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Visible Light-Driven Strain-Increase Ring Contraction Allows the Synthesis of Cyclobutyl Boronic Esters

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Abstract: There are a limited number of ring contraction methodologies which convert readily available 5-membered rings into strained 4-membered rings. Here we report a photo-induced radical-mediated ring contraction of 5-membered ring alkyl boronate complexes into cyclobutanes. The process involves addition of an electrophilic radical to the electron-rich alkyl boronate complex, leading to an α-boryl radical. Upon one-electron oxidation, ring-contractive 1,2-metallate rearrangement occurs to give a cyclobutyl boronic ester. A range of radical precursors and vinyl boronates can be employed, and chiral cyclobutanes can be accessed with high levels of stereocontrol. The process was extended to the preparation of benzo-fused cyclobutanes and the versatility of the boronic ester was demonstrated by conversion to other functional groups.

Cyclobutanes are commonly occurring structural motifs, which are finding increasing applications in medicinal chemistry owing to their diverse bioactivities (Scheme 1a).[1,2] This is attributed to their structural rigidity, which provides a well-defined spatial arrangement of their substituents.[3] Whilst a number of methods for the synthesis of cyclobutanes have been reported, only a few different strategies have been described, such as [2+2] cycloadditions, 1,4- cyclization reactions, or ring expansion of cyclopropanes.[4] A much less explored strategy is ring contraction from a 5- to 4-membered ring, which is particularly attractive because it converts one of the easiest to make ring sizes into one of the most difficult.[4a,5] However, this approach is challenging due to the increase in strain energy between the substrate and the product, which has limited the scope of methodologies that can be applied, as they generally rely on the release of high energy by-products, such as in the photochemical Wolff rearrangement.[4b]

We, and others, recently reported that alkanyl boronates 1 readily react with electrophilic radicals to give highly functionalized boronic ester products 4 (Scheme 1b).[7a] The reaction proceeds via radical anion intermediates 2, which undergo single-electron oxidation to zwitterionic species 3, triggering a 1,2-metallate rearrangement. We reasoned that if cyclic 5-membered ring alkanyl boronates 5 were used, application of a similar strategy should lead to cyclobutanes 6 via ring contraction, providing there was sufficient driving force in the 1,2-metallate rearrangement to overcome the increase in strain energy (Scheme 1c).[8] Herein, we report the development of a novel visible light-induced strain-increasing 5 → 4 ring contraction. Furthermore, a variety of cyclobutyl boronic esters can be accessed in high yields and with excellent stereocontrol, including those with contiguous quaternary stereocenters and substantially more strained benzo-fused cyclobutanes.[10]

a) Bioactive cyclobutanes

paeslerin A
cytotoxic natural product

ivabradine
treatment of heart-ralted chest pain

b) Radical functionalization of alkanyl boronate complexes

visible light

Scheme 1. a) Cyclobutanes in natural product and drugs. b) Radical reactivity of alkanyl boronate complexes. c) Proposed ring contractive synthesis of cyclobutyl boronic esters.

Our investigations initially focused on designing a reliable route to cyclic 5-membered ring alkanyl boronate complexes. We found that boronate complex 5 (R1 = R2 = H) could be formed quantitatively upon treatment of a THF solution of the bench-stable and easily accessible alkyl iodide 7 with 8BuLi at −78 °C (Scheme 2, see SI for further details). Subsequent addition of a solution of iodoacetophenone in 1,3-dimethyl-2-imidazolidinone (DMI) at RT and irradiation using blue LEDs[8] led to the formation of the desired geminal-disubstituted cyclobutane product 6a in good yield. Having identified suitable conditions, we investigated the generality of the reaction by testing different alkyl iodide radical precursors 8. A variety of α-iodoketones could be employed to provide 6a-c in moderate to good yields. Cyclobutyl boronic esters substituted with synthetically versatile nitrile, ester
and amide moieties (6d-f) were prepared in good yields from the corresponding alkyl iodides. Sulfone 6g could also be efficiently synthesized, providing additional opportunities for product manipulation.\textsuperscript{[11]} Finally, cyclobutane 6h bearing a trifluoromethyl group, a privileged motif in medicinal chemistry,\textsuperscript{[12]} could be synthesized in synthetically useful yield from commercially available CF$_3$-2DMSO complex.\textsuperscript{[13]}

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**Scheme 2** Investigation of the reaction scope. All values refer to isolated yields from reactions performed on a 0.3 or 0.2 mmol scale, using 1 equiv of boronic ester, 2.1 equiv of iBuLi, and 1.5 equiv of alkyl iodide under Schlenk techniques. See SI for full experimental details. [a] Ru(bpy)$_2$Cl$_2$ (1 mol%) was used. [b] Photochemical step carried out in EtCN at 0 °C. [c] Photochemical step carried in EtCN at −60 °C and solvent exchange from THF to EtCN performed at −40 °C. [d] Photochemical step carried out in THF at −78 °C.

Encouraged by the broad scope of radical precursors that could be used, we sought to extend our methodology to the stereocontrolled synthesis of chiral polysubstituted cyclobutyl boronic esters. Under slightly modified reaction conditions,\textsuperscript{[14]} we found that enantioenriched secondary boronic esters (readily prepared through lithiation−borylation methodology)\textsuperscript{[15]} bearing substituents of varying steric demand at the α-position afforded 1,1,2-trisubstituted cyclobutyl boronic esters 6i–k in good to excellent yield (Scheme 2). Pleasingly, in addition to the 1,2-migration occurring with complete stereospecificity with respect to the migrating carbon, the newly generated quaternary stereocenters were formed with high levels of diastereoselectivity, thus providing 6i–k with excellent enantio- and diastere control.

We also explored the potential of this methodology for the asymmetric construction of contiguous quaternary stereocenters, which presents a considerable synthetic challenge.\textsuperscript{[16]} In the context of cyclobutane synthesis, there is additional strain imparted by creating adjacent quaternary centers, which must be compensated for in the 1,2-metalate rearrangement. Using readily available enantioenriched tertiary boronic esters, we found that our methodology enabled efficient access to cyclobutane 6l, featuring two contiguous quaternary stereocenters, in high yield and with complete diastero- and enantiocontrol (Scheme 2). The process was successfully extended to other radical precursors bearing ester, nitrile and sulfone substituents, giving cyclobutanes 6m–o, again with complete stereoselectivity.

Having found that there was indeed sufficient driving force in the 1,2-metalate rearrangement to overcome the increase in strain energy going from a 5- to a 4-membered ring, including those bearing contiguous quaternary centers, we sought to test the limit of our methodology in the synthesis of benzo-fused cyclobutanes. These motifs are generally more difficult to access than saturated cyclobutanes due to their enhanced strain energy (6 kcal mol$^{-1}$ higher).\textsuperscript{[10,17]} In practice, after a brief optimization of the reaction parameters in the photochemical step (MeCN, 0 °C; see SI for details), we found that benzo-fused cyclobutanes 9a–c, decorated with a versatile boronic ester moiety and different functional groups, could be readily prepared in synthetically useful yields from aryl boronic ester 10 (Scheme 3).

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**Scheme 3** Synthesis of benzoannulated cyclobutene boronic esters. All values refer to isolated yields from reactions performed on a 0.2 mmol scale, using 1 equiv of boronic ester, 2.1 equiv of iBuLi, and 1.5 equiv of alkyl iodide under Schlenk techniques. See SI for full experimental details.
Finally, we explored the versatility of the boronic ester moiety in the benzo-fused cyclobutenes since functionalization of less strained cyclobutyl boronic esters has already been described. As depicted in Scheme 4, spirolactone 11a could be quantitatively prepared by an oxidation/lactonization sequence.[19] Zweifel olefination[20] or Matteson homologation[21] enabled the construction of new C–C bonds, leading to alkenes 11b and boronic ester 11c in good yields, respectively. Finally, fluoride-induced protodeboronation gave benzo-fused cyclobutene 11d.[22]

We propose that the mechanism of our cyclobutane synthesis resembles the radical reactivity of acyclic vinyl boronate complexes.[23] As depicted in Scheme 5a, visible light-induced homolytic cleavage of the carbon–iodine bond in alkyl iodide 8 leads to electrophilic radical 12, which readily adds to the electron-rich double bond within boronate complex 5, giving spirocyclic radical anion 13. Single-electron transfer (SET) from this electron-rich species to the electron-deficient alkyl iodide 8 regenerates 12 to propagate the radical chain, and forms zwitieronic intermediate 14, triggering a 1,2-metallate ring contraction to afford cyclobutene 6.

In reactions of substrates with stereocenters α to the boronic ester, we believe that the stereoselectivity is dictated by the preferred conformation of the radical intermediates. Our preliminary computational studies (B3LYP/6-31G*, see SI for full computational details and discussion) suggest that the selectivity gets “locked in” between 13 and the 1,2-metallate rearrangement step, which is likely fast, as the product 6 is predicted to be thermodynamically very favourable. For both tertiary and quaternary stereocenters, a destabilizing gauche interaction between the pinacol moiety and the alkyl substituent occurs in the disfavoured conformers (13a’ and 13l’ respectively). The energy difference between 13a and 13a’ conformers is calculated to be very small, suggesting that other effects may play a role e.g. interactions between a lithium-solvent cluster and the EWG. Indeed, in strongly co-ordinating solvents (e.g. THF) the selectivity is considerably lower (2.4:1 vs >20:1 in EtCN; see SI for details). More detailed studies of the interactions with the lithium counterion will be needed to fully evaluate the balance of competing effects.

In conclusion, we have reported the synthesis of a variety of cyclobutyl boronic esters through a rare 5 → 4 ring contraction strategy triggered by a 1,2-metallate rearrangement. The process conveniently occurs under visible light irradiation and affords geminal and 1,2-substituted cyclobutyl boronic esters in high yield and excellent stereocontrol. Remarkably, this methodology enables the construction of contiguous quaternary stereocenters and benzannulated motifs, opening up new chemical space for drug design.

Scheme 4: Product derivatization. See SI for full experimental details.

Scheme 5. Proposed reaction mechanism and stereochemical models. Calculated energy differences are potential energies (B3LYP/6-31G*, acetonitrile solvated) with R = Me for 13a/13a’ and using a methyl group in place of the (CH2)2EWG for 13a/13a’ and 13l/13l’. See SI for full computational details and discussion.
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Keywords: Photoredox catalysis • Boron chemistry • Ring contraction • Metallate rearrangement • Cyclobutanes


[14] After boronate complex formation, solvent exchange to EICN was carried out prior to conducting the photochemical step at –60 °C. See SI for optimization studies.


Easy to access cyclic vinyl boronate complexes undergo a strain-increase ring contraction through reaction with electrophilic radicals generated by visible light. A variety of cyclobutyl boronic esters can be obtained in high yields and excellent stereocontrol, including those containing contiguous quaternary stereocenters and also substantially more strained benzo-fused cyclobutenes.