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Selective uni- and bidirectional homologation of diborylmethane†

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Diborylmethane can be homologated uni- and bidirectionally by using enantiomerically pure lithium-stabilized carbenoids to give 1,2- and 1,3-bis(boronic esters), respectively, in good yield and with excellent levels of enantio- and diastereoselectivity. The high sensitivity of the transformation to steric hindrance enables the exclusive operation of either manifold, effected through the judicious choice of the type of carbenoid, which can be a sparteine-ligated or a diamine-free lithiated benzoate/carbamate. The scope of the 1,2-bis(boronic esters) so generated is complementary to that encompassed by the asymmetric diboration of alkenes, in that primary–secondary and primary–tertiary 1,2-bis(boronic esters) can be prepared with equally high levels of selectivity and that functional groups, such as terminal alkynes and alkenes, are tolerated. Methods for forming C₂-symmetric and non-symmetrical anti and syn 1,3-bis(boronic esters) are also described and represent a powerful route towards 1,3-functionalized synthetic intermediates.

Introduction

Investigations into the utility of organic molecules containing multiple C-sp³ boryl units continue to flourish, enabled in part by recent developments in the asymmetric diboration of alkenes.¹ It is now clear that polyboronic esters are powerful intermediates in organic synthesis owing to the abundance of functional groups in which the C–B bonds can be transformed.² Many of these methods are stereospecific and regioselective transformation of polyboronic esters is feasible through the judicious manipulation of steric effects³ and proximal functional groups.⁴ Despite these advances, the types of polyboronic esters available for further functionalization remain limited. For example, although primary–secondary and a very limited number of secondary–secondary 1,2-bis(boronic) esters are readily available with high levels of enantiopurity, obtained through the platinum⁵ or rhodium-mediated⁶ diboration of the corresponding alkenes or the hydroxyl-directed diboration⁷ of enantioenriched alkynyl alcohols (Fig. 1A), 1,2-bis(boronic) esters with higher levels of substitution are not.⁸ Furthermore, metal-catalyzed diboration reactions are not tolerant of several functional groups, for example alkynes, thus further limiting the diversity of polyboronic esters available. Herein, we present an alternative method for preparing 1,2-bis(boronic esters)—the one-carbon homologation of diborylmethane 1. Specifically, when treated with enantioenriched lithiated benzoates or carbamates, diborylmethane 1 undergoes stereospecific homologation to give primary–secondary and primary–tertiary 1,2-bis(boronic esters). Furthermore, we show that diborylmethane can be homologated in both directions in a one-pot process to give secondary–secondary 1,3-bis(boronic esters),

Fig. 1  Context, proposal and challenges.
a class of polyboronic esters with similar potential for application to their 1,2-related counterparts.9

We have recently developed efficient methodology for the homologation of boronic esters by using stereodefined lithiated carbamates10 and 2,4,6-trisopropylbenzoates11 (TIB esters). The transformation involves the stereoretentive complexation of the lithiated carbamate12/TIB ester13 with the boronic ester to form a boronate complex, which then undergoes a stereoinvertive 1,2-metallate rearrangement14 to generate a homologated boronic ester. Our attention was drawn to commercially available diborylmethane 1,15 which we envisioned serving as a valuable reagent for the elaboration of stereodefinned carbamoids (Fig. 1B). Specifically, the complexation of one boryl moiety of diborylmethane 1 with a carbenoid followed by 1,2-metallate rearrangement would give a 1,2-bis(boronic ester). In a second manifold, the complexation of both boryl groups to the same or different carbenoids, thus forming a dianionic 1,1-bis(borinate), with subsequent rearrangement at both centers, would give a 1,3-bis(boronic ester), thus representing a three-component coupling with diborylmethane 1 acting as a linchpin. For these transformations to be successful, a number of key criteria would have to be met: (i) the acidic methylene group of diborylmethane 1 must not undergo deprotonation (I);16 (ii) fragmentation of the intermediate boronate complex to form stabilized α-carbon carbanions must not occur (II);17!! (iii) single versus double homologation must be controlled (III) (Fig. 1B).

Results and discussion

(+)-Sparteine-ligated lithi­ated TIB ester 17 met all three of the criteria outlined above: by generating this carbenoid through the sparteine-mediated deprotonation of the corresponding benzoate and then treatment with diborylmethane 1, the single-homologation product 3 was isolated in high yield and with very high levels of enantiospeciﬁcity (Fig. 2). Surprisingly, when using the corresponding diamine-free carbenoid (generated by tin–lithium exchange of the corresponding enantioenriched α-stannyl benzoate) the double-addition product 4 was obtained exclusively; none of the monoaddition product 3 was observed.18 In contrast, Shibata and co-workers have shown that the diamine-free Matteson-type carbenoid (LiCH2Cl), which was generated in situ, reacts with the more sterically hindered 1,1-diborylphenylethene to give the single-homologation product.19!!20 Clearly the level of homologation of geminal diboryl compounds is very sensitive to the nature of the carbenoid employed.

Having established the optimal conditions for single and double homologation we set out to demonstrate the generality of our protocol for the synthesis of chiral non-racemic 1,2-bis(boronic esters). The homologation of diborylmethane 1 with lithiated primary benzoates containing a pyrrole-masked primary amine,21 a terminal olefin, and a steroidal group gave the corresponding 1,2-bis(boronic esters), 5–7, in high yield and enantioselectivity (Fig. 3A). Additionally, the 1,2-bis(boronic ester) 5 was prepared on gram scale with comparable yields and selectivity. In contrast to metal-mediated diboration, the stereo-selectivity of this homologative process appears to be insensitive to proximal stereogenic centers as epimeric 1,2-bis(boronic esters) 8 and 9 were prepared with similarly high levels of diastereoselectivity. The potential adverse effect of acidic functional groups on the carbenoid partner could be mitigated by their in situ protection as the corresponding conjugate bases by using excess s-BuLi. This protocol facilitated the diborylative transformation of a carbenoid bearing a terminal alkene (to give 10). Again, this particular transformation is signiﬁcant in that alkene groups are incompatible with alkene diboration reactions.

Based on our observation that sterically hindered dianion-ligated primary carbenoids are highly selective for the single homologation of 1, we reasoned that secondary benzyllic boronic esters, which can be generated through the stereospecific deprotonation of the corresponding carbamates in the absence of a diamine, should be similarly selective. We were also mindful that the products, primary–tertiary 1,2-bis(boronic esters), are not accessible in useful yields or levels of enantiospeciﬁcity through the asymmetric diboration of 1,1-disubstituted alkenes, thus giving such a process extra signiﬁcance. Pleasingly, the treatment of enantiopure (S)-1-phenylethanol-derived lithiated carbamate with diborylmethane 1 gave primary–tertiary 1,2-bis(boronic ester) 11 in high yield and with a high level of enantiospeciﬁcity (96 : 4 e.r.; Fig. 3B). The addition of a Lewis acid (MgBr2) and MeOH at −78 °C immediately after the formation of the boronate complex, yet prior to warming to room temperature (the 1,2-metallate rearrangement only occurs at elevated temperatures), was essential for achieving high yields and high levels of enantiospeciﬁcity.22

These homologation reactions were insensitive to the electronic demands of the aromatic ring as p-Ph, p-CI, p-Me, p-MeO and p-F substituted carbamates gave the desired 1,2-bis(boronic esters) 12–16 in high yields and high levels of enantioselectivity. These transformations were similarly effective on gram scale (15). Although the transformation of ortho-substituted benzyllic carbamates (o-F and o-MeO: 17 and 18) gave more moderate yields of the products, the levels of enantiospeciﬁcity remained very high. The transformation of secondary alkyl benzoates (i.e. non-benzyllic)23 necessitated the generation of the chiral carbeneid from the corresponding stannane through tin–lithium exchange. The carbeneid so generated from 19 (>99 : 1 e.r.) reacted with diborylmethane 1 to give the corresponding 1,2-bis(boronic ester) 20 in 62% yield and with high levels of enantiospeciﬁcity (96 : 4 e.r.), the slight erosion of stereochemical information being most likely due to competing stereo(over)ionization of the carbaneid during the formation of the boronate complex.22
Our initial studies established that diamine-free primary lithiated benzoates react with diborylmethane 1 to give $C_2$-symmetric secondary–secondary 1,3-bis(boronic esters), that is, both ends of the diborylmethane undergo homologation (Fig. 2). We explored the scope of this transformation by using a range of diamine-free lithiated benzoates, which were generated through tin–lithium exchange of the corresponding enantiopure $\alpha$-stannyl benzoates (Fig. 4A). The double-homologation reactions of diborylmethane 1 with primary lithiated benzoates gave a range of $C_2$-symmetric secondary–secondary 1,3-bis(boronic esters) (21–24) in high yield and near-perfect diastereoselectivity. In contrast, one-pot double homologation with the more hindered secondary benzyl lithiated carbanionates proved more challenging: a low yield of $C_2$-symmetric tertiary–tertiary 1,3-bis(boronic ester) 25 was obtained, even when using a large excess of the requisite lithiated carbanion (Fig. 4B). However, we overcame this limitation through the isolation of the mono-homologation product, 15, and resubjecting it to the homologation conditions, a protocol that gave tertiary–tertiary 1,3-bis(boronic ester) 25 in moderate yield and very high levels of diastereoselectivity. Presumably formation of the dianionic geminal bis(boronic ester), which would be required for the one-pot process, is disfavored due to steric hindrance. Attempts to homologate 15 with (+)-sparteine-ligated primary benzoates were unsuccessful, underscoring the sensitivity of primary–tertiary 1,2-bis(boronic esters) to steric hindrance. Pleasingly, both the selective homologation of the primary boronic ester moiety of 15 (to give secondary–tertiary 1,3-bis (boronic ester) 26) and the double homologation of 15 (to give secondary–secondary 1,4-bis(boronic ester) 27) could be carried out by using 0.9 and 2.1 equivalents, respectively, of diamine-free lithiated benzoate.

The regioselective single homologation of diborylmethane 1 with sparteine-ligated carbanionoids, and the relative insensitivity of the diamine-free carbanionoids to steric hindrance in their reactions with boronic esters, suggested that these types of carbanionoids could be coupled in a one-pot three-component coupling reaction with diborylmethane 1 acting as a linchpin. Specifically, the generation of a (+)-sparteine-ligated carbanionoid at $-78 \, ^\circ{C}$ and the addition of diborylmethane 1 would give the mixed-valent diboryl species 29. Subsequent addition of an enantiomERICally pure $\alpha$-stannyl benzoate followed by an equivalent portion of n-BuLi would lead to rapid and selective tin–lithium exchange followed by the reaction of the resulting diamine-free carbanionoid with the remaining boronic ester moiety to give the heteroleptic geminal 1,1-bis(boronic ester) 30. Finally, upon warming to room temperature 1,1-bis(boronic ester) 30 would undergo 1,2-metallate rearrangement at both boron centers to give the corresponding non-symmetrical secondary–secondary 1,3-bis(boronic esters) 31–34 in moderate yield and with very high levels of diastereoselectivity. As is the nature of the transformation, 1,3-syn-bis(boronic esters), such as 35, can be formed with equal ease and selectivity simply by using the enantiomERICally $\alpha$-stannyl benzoate. This transformation is a rare example of a fragment coupling reaction in which 1,3-related stereo centers are formed.

Fig. 3 Stereoselective synthesis of 1,2-bis(boronic esters) from primary benzoates (A), secondary benzyl carbamates (B) and secondary dialkyl benzoates (C). Footnotes: (a) enantiomeric ratios determined by HPLC, GC or SFC analysis using chiral stationary phases. (b) Diastereomeric ratios determined by $^1$H NMR analysis. (c) Prepared from the corresponding carbamate (d) using (+)-sparteine in place of (+)-sparteine. (e) 2.2 equivalents of (+)-sparteine, sBuLi and 1. Abbreviations: CB = N,N-diisopropyl carbamoyl, MGM = methoxymethyl, PMP = para-methoxyphenyl, TBS = tert-butyldimethylsilyl, TIB = 2,4,6-trisopropylbenzoyl, TMEDA = N,N,N’,N’-tetramethylethylene diamine, pin = pinacolato.
directly with complete control of the relative and absolute configuration, suggesting that it could be used as a strategy for bringing together advanced fragments for the preparation of complex molecules.

We briefly explored a number C–B functionalisation reactions of primary–tertiary 1,2-bis(boronic ester) 15 (Fig. 5). Its subjection to standard Matteson homologation,\(^3\) Zweifel olefination\(^2\) and standard oxidation conditions gave the corresponding difunctionalisation products 36–38, respectively, in good yield. We were also particularly interested in whether selective functionalisation of either the primary or the tertiary boronic ester could be achieved. As expected, selective protodeboronation of the tertiary benzylic boronic ester of 15 (98 : 2 e.r.) was possible, but with only moderate enantiospecificity (primary boronic ester 39 was obtained in 88 : 12 e.r.).\(^27\) The group of Morken has shown that primary boronic esters can be transformed selectively in the presence of a vicinally-positioned secondary boronic ester under Suzuki cross-coupling conditions.\(^3\) However, although facile cross coupling of the primary boronic ester in 15 was evident, the conditions were also favourable for protodeboronation of the tertiary boronic ester, giving 1,2-diarylpropane 40 in 75% yield. Clearly, further exploration and optimisation of the conditions for the group-selective functionalisation of primary–tertiary bis(boronic esters) is warranted.

**Conclusions**

In summary, we have developed a regiodivergent strategy for the stereoselective synthesis of 1,2- and 1,3-bis(boronic esters) from commercially available diborylmethane 1. Using hindered chiral carbenoids we have been able to effect the selective single homologation of diborylmethane 1 to prepare a wide range of 1,2-bis(boronic esters). Generating primary chiral carbenoids in the absence of diamines enabled the exclusive double homologation of diborylmethane 1 to afford C\(_2\)-symmetric 1,3-bis (boronic esters). The strategic combination of these carbenoids (sparteine-ligated and diamine-free) with diborylmethane 1, representing a formal carbenoid–carbenoid coupling reaction, allowed non-symmetrical 1,3-bis(boronic esters) to be prepared directly.
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