure cyclobutyl boronic esters (**H**).^[17]



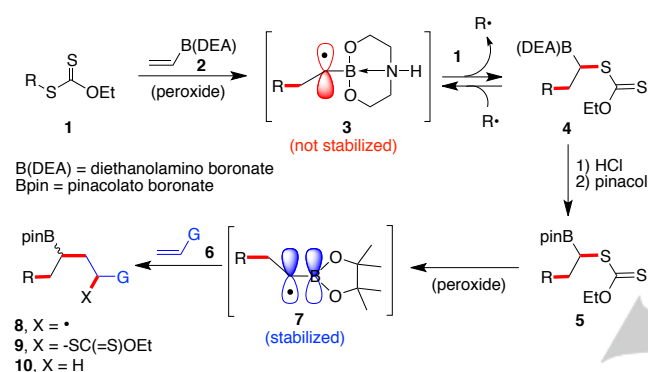
Scheme 1. Main routes to cyclobutylboronic esters.

Results and Discussion

Over the years, we applied the degenerative radical exchange addition-transfer of xanthates to access a variety of organoboron scaffolds.^[18] Our foray into the area of boronic esters started in fact when we examined extending our chemistry to the synthesis of tertiary boronic esters. Recently, we unveiled an approach relying on tuning the stability of a radical adjacent to the boron atom to produce primary and secondary boronic esters (Scheme 2).^[19] For the xanthate addition-transfer to be efficient, and neglecting for simplicity polar effects which could be important,

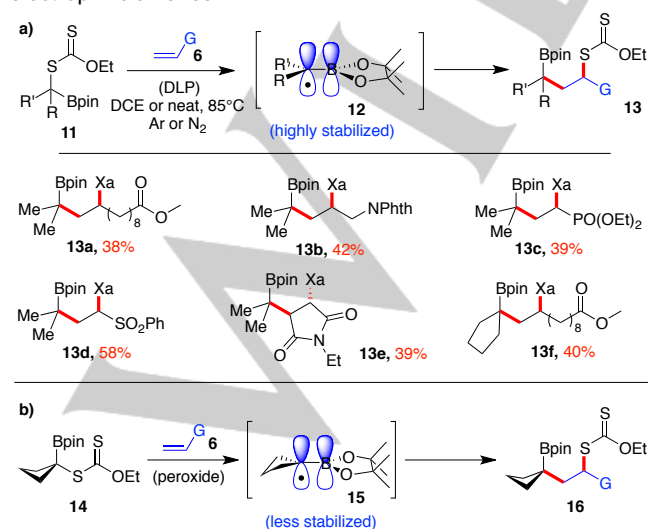
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the starting radical $R\cdot$ arising from xanthate **1** has to be *more* stable than adduct radical **3** arising from addition to alkene **2** since it is necessary to favor the equilibrium leading to adduct **4** by a reversible xanthate exchange with starting xanthate **1** (see the Supplementary Information for a more detailed discussion).^[20] This is usually the case because the diethanolamino boronate [B(DEA)] group does not stabilize adduct radical **3**, since the boron is sp^3 hybridized and does not contain a vacant orbital available for delocalization. In the second addition, however, the presence of the Bpin with an available vacant p-orbital stabilizes initial radical **7**, which now becomes more stable than adduct radical **8** resulting from the addition to the second alkene **6**. This modulation of the radical stabilities allows the intermolecular creation of two new C-C bonds and the production of highly functional organoboron derivatives **9**. If desired, the xanthate group can be readily reduced off by a variety of reagents to furnish simpler compounds **10**.



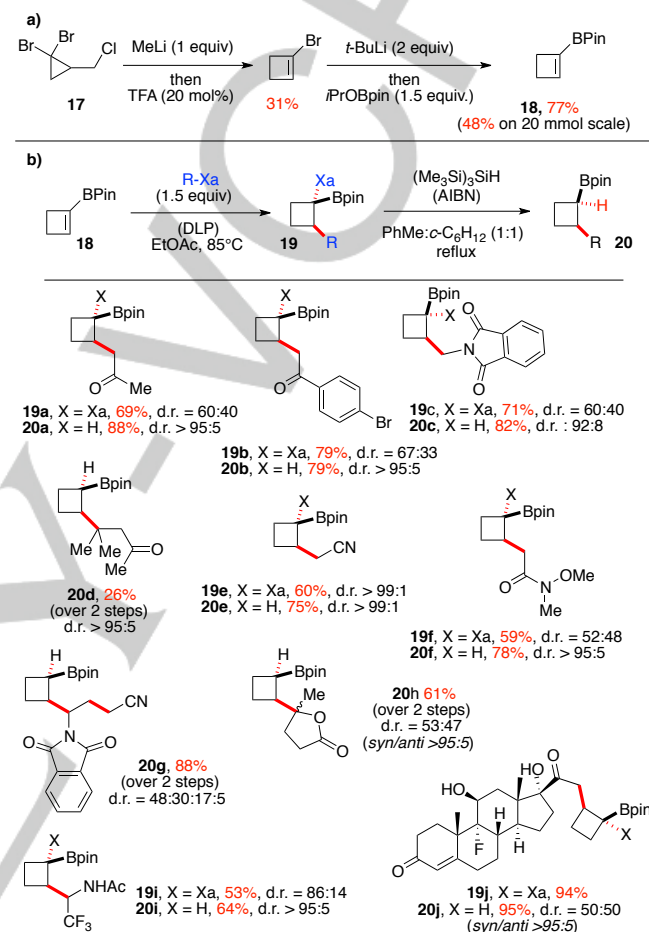
Scheme 2. Sequential radical additions to access secondary boronic esters.

The next logical step is to extend this strategy to the synthesis of *tertiary* boronic esters **13** (Scheme 3a). The corresponding radical **12** is now quite stabilized and the condition for success stated above should be even more easily satisfied. Indeed, several such boronic esters **13a-f** [Xa = $-\text{SC}(=\text{S})\text{OEt}$ throughout] could be prepared under initiation by di-lauroyl peroxide (DLP, also sold as lauroyl peroxide, Laurox® or Luperox®) in refluxing 1,2-dichloroethane (DCE), except for **13e** which was performed neat, without any solvent. Unfortunately, the reactions were disappointingly sluggish, requiring undue amounts of peroxide for completion, and the yields were moderate even with activated electrophilic alkenes.^[21]



Scheme 3. Radical additions of open-chain tertiary boronic esters and destabilization by the cyclobutyl ring [Xa = $-\text{SC}(=\text{S})\text{OEt}$].

Radicals **12**, now further stabilized by the additional alkyl group, have become in fact *too stable* (and bulky) and their reactivities in the addition step correspondingly diminished. Nevertheless, despite its failings, this approach to tertiary boronic esters **13** remains useful because of its directness.



Scheme 4. Synthesis and radical additions to cyclobutenylboronic ester **18** [Xa = $-\text{SC}(=\text{S})\text{OEt}$]. The d.r. were measured by NMR.

Notwithstanding these positive observations, expansion of the scope and utility of this approach requires some destabilization of tertiary radical **12** in order to increase its reactivity while at the same time fulfilling the key condition that the initial radical be more stable than the adduct radical. To this end, we examined (α -boryl)cyclobutyl xanthates **14** (Scheme 3b), since the ring strain increases the σ -character of the SOMO and thus decreases the stability of the corresponding radical **15** and increases its reactivity. The estimated difference in stabilization energy between the isopropyl and cyclobutyl radicals is around 1.7 kcal/mol in favor of the former.^[22] This value is similar in magnitude to the difference in stability between a tertiary and a secondary radical (the difference between a *t*-butyl and an isopropyl radical is about 1.3 kcal/mol),^[22c] so we anticipated that the destabilization by the strained cyclobutyl ring in radical **15** would compensate for the untoward stabilization due to the additional alkyl group in radical **13**. This would bring us to the favorable situation we encountered with secondary radicals **7** (Scheme 2) and allow us to access adduct **16** (Scheme 3b).

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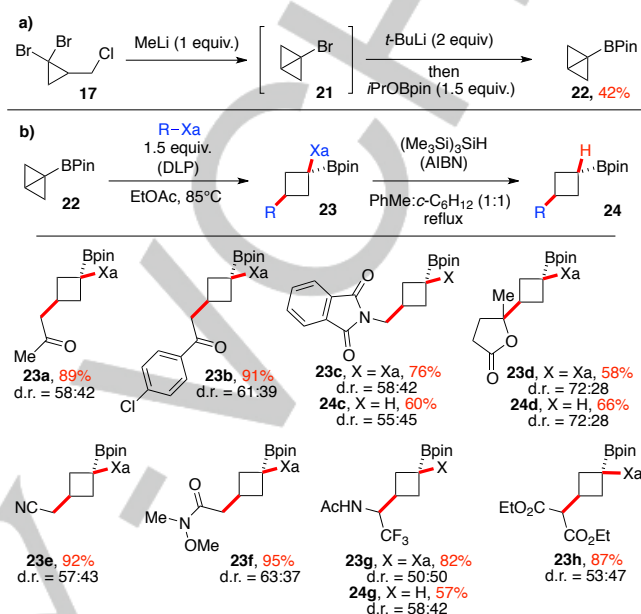
These expectations were borne out in practice as demonstrated by the results presented hereafter.

Our initial attempts at obtaining the requisite starting xanthate **14** by radical bromination or by bicyclo[1.1.0]butane opening^[14a] failed; however we realized that the family of (α -boryl)cyclobutyl xanthates should be accessible by radical addition-transfer of suitable xanthates to pinacolato cyclobutenylboronic ester **18** and the bicyclobutyl (pinacolato)boronic ester **22** (Schemes 4 and 5).^[23,24]

The first, cyclobutene **18**, has not been reported previously. It could be accessed in a straightforward manner by lithiation-borylation of 1-bromocyclobutene (Scheme 4a). This compound is prepared from dibromocyclopropane **17**, itself obtained by dibromocyclopropanation of allyl chloride, by taking advantage of the rearrangement of the intermediate bicyclobutyl bromide under acidic conditions.^[25] After a brief optimization (see the SI), several xanthates could be added to cyclobutene **18**, providing a broad range of (α -boryl)cyclobutyl xanthates **19a-j** [first step in Scheme 4b; X = -SC(=S)OEt] in good yield but with generally modest diastereoselectivity (in the range of 6:4). The notable exceptions are compounds **19e** and **19i** which were obtained with good selectivity, reflecting possibly an interaction between the nitrogen and the boron in the adduct radical. This procedure could be easily scaled up to a 3.4 mmol scale for **19a**. The (α -boryl)cyclobutyl xanthates were then reduced to cyclobutyl boronic esters **20a-20j** with tris(trimethyl)silyl silane and AIBN (second step in Scheme 4b; X = H) in order to facilitate the analysis of the spectra. In a few cases (**20d**, **20g**, and **20h**), the intermediate xanthate was not purified. In essentially all the examples, the diastereoselectivity is very high. Note that 2-substituted cyclobutylboronic esters **20a-j** constitute interesting *stereodefined* (on the cyclobutyl ring) building blocks. The diastereoselectivity in the case of **19i** (and **20i**) was unexpected and may be the result of an attractive interaction between the acetamide motif and the empty orbital on boron (the stereoselectivity issues are discussed in greater detail in the SI). Finally, the fluorocortisone derivatives **19j** and **20j** illustrate best the mildness of the reaction as they bear several functional groups that do not need protection. Furthermore, the xanthate used to prepare compound **19g** (not isolated) and **20g** itself derives by addition of cyanomethyl xanthate to *N*-vinyl phthalimide.^[27] Thus, two C-C bonds have been created in an intermolecular fashion. Finally, note that the methylbutyrolactone motif in **20h** is exactly the one present in rumphellaone A (Figure 1). The corresponding xanthate used to introduce this subunit is made in a two-step one-pot procedure from levulinic acid.^[28]

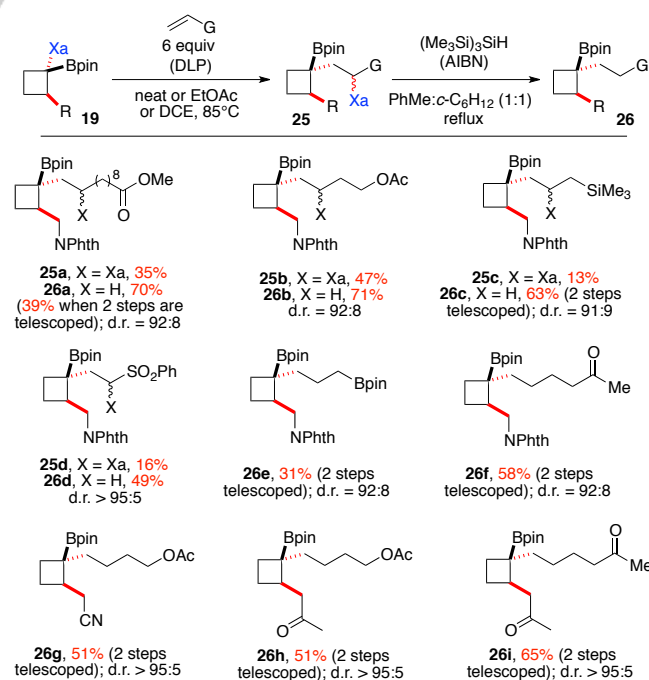
The second route to (α -boryl)cyclobutyl xanthates involves addition of a xanthate to bicyclobutylboronic ester **22**, as it has been shown that this highly strained class of compounds are good radical acceptors.^[24] Bicyclobutylboronic ester **22** was unknown when we started our work but was soon reported by Aggarwal and co-workers, who also described its selective addition reaction with nucleophiles.^[14a] Both routes to boronic ester **22** started from the same intermediate **17** used previously (Scheme 4a); however, Aggarwal's procedure was more efficient than ours and was therefore adopted for the rest of our study. We were pleased to see that the addition of various xanthates to boronic ester **22** gave a good range of 3-substituted (α -boryl)cyclobutyl xanthates **23a-**

23h in good yield but poor diastereoselectivity (Scheme 5b). In three cases, **23c**, **23d**, and **23g**, these unusual adducts were reduced into 3-substituted cyclobutylboronic esters **24c**, **24d**, and **24g**, again with low diastereoselectivity, both to facilitate characterization and to examine the selectivity of the reduction step. It is worth noting that the group of Riant recently described additions of xanthates on strained [1.1.1] propellane.^[26]



Scheme 5. Synthesis and radical additions to bicyclo[1.1.0]butanyl boronic ester **22** [Xa = -SC(=S)OEt]. The d.r. were measured by NMR.

With a substantial library of (α -boryl)cyclobutyl xanthates in hand, we examined the feasibility of a subsequent addition to mostly electronically unbiased alkenes. We thus reacted a number of 2-substituted (α -boryl)cyclobutyl xanthates **19** with different alkenes either neat or in refluxing ethyl acetate or DCE with initiation with DLP (first step in Scheme 6) and obtained the corresponding adducts **25** in moderate yield but high diastereoselectivity.

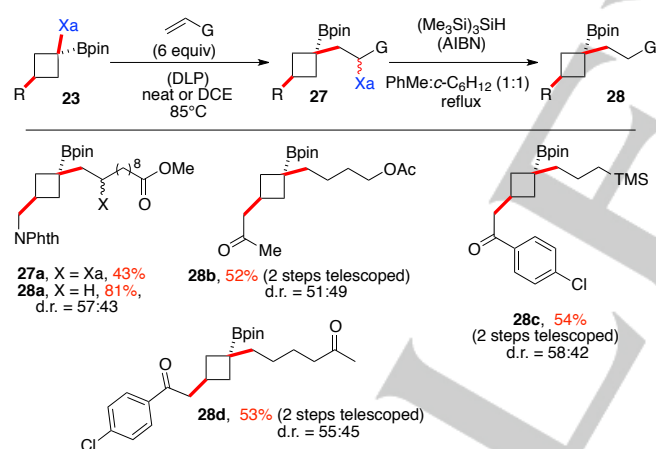


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Scheme 6. Synthesis of 1,2-disubstituted cyclobutylboronic esters [Xa = -SC(=S)OEt]. The d.r. were measured by NMR.

Again, to simplify the structures, the xanthate was reductively removed to give compounds **26a-i** (second step in Scheme 6). The main by-products in these additions were the corresponding cyclobutanones from partial decomposition of starting (α -boryl)cyclobutyl xanthates **19** (see Scheme 9c). Moreover, the intermediate xanthates proved somewhat unstable on silica and eluted close to the unwanted cyclobutanones, which complicated the purification. It was therefore advantageous to combine both steps and reduce off the xanthate without prior purification of the intermediate primary adduct. Since this involved evaporation and change of solvent, the term “telescoped” is used instead of “one-pot”. The striking example is allyl trimethylsilane adduct **25c**, isolated in a mediocre yield of 13% but the dextranthyated derivative **26c** is obtained in a relatively good overall yield of 65% when the two steps are telescoped. In all cases, the diastereoselectivity is high and various functional groups can be introduced. It is perhaps worth highlighting example **26e** where a primary and a tertiary boronic ester are present in the same molecule.

In the case of 3-substituted (α -boryl)cyclobutyl xanthates **23**, the addition takes place in comparable yield but with poor diastereoselectivity (Scheme 7). The initial adducts **27** were again conveniently reduced, in most instances without purification, to provide xanthate-free 1,3-disubstituted cyclobutylboronic esters **28a-d**.

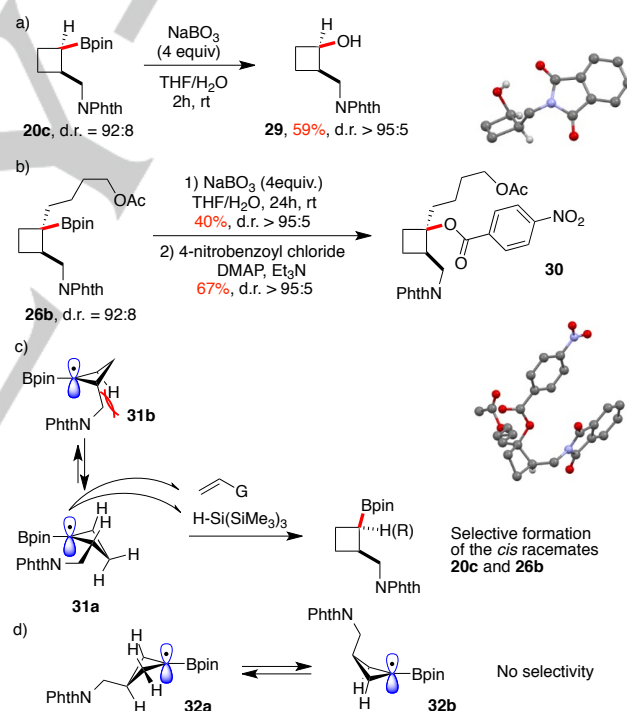


Scheme 7. Synthesis of 1,3-disubstituted cyclobutylboronic esters [Xa = -SC(=S)OEt]. The d.r. were measured by NMR.

The examples in Schemes 6 and 7 illustrate novel, convergent, routes to both 1,2- and 1,3-disubstituted cyclobutylboronic esters that complement existing approaches. The stereoselectivity is high in the former case and the relative stereochemistry of the products was confirmed through X-ray crystallography on two derivatives obtained by converting the boronic esters into the corresponding alcohols through the action of perborate (Scheme 8). This classical reaction proceeds with retention of configuration.^[5,29] In this manner, boronic ester **20c** was transformed into crystalline alcohol **29**. The structure determined by X-ray diffraction (shown in Scheme 8a) confirmed that hydrogen atom transfer took place from the face opposite to the side-chain. In the case of boronic ester **26b**, the corresponding

alcohol had to be converted into its *p*-nitrobenzoate ester **30** in order to produce crystals suitable for X-ray diffraction. Again, the structure obtained shown in Scheme 8b confirmed that the addition to the alkene proceeded as expected from the least hindered side.

The equilibrium between the two conformers **31a** and **31b** of the radical derived from xanthate **19c** favors the former where the side-chain occupies a pseudo-equatorial position thus avoiding the repulsive 1,3-pseudo-axial interaction that is present in conformer **31b** (Scheme 8b). The proximity of the side-chain to the radical center is nevertheless sufficient to shield effectively the top face of the molecule and force the hydrogen atom transfer or the addition to the alkene to proceed essentially exclusively from the opposite face to give cyclobutylboronic esters **20c** and **26b** (and more generally **20a-i** and **26a-i**). In the case of 3-substituted boronyl radical **32**, the absence of 1,3-diaxial strain results in a relatively unbiased equilibrium between conformers **32a** and **32b** and in either conformer the shielding of one face by the more distant substituent is poor. Hence, the little diastereoselectivity is observed in this series. It is worth mentioning that we examined briefly sequential radical additions starting with chiral, non-racemic cyclobutenylboronic esters but the stereoselectivities observed were relatively disappointing. These experiments are



Scheme 8. Confirmation of the stereochemistry by X-ray diffraction. The d.r. were measured by NMR.

The above results reflect the subtle but crucially important role small differences in energy play in the ability to control the xanthate addition-transfer process. The modest destabilization of the α -boryl radical by the increased σ -character caused by the angle strain in the cyclobutene ring allows numerous different xanthates to be added to cyclobutenylboronic ester **18** (Scheme 4) and bicyclo[1.1.0]butylboronic ester **22**, since the condition that the initial radical be more stable than the adduct radical is easily fulfilled. At the same time, this slight destabilization increases the reactivity of the radical and improves the chances of the *second*

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radical addition, thus allowing access to compounds **25-28** as illustrated by the examples in Schemes 6 and 7. The stability of the α -boryl cyclobutyl radical (e. g. **15**, Scheme 2c) is therefore in the correct range to allow *both* intermolecular additions.

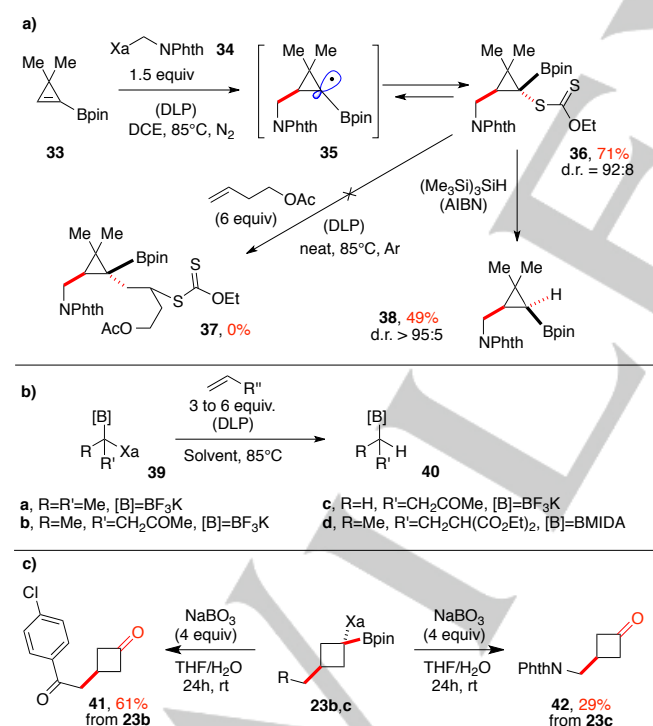
It is instructive to contrast these observations with the behavior of the highly strained cyclopropenylboronic ester **33** (Scheme 9a). The addition of xanthate **34** proceeds readily to give adduct **36** in good yield but the subsequent reaction with butenyl acetate fails to furnish the corresponding addition product **37**. Cyclopropyl radicals such as **35** have a strong σ -character and are quite destabilized. Indeed, the parent cyclopropyl radical is even less stable than a methyl radical by about 5 kcal/mol.^[22] In the first addition, radical **35** is the adduct radical and is less stable than the initial radical derived from xanthate **34**,^[30] as it should be. In the second addition, radical **35** becomes the initial radical but, unlike the cyclobutyl analogue **15**, it is too destabilized. The relative stabilities between initial and adduct radical is now the *opposite* to what is required: initial radical **35** is less stable than the secondary radical (not shown) arising from its addition to butenyl acetate. The chain process cannot therefore be sustained. It is nevertheless still possible to reduce off the xanthate to form **38** since the transfer of hydrogen atom from the silane is irreversible and not dependent on a favorable equilibrium, as required in the reversible exchange of the xanthate group. The xanthate addition to cyclopropenylboronic esters thus constitutes a convenient approach to stereo-defined functional cyclopropylboronic esters.^[6, 31]

BF₃K or with with a B(MIDA). Unfortunately, compounds **39a-d** did not add cleanly to alkenes and gave mostly reduced products **40a-d** along with, in some cases, alkenes formed by disproportionation (Scheme 9b). More details can be found in the SI.

Finally, while the focus of the present study was to demonstrate the ability to accomplish two successive intermolecular radical additions by tuning the radical stabilities, the geminal disposition of the xanthate and boronic ester in the first adducts, **19** and **23**, opens access to 2- and 3-substituted cyclobutanones (or, potentially, a cyclopropanone in the case of **36**). Two examples, **41** and **42**, 3-substituted cyclobutanones are shown in Scheme 9c. Interestingly, such cyclobutanones can be used in various desymmetrization reactions.^[32]

Conclusion

We have described a modular, convergent, and flexible approach to substituted cyclobutylboronic esters proceeding by successive intermolecular radical additions of xanthates to pinacolato 1-cyclobutenylboronate and pinacolato bicyclo[1.1.0]but-1-ylboronate. It hinges on tuning the stability of the α -boryl radical by exploiting the stabilizing influence of the trivalent boronic ester and the slightly destabilizing cyclobutane, which increases the σ -character of the radical. Reductive removal of the xanthate group finally provides a range of 1,2- and 1,3-disubstituted cyclobutylboronic esters. The contrast with cyclopropylboronic esters is striking, since the strong destabilization by the more highly strained cyclopropane ring allows the first radical addition to take place but not the second. Cyclobutyl- and cyclopropylboronic esters participate readily in all types of boronic ester-based reactions, whether they are ionic, organometallic or radical.^[6] Perhaps most importantly, they are competent partners in the Suzuki-Miyaura coupling owing to the increased polarization of the carbon-boron bond. This unique versatility endows such compounds with a particular importance. The chemistry reported herein complements existing methods and expands significantly the range of accessible structures.



Scheme 9. Synthesis of cyclopropylboronic esters and cyclobutanones [Xa = -SC(=S)OEt].

In an effort to expand the scope of the open chain tertiary α -boryl xanthates discussed in Scheme 3, we explored briefly the possibility of destabilizing the tertiary α -boryl radicals to improve the reactivity by replacing the trivalent Bpin with the tetravalent -

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Keywords: cyclobutylboronic esters • cyclopropylboronic esters • xanthates • radical addition • radical stabilities

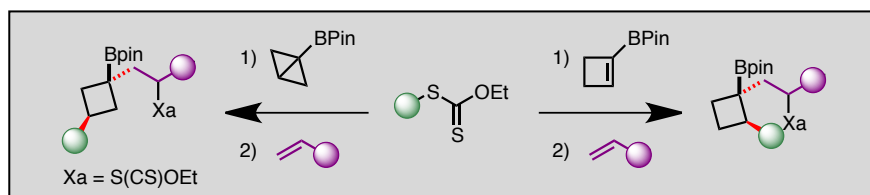
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RESEARCH ARTICLE

Entry for the Table of Contents



Insert text for Table of Contents here. Using the strain inherent in a cyclobutyl ring to counteract the stabilization of a radical adjacent to a boronic ester allows the synthesis a broad variety of 1,2- and 1,3-disubstituted cyclobutylboronic esters.

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