Synthetic Methods

Studies on the Lithiation, Borylation, and 1,2-Metalate Rearrangement of O-Cycloalkyl 2,4,6-Triisopropylbenzoates
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Abstract: A broad range of acyclic primary and secondary 2,4,6-triisopropylbenzoate (TIB) esters have been used in lithiation-borylation reactions, but cyclic TIB esters have not. We have studied the use of cyclic TIB esters in lithiation-borylation reactions and looked at the effect of ring size (3- to 6-membered rings) on the three key steps of the lithiation-borylation protocol: deprotonation, borylation, and 1,2-metalate rearrangement. Although all rings sizes could be deprotonated, the cyclohexyl case was impractically slow, and the cyclopentyl example underwent α-elimination faster than deprotonation at −78°C and so could not be used. Both cyclobutyl and cyclopropyl cases underwent rapid borylation, but only the cyclobutyl substrate underwent 1,2-metalate rearrangement. Thus, the cyclobutyl TIB ester occupies a “Goldilocks zone,” being small enough for deprotonation and large enough to enable 1,2-migration. The generality of the reaction was explored with a broad range of boronic esters.

Introduction

Boronic ester homologation represents a powerful method in asymmetric synthesis.[1] Originally done through substrate control using a chiral diol on the boronic ester backbone,[2] it was later shown that reagent control offered greater flexibility and when used in an iterative manner was also more effective and more efficient. Both substituted chlorosulfoxides[3] and hindered carbamates or benzoates[4] have been investigated for reagent-controlled homologation, the latter showing broader substrate scope. The hindered carbamates or benzoate esters (for example, O-alkyl 2,4,6-triisopropylbenzoate esters (TIB esters))[5] are deprotonated by strong base in the presence of diamine ligands and trapped by boronic esters, leading to intermediate boronate complexes, which upon warming, undergo 1,2-migration to form homologated boronic esters (Scheme 1A).[5]

The carbamate (or TIB ester) serves not only as a directing and stabilizing group for the lithiation step, but also as a leaving group in the 1,2-metalate rearrangement step. The reaction is stereospecific, enabling homologated boronic esters to be produced with high enantioselectivity from enantioenriched lithiated carbamates/TIB esters. This lithiation–borylation protocol has been used extensively in the synthesis of natural[1,7] and unnatural[8] products.

Scheme 1. A) Current lithiation–borylation conditions with acyclic alkyl substrates. B) Factors affecting deprotonation and 1,2-migration of cyclic TIB esters. C) This work: the effect of ring size on lithiation–borylation processes. TMEDA = N,N,N',N'-tetramethylmethylenediamine, TIB = 2,4,6-i-Pr3C6H2C(=O), TP = 2,4,6-i-Pr3C6H2.
mary and secondary carbamate/TIB esters can be employed, however in the case of the cyclobutanol, a small amount (5%) of cyclopropylmethyl TIB ester 5 was obtained. This was presumably formed from rearrangement of a cyclobutyl carboxylation, generated by an S$_1$ pathway, to a cyclopropylmethyl carboxylation which was then trapped by the carboxylic acid (Scheme 2).[13] This side product was not separable by chromatography, but fortunately the minor component did not interfere with the subsequent chemistry.

There are three steps associated with lithiation-borylation reactions: 1) deprotonation to form the organolithium; 2) borylation to form the boronate complex; and 3) 1,2-metallate rearrangement. In situ IR spectroscopy was used to optimise the first two steps, lithiation and borylation, as it allows determination of reaction times and desired stoichiometry in each intermediate.[19] In all examples, a solution of TIB ester 1–4 (0.3 M, Et$_2$O) and N,N,N',N'-tetramethylethylenediamine (TMEDA, 1.2 equiv) was cooled to −78°C and then s-BuLi was added (1.3 M in cyclohexane, 1.2 equiv). Studying the most acidic cyclopropyl variant first (Scheme 3 A), upon addition of base a rapid decrease in the intensity of the signal attributed to the starting TIB ester (∼1730 cm$^{-1}$) was observed. At the same time, a signal at a lower wavenumber 1648 cm$^{-1}$ grew in intensity, which we attributed to the lithiated species 1-Li, which then plateaued and remained horizontal over 10 minutes showing that the lithiated cyclopropyl TIB ester was chemically stable under the reaction conditions. The lithiation was essentially instantaneous, being complete by the end of the dropwise addition of the base. A solution of phenethylboronic acid pinacol ester (1.0 M, Et$_2$O) was then added over 2 minutes and another peak appeared (1682 cm$^{-1}$), again instantaneously, which is indicative of the boronate complex 1-B. Even though the organolithium is tertiary (albeit bearing a small cyclopropyl group) rapid borylation ensued.

The cyclobutyl TIB ester 2 was then subjected to the same sequence (Scheme 3 B). In this case deprotonation was no longer instantaneous but it was still rapid, taking 10 minutes to reach a plateau. In contrast to the cyclopropyl example, the lithiated cyclobutyl substrate 2-Li was not chemically stable under the reaction conditions and decayed slowly over time. A broader second peak appeared at lower wavenumber 1581 cm$^{-1}$, which is attributed to the carboxylate salt 6, and

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**Results and Discussion**

Our investigation began with the synthesis of the cyclic TIB esters 1–4. After some experimentation we found that the cyclopropyl ester could be made by S$_2$2 displacement of the corresponding bromide with 2,4,6-triisopropylbenzoic acid (TIB acid) (Scheme 2), whilst the 4–6-membered ring TIB esters were best made by Mitsuobu reaction of the corresponding alcohols. Cyclopentanol and cyclohexanol proceeded smoothly (see Supporting Information for details),

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**Scheme 2.** Synthesis of small ring benzoates and side-products observed.
was observed to grow after \( \approx 50 \) minutes indicating slow decomposition by \( \alpha \)-elimination. Addition of phenethyl boronic acid pinacol ester then led to instantaneous borylation, like the cyclopropyl example, affording the cyclobutyl boronate complex \( \text{2-B} \). As the deprotonation of the cyclobutyl TIB ester was especially facile, we also attempted the lithiation-borylation of bromo- and chlorocyclobutane, in a similar way to that employed for bromocyclopropane. However, we only observed trace product, presumably due to the enhanced rate of \( \alpha \)-elimination from having a better leaving group (see Supporting Information for details).

Increasing the ring size further to the cyclopentyl TIB ester led to unexpected results. While the starting material was converted more slowly than the smaller ring systems (as expected), there was no observable lithiated species \( \text{3-Li} \). Instead, only the broad peak of the carboxylate \( \text{6} \) was observed (Scheme 3C). This indicates that the lithiated species undergoes decomposition (presumably by \( \alpha \)-elimination) at a faster rate than its formation. This was confirmed by addition of \( d_4 \)-methanol (5 equiv) 4 h after addition of the base (when the formation of carboxylate had stopped by in situ IR spectroscopy), which led to a low recovery (27%) of non-deuterated (0% deuteration incorporation) starting material. Attempts to stabilize the cyclopentyl lithiated species using the diisopropyl carbamate (a better stabilizing group and worse leaving group) were unsuccessful and no lithiated species was observed by in situ IR spectroscopy (see Supporting Information for details). We were surprised at the high instability of the lithiated cyclopentyl TIB ester and carbamate. Finally, the cyclohexyl TIB ester showed much slower deprotonation still. After 22 h at \(-78^\circ\text{C}\) the reaction reached a plateau, with the in situ IR spectroscopy trace showing low conversion (Scheme 3D). Quenching the reaction at this time with \( d_4 \)-methanol gave 93% recovery with only 26% deuteration which is clearly impractical. Being able to observe the lithiated benzoate \( \text{4-Li} \) by in situ IR spectroscopy.

Scheme 3. In situ IR spectroscopy traces for 3–6-membered cycloalkyl TIB esters. A) Lithiation and borylation of the cyclopropyl TIB ester. The trace shows that the deprotonation is very rapid, the lithiated species is stable at \(-78^\circ\text{C}\), and that borylation is rapid. B) Lithiation and borylation of the cyclobutyl TIB ester. The trace shows that deprotonation is rapid, the lithiated species slowly decomposes at \(-78^\circ\text{C}\), and that borylation is rapid. C) Lithiation of the cyclopentyl TIB ester. The trace shows that the lithiated species is not stable and decomposes to the carboxylate. D) Partial lithiation and deuteration of the cyclohexyl TIB ester. The trace shows that the lithiation is slow and inefficient.
spectroscopy and the fact that we isolated 4-D showed that the lithiated benzoate 4-Li was much more stable than the 5-membered ring analogue 3-Li. At –60°C the deprotonation plateaued after 4 h and quenching with d₄-methanol gave similar levels of recovery (95%) and deuterium incorporation (21%) as at –78°C. We have previously shown that s-butyl TIB ester gave 35% yield in a lithiation–borylation process at –60°C after a 2 h lithiation time, indicating that cyclohexyl TIB ester is deprotonated even more slowly than acyclic substrates. Having established that both the cyclopropyl and cyclobutyl TIB esters could be lithiated and borylated, our attention turned to the 1,2-metalate rearrangement. Beginning with the cyclopropyl boronate complex 1-B we attempted to promote 1,2-metalate rearrangement but even under a variety of conditions (e.g. MgBr₂, solvent swap to CHCl₃), all reactions either returned starting material or resulted in decomposition (see Supporting Information for details). This clearly indicated that the barrier to 1,2-migration for the 3-membered ring was higher than alternative decomposition pathways or reversion to the starting components. Interestingly, cyclopropyl boronate complexes bearing a bromide leaving group do undergo 1,2-metalate rearrangement, highlighting the difference the nature of the leaving group can make. Turning to the cyclobutyl boronate complex 2-B, we found that this time the 1,2-metalate rearrangement began to occur at room temperature, but the reaction was slow. Even with heating in Et₂O, boronate complex remained (Table 1, entries 1 and 2). Use of MgBr₂ was not effective at promoting the 1,2-metalate rearrangement (entry 3), but we found that a solvent switch to CHCl₃ followed by heating to 60°C enabled complete 1,2-metalate rearrangement to occur in just 3 h, furnishing the cyclobutylboronester 7 in 67% isolated yield. Solvent exchange to a non-coordinating solvent, like CHCl₃, has previously been found to promote 1,2-migration of recalcitrant boronate complexes. A small amount of O-migration of the pinacol group was also observed for all reactions (8: < 10%). Having developed a successful lithiation-borylation protocol for the cyclobutyl TIB ester (entry 4), we explored the scope of this process with different boronic esters (Scheme 4).

The reaction proceeded well for a diverse collection of primary boronic esters including those bearing nitrile (10), ester (11) and azide (12) functional groups. A lower yield was observed for the azide 12 presumably due to competing nucleophilic addition of the organolithium 2-Li to the azide in the starting boronic ester. Reaction with a complex lithocholic acid derivative 13 also proceeded in good yield. Secondary boronic esters also worked well, with examples including cyclohexyl 14, cyclopropyl 17, N-Boc-pyrrolidine 18 and piperidines 19 and 21. Although α-amino substrates are poor migrating groups, they nevertheless proceeded in moderate yields (18 and 21). Furthermore, using chiral and non-racemic boronic esters the 1,2-metalate rearrangement was found to be completely stereospecific (15 and 16). To demonstrate scalability, N-Boc-piperidine 19 was prepared on gram scale. In the case of the menthyl derivative 20, little product was formed but switching to the less hindered neopentyl glycol ester resulted in an increased 60% yield. Unusually, the neopentyl glycol boronic ester product was stable to silica gel chromatography. This hindered secondary boronic ester turned out to be the limit of reactivity with secondary TIB esters. No boronate complex was observed by in situ IR spectroscopy with s-Bu pinacol boronic ester but boronate was observed using the neopentyl glycol ester (see Supporting Information for details). However, despite formation of the neopentyl glycol boronate complex, no product was obtained after attempted 1,2-metalate rearrangement. Presumably, the hindered boronate complex reversed to starting materials upon heating. Similar observations were observed with acyclic secondary TIB esters, indicating that it is apparently too demanding for this methodology to place two quaternary centres next to each other using boronic esters, although this problem could be overcome using boranies.

A range of sp² boronic esters were also explored. Both electron poor and electron rich aromatics 22–24, as well as heteroaromatics, such as benzofuran 26 and indole 27 worked well giving the products in good yield. Finally, alkenyl boronic esters performed well, providing tertiary allylic boronic esters 28–30 in good yields.

To further illustrate the utility of the cyclobutyl boronic ester products, we transformed the boronic ester functionality present in substrate 19 into a range of functional groups (Scheme 5). Zweifel olefination with propenyllithium gave the olefin 31 in excellent yield, and alkynylation with vinyl carbamate gave the alkyne 34 in high yield. The tertiary boronic ester underwent a Matteson homologation to give a primary boronic ester product 32. The boronic ester was also converted into the tertiary amine in moderate yield, which was protected as the carbamate 33.

**Table 1**: Optimization of 1,2-migration.

| Entry | X    | Equiv | Solvent | T [°C], t [h] | 8: 7:2-2B⁻¹ | Yield [%] |
|-------|------|-------|---------|--------------|-------------|----------|
| 1     | TP   | 1.2   | Et₂O    | 22, 16       | 10:70:20    | 64[H] (59[S]) |
| 2     | TP   | 1.2   | Et₂O    | 30, 16       | 10:70:20    | 67[H] (53[S]) |
| 3     | TP   | 1.5   | Et₂O    | 40, 16       | 15:65:25    | 42[4][4]   |
| 4     | N[P(Pr)₂] | 1.5 | CHCl₃   | 60, 3       | 10:90:00    | 86[H] (67[S]) |
| 5     | N[P(Pr)₂] | 1.5 | CHCl₃   | 60, 16      | 10:70:20    | 57[H]     |

[a] The ratio of O-migrated side-product (δ ≈ 50 ppm) to C-migrated product (δ ≈ 32 ppm) to boronate complex (δ ≈ 8 ppm), ratio determined by <sup>1</sup>HNMR spectroscopy. [b] Crude <sup>1</sup>HNMR yield relative to 1,3,5-trimethoxybenzene. [c] 8 equivalents of a 1 M solution of MgBr₂ in MeOH were added to the reaction. [d] Isolated yield after flash column chromatography.

**Conclusion**

We have studied the lithiation-borylation of a series of cyclic TIB esters and have shown that the success of the process is governed by a delicate balance of factors involving...
ease of lithiation, stability of the organolithium, and ease of 1,2-migration. Of the ring sizes studied, deprotonation became progressively slower going from 3- to 6-membered rings, with the cyclohexyl substrate being too slow to be practical. The organolithium intermediate was prone to α-elimination and while the lithiated 3- and 4-membered rings were stable, the lithiated cyclopentyl TIB ester underwent α-elimination faster than deprotonation. The 3- and 4-membered rings both underwent rapid deprotonation and trapping with boronic esters but the 3-membered ring did not undergo 1,2-metalate rearrangement, presumably because of the high strain in the TS of the migration. The cyclobutyl ring did undergo 1,2-metalate rearrangement. Thus, the cyclobutyl ring occupies a “Goldilocks zone”, where the ring is small enough to promote deprotonation, but large and flexible enough to allow the 1,2-metalate rearrangement to occur, and the organolithium is sufficiently stable. The process shows broad substrate scope, and the applicability of these boron substituted cyclobutanes has been demonstrated by transforming the boronic ester into a range of functional groups.

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**Conflict of interest**

The authors declare no conflict of interest.

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