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Construction of Multiple, Contiguous Quaternary Stereocenters in Acyclic Molecules by Lithiation-Borylation

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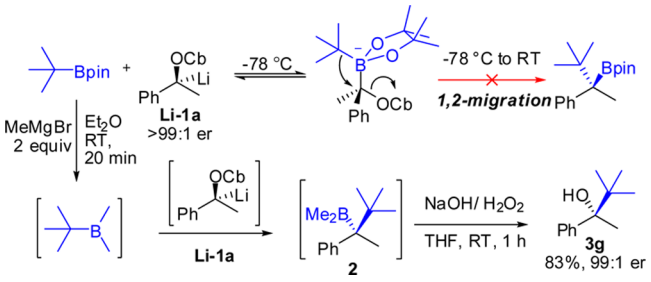
Supporting Information

ABSTRACT: Lithiation of carbamates followed by borylation provides a powerful method for the homologation of boron reagents. However, when applied to hindered systems (secondary carbamates with *t*Bu-boronic esters) for the construction of two quaternary centers, this methodology fails. Instead, using mixed boranes (*t*BuBMe$_2$), the synthesis of adjacent quaternary stereogenic centers with full stereocontrol was successful. The process can be repeated two or three times in one pot leading to carbon chains bearing multiple contiguous quaternary stereogenic centers. The boranes were converted into tertiary alcohols or C-tertiary amines using chloramine. The origin of the high selectivity for alkyl over Me group migration was determined computationally.

The asymmetric control of quaternary stereogenic centers in acyclic molecules is a considerable synthetic challenge. While numerous methods have been described to achieve this goal,[1] the control of absolute and relative stereochemistry of *multiple*, *contiguous* quaternary centers is much more difficult and beyond the reach of current methodology.[2] This problem rises significantly the more contiguous quaternary centers are present since the average C−C bond strength becomes progressively weaker.[3] Indeed, some congested molecules are so sterically hindered they simply cannot be made.[4] We recently reported a method for the creation of quaternary stereogenic centers in >99:1 e.r. using lithiation-borylation of secondary carbamates (Scheme 1).[5] In the process, tertiary boronic esters are formed as intermediates. We reasoned that if these intermediates could be used in a second or even third lithiation-borylation reaction we would have the potential to generate contiguous quaternary centers. Herein, we describe our success in achieving this goal although considerable modifications were required to overcome the significant problems that were encountered.

Scheme 1. Lithiation-Borylation of Hindered Boron Reagents



We initially tested the reaction of **Li-1a** with the simple, hindered tertiary boronic ester *t*BuBpin, but none of the desired product was obtained, just decomposition products of the lithiated carbamate (Scheme 1). From previous studies, we were aware that the intermediate ate complex had two possible fates: reversal back to starting materials or 1,2-migration.[5c] With increasing steric hindrance of either partner, the former process increasingly competes and evidently dominates in the case of *t*BuBpin. We therefore considered the possibility of using the mixed borane, *t*BuBMe$_2$. Not only is this sterically less hindered and electronically more electrophilic but, being a borane rather than a boronic ester, its ate complex has a considerably lower barrier to 1,2-migration.[5b,6] Even though both highly hindered (thexyl) and small (Me) groups have occasionally been used in different situations as nonmigrating groups,[6a,7] we expected the small Me substituent to act as nonmigrating groups and for the hindered group to migrate.[8]

The mixed borane, *t*BuBMe$_2$, was easily prepared by reaction of MeMgBr (2 equiv) with *t*BuBpin in Et$_2$O,[9] followed by distillation.[10] Borylation of **Li-1a** at low temperature and subsequent warming to RT and oxidation now gave the tertiary alcohol **3g** in high yield and essentially perfect enantioselectivity. It should be noted that boranes react with lithiated carbamates with inversion of stereochemistry while boronic esters react with retention.[5b] Furthermore, the chemoselectivity for migration of the tertiary group was very high, with no methyl migration being observed by ^{1}H NMR.

With this success, we focused our attention on *i*PrBMe$_2$, which was prepared in the same way as *t*BuBMe$_2$. In order to generate molecules with contiguous quaternary centers, we would need to conduct iterative, one-pot homologations since the intermediate boranes are air sensitive and cannot be easily purified. Thus, treatment of **Li-1a** with *i*PrBMe$_2$ led to the mixed borane **2a**, which, without isolation, was reacted with a second solution of **Li-1a**. Subsequent warming to RT and oxidation now gave the tertiary alcohol **4a** in good yield, very high diastereoselectivity, and perfect enantioselectivity in effectively a one-pot process (Scheme 2). The alternative diastereoisomer was equally easily made simply by using ***ent*-Li-1a** in the second lithiation-borylation reaction, although conditions had to be modified to ensure high diastereoselectivity.[11] The scope of the one-pot

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Scheme 2. General Procedure for the Double Lithiation-Borylation of Secondary and Tertiary Alkyl Dimethyl Boranes

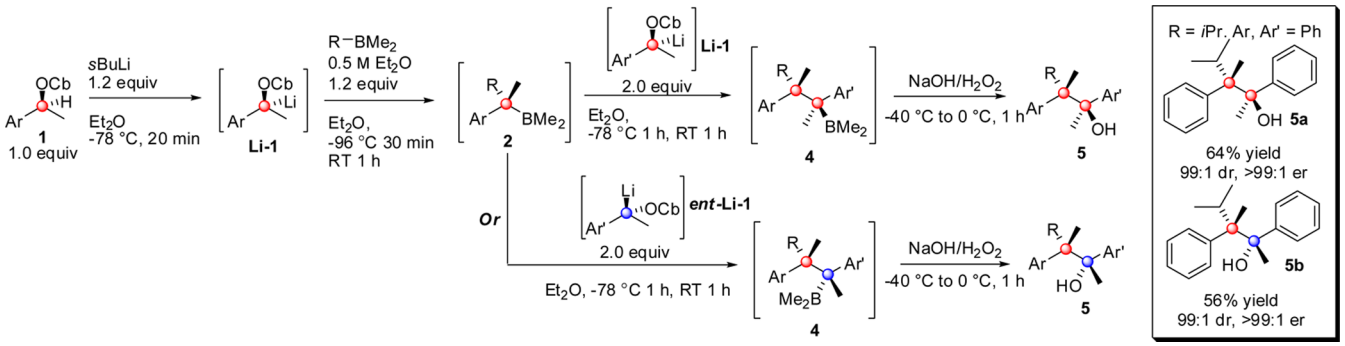
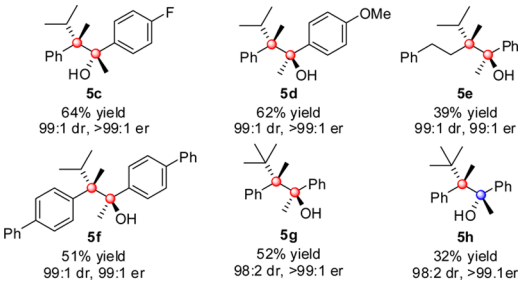


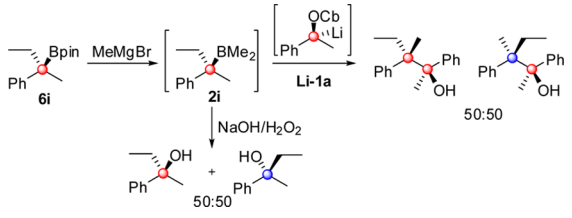
Chart 1. Products of the Double Homologation Reaction



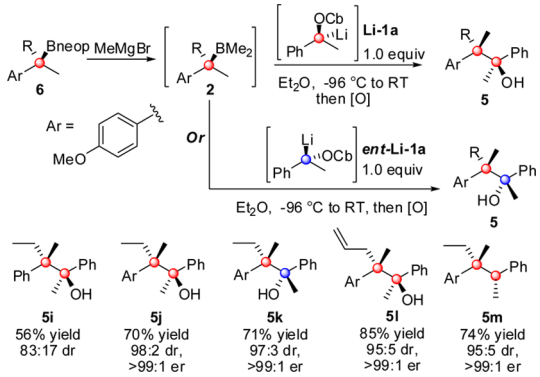
multiple homologation reaction was briefly investigated (Chart 1). Electron withdrawing and donating groups on the aromatic group of the second carbamate were well tolerated, and nonbenzylic substrates[12] worked well too, giving the double homologation product **5e** in excellent enantio- and diastereoselectivity. The multiple homologation reaction was also extended to the more sterically demanding *t*BuBMe$_2$, giving three adjacent quaternary substituted carbons (**5g**/**h**). It was found that in these particular demanding cases, an additional dose of the lithiated carbamate in the second homologation improved conversion of the intermediate boranes **2g**/**h**. However, we observed some protodeboronation of the final boranes during oxidation, particularly with **5h**, which lowered the overall yield.

While mixed boranes bearing *i*Pr and *t*Bu groups showed high chemoselectivity for migration of the more hindered substituent, mixed boranes bearing a primary substituent did not and competing methyl migration was observed.[13] We therefore attempted to make the mixed borane **2i** directly from the tertiary boronic ester **6i** (Scheme 3). This seemed to work well but subsequent reaction with **Li-1a** surprisingly gave a 1:1 mixture of diastereoisomers. Following careful analysis we were further surprised that of the two stereogenic centers, it was the static borane center that had undergone complete racemization[14] (rather than the sensitive benzylic stereocenter) presumably

Scheme 3. Formation and Use of a Mixed Borane Derived from a Tertiary Boronic Ester and the Source of Racemization



Scheme 4. Formation of Mixed Boranes from Tertiary Boronic Esters and Subsequent Homologation



during its formation from the chiral boronic ester **6i**. This was unexpected as this method had been previously used to make mixed boranes from chiral, secondary dialkyl pinacol[8,9c] and arylalkyl[9d] catechol boronic esters *without* racemization. We reasoned that racemization should be minimized by shortening the time required to make the borane using a more easily displaceable diol. In practice, use of the corresponding neopentyl glycol ester allowed displacement of the boronic ester in just 5 min, and subsequent reaction with **Li-1a** gave an 83:17 mixture of diastereoisomers. Even higher dr (97:3) was observed using the *p*-methoxyphenyl boronic ester leading to alcohols **5j** and **5k** in good yield or **5m** after protodeboronation with TBAF·3H$_2$O in place of oxidation[15] (Scheme 4). The reaction was also extended to a more functionalized system bearing an allyl group.

We recently reported a multiple homologation (x9) of a boronic ester leading to a carbon chain bearing 10 contiguous tertiary stereocenters with full control.[16] Indeed, there seemed to be no limit on the number of homologations that could be achieved, perhaps reflecting the stabilizing effect of contiguous methyl substituents along the carbon chain.[3] In order to probe the limits of the number of homologations that can be carried out in the creation of carbon chains bearing contiguous quaternary stereocenters (where more contiguous quaternary centers result in destabilization[3]), we subjected the Et- and *i*Pr derived boranes **4j** and **4a** to an additional (one pot) homologation (Scheme 5). Borane **4j** performed well giving tertiary alcohol **8j** in 56% yield and >95:5 dr. Again higher yields of **8j** and greater conversion of **4j** was observed with an additional dose of the **Li-1a**. In contrast, further homologation of **4a** was unsuccessful. The small amount of cumyl alcohol formed showed that any boronate that might have formed (**7**) resulted in Me migration, not *t*-alkyl migration. Similarly, no further homologation of the borane precursor to **8j**

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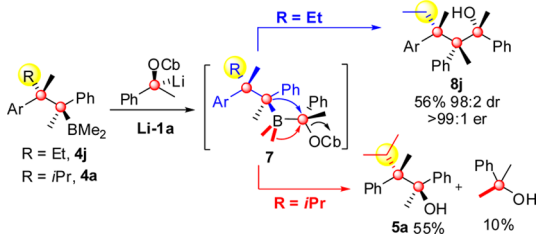
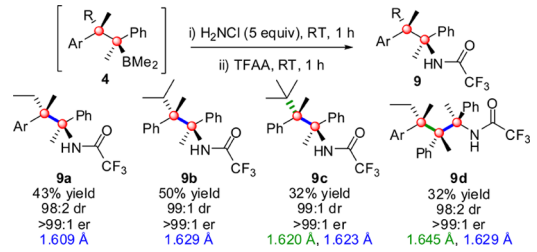
Scheme 5. Limit of Extended Homologations



Scheme 6. Synthesis of C-Tertiary Amides and C−C Bond Length between Adjacent Fully Substituted Carbons



could be achieved. The results show the limit to the number of sequential homologations that can be conducted using this protocol and how subtle steric effects on the remote quaternary center can have a big impact on the feasibility of a distant homologation reaction.

Other transformations of the hindered boranes were also explored. Although both Zweifel olefination and Matteson homologation were unsuccessful,[17] amination using chloramine[18] worked well leading to the trifluoroacetamide **9a** after work up (Scheme 6).[19] This protocol was applied to the series of representative boranes of increasing steric congestion delivering the amides in moderate-good yield considering the number of steps involved. The amides were all crystalline and this not only enabled us to determine their relative and absolute stereochemistry but also to study this substrate class further.[20] Examples of quaternary substituted adjacent carbons in acyclic systems indicate an exceptionally long C−C bond length between the quaternary carbons[21] due to Pauli repulsions between their substituents. Indeed, the quat-quat C−C bond length in our trifluoroacetamides increased with increasing steric properties of the substituents from 1.609 to 1.645 Å.

Table 1. Relative Gibbs Free Energies (kcal mol^{-1}) Computed with LCCSD(T0)-F12/AVDZ//B3LYP-D2/6-31+G(d)

species [migrating group]	ate complex	TS	barrier[a]
BMe_3 [Me]	−15.6	13.0	28.5
*t*Bu-BMe_2 [Me]	−11.0	15.0	26.0
*t*Bu-BMe_2 [*t*Bu]	−8.1	14.8	25.8 [22.9[b]]
*t*BuCMe_2-BMe_2 [Me]	−1.4	−[c]	−[c]
*t*BuCMe_2-BMe_2 [*t*BuCMe_2]	1.0	−[c]	−[c]

[a]Barrier height relative to the most stable conformer of the corresponding ate complex unless mentioned otherwise. [b]Intrinsic activation barrier, i.e., with respect to the corresponding conformer of the ate complex. [c]Not computed.

In order to understand the trends in migratory group behavior, accurate correlated electronic structure calculations (local coupled cluster theory,[22] see details in the Supporting Information) have been performed. From reactants, ate complex formation is predicted to be favorable in free energy terms and presumably involves a low barrier. The 1,2 migration step is highly exothermic (Figure 1) but has a significant barrier and should therefore be rate-limiting.

Migration of *t*Bu in the case of reaction with *t*BuBMe_2 is found to be intrinsically easier than Me migration[23] (with an intrinsic barrier relative to the corresponding conformation of the ate complex 3.1 kcal mol^{-1} lower, see Table 1), in line with the stronger nucleophilicity of *t*Bu. However, the conformation required for *t*Bu migration is less stable by 2.9 kcal mol^{-1}. Hence overall, at the "best" level of theory used here, as shown in Table 1, the transition state for *t*Bu migration lies just 0.2 kcal mol^{-1} lower in free energy than that for Me migration. This would imply much lower selectivity than is found experimentally. We suggest that this discrepancy is due to the use of truncated models of the carbamate group and the diethyl ether solvent or remaining inaccuracies in the computational protocol.[24] As the borane increases in size, formation of the ate complex is increasingly difficult (see *t*BuCMe_2-BMe_2 entries in Table 1) due to increasing steric hindrance. If ate complex formation then becomes reversible, this could account for why additional doses of the lithiated carbamate improve conversion of the especially hindered intermediate boranes **4g/h/j**. This will also make the homologation TSs increasingly high in energy, consistent with the inability to go beyond making three contiguous quaternary centers shown in Scheme 5. Our computations also help to understand why patterns in migratory group aptitude are so

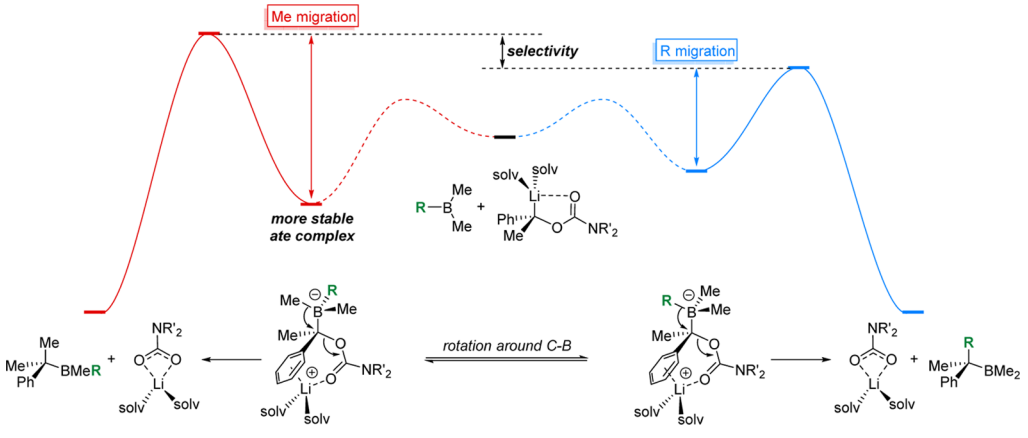


Figure 1. Schematic Gibbs free energy surface for the reaction of $RBMe_2$ (R = alkyl) with a generic lithiated carbamate (R′ = Me).

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complex, with, e.g., both Me and bulky groups considered to be nonmigrating in specific cases. The final outcome is a delicate balance between the intrinsic reactivity of the migrating group and conformational effects.[25]

In conclusion, lithiation-borylation methodology has been used to construct adjacent multiple quaternary substituted stereocenters with full control over relative and absolute stereochemistry. The key to success has been the use of mixed boranes which are more electrophilic and have a lower barrier to 1,2-migration than boronic esters. In addition, an expedient amination of tertiary boranes was developed, giving highly hindered C-tertiary amines with excellent diastereo- and enantioselectivity.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data for all products, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) Without modification of conditions, 5−10% of **ent-5a** was also formed. We believe this originates from the presence of a small amount of unreacted iPrMe$_2$B which remained after the first homologation and then reacted twice with excess **ent-Li-1**. This was solved by evaporation of all the volatiles after the first homologation which removed the excess iPrMe$_2$B and thus led to high diastereoselectivity.

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(24) As shown in the Supporting Information, the relative free energy of the key TSs is sensitive to the level of theory and the model used, though in all calculations tBu migration is predicted to be favored (see the Supporting Information). Indeed, the 0.2 kcal mol^{-1} free energy gap obtained with our "best" level of theory, using a truncated model of the carbamate group, is the smallest gap obtained. Dispersion-corrected DFT and use of a larger model both lead to larger energy gaps.

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