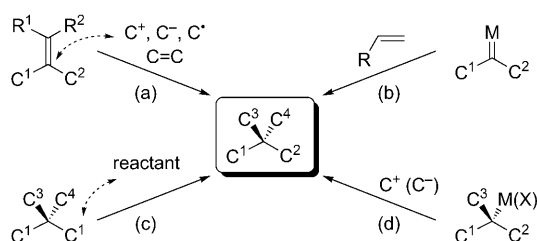# Construction of Asymmetric Quaternary Carbon Centers with High Enantioselectivity

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asymmetric synthesis · borates · carbenoids · enantioselectivity · synthetic methods

The enantioselective construction of a quaternary carbon center substituted with four distinct carbon-centered groups is one of the great challenges in organic synthesis.[1] The possible approaches can be classified conceptually into the following four categories (Scheme 1): a) C−C bond formation at an sp²-hybridized carbon center substituted with two carbon groups


Scheme 1. General approaches to the enantioselective construction of quaternary carbon centers (C¹, C², C³, and C⁴ denote carbon substituents).

upon reaction with a carbon-centered reagent (an electrophile, nucleophile, radical, or olefin; e.g., alkylation of enolates, Michael addition, Diels–Alder reaction); b) simultaneous double C−C bond formation between a carbene and an unsymmetrical olefin (cyclopropanation); c) desymmetrization of a prochiral quaternary carbon atom (i.e., group-selective reaction of enantiotopic C¹ moieties); and d) stereospecific reaction of an optically active *tert*-alkyl metal reagent or (pseudo)halide with a carbon electrophile or nucleophile. The first three methods involve the development of enantioselective reactions with the aid of chiral catalysts, reagents, and auxiliaries. Most successful examples reported to date of the asymmetric synthesis of quaternary carbon centers belong to these categories.[1] In contrast, the fourth strategy remains unexplored, because the preparation of optically active *tert*-alkyl metal compounds or (pseudo)ha-

lides and stereospecific carbon–carbon bond-forming reactions of these compounds are extremely difficult.[2]

Recently, a versatile and powerful approach to the construction of quaternary carbon centers with high enantioselectivity was established by Aggarwal and co-workers (Scheme 2).[3] Previously, they had succeeded in preparing
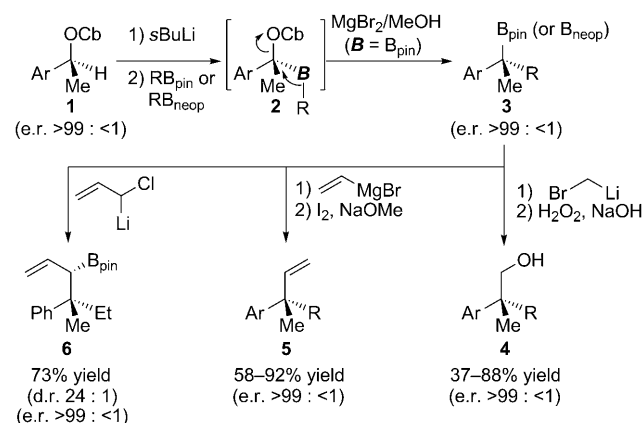
Scheme 2. Preparation of optically active *tert*-alkyl boronates **3** and their conversion into compounds **4–6** containing quaternary carbon centers (Cb = CON*i*Pr₂, B_pin = pinacolatoboryl, B_neop = neopentyl glycolatoboryl, e.r. = enantiomeric ratio).

tert-alkyl boronates with excellent enantioselectivity from carbamates **1**, which are derived from readily available optically active secondary alcohols, through homologation of a borate complex.[4] The deprotonation of **1** with *s*BuLi, followed by treatment with RB_pin or RB_neop at low temperatures, generated the corresponding borate **2**. Upon warming of the reaction mixture to room temperature, a carbon substituent R underwent 1,2-migration from the boron to the carbon atom with elimination of the OCb group to yield the *tert*-alkyl boronic acid pinacolyl ester **3**.

The synthetic utility of boronates **3** was demonstrated by their use for the preparation of enantiomerically enriched tertiary alcohols. When RB_pin was used for the synthesis of **3**, the addition of MgBr₂ and MeOH after borate formation was essential to obtain **3** in an enantiomerically pure form in good to high yields. Because **2** with sterically demanding groups can undergo dissociation back to RB_pin and the lithiated carba-

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mate, which is prone to racemization upon warming, $MgBr_2$ and MeOH are thought to accelerate the 1,2-migration of R by acting as a Lewis acid and by quenching (protonating) the liberated lithiocarbamate, respectively. On the other hand, no additive was necessary for the homologation with RB_{neop}. This result implies that **2** generated from RB_{neop} does not experience the severe steric hindrance that causes dissociation.

With enantiomerically pure **3** in hand, Aggarwal and co-workers examined Matteson homologation,[5] vinylation as described by Zweifel and co-workers,[6] and three-carbon-atom homologation according to Brown et al. (Scheme 2).[7]

When pinacol boronate **3a** (Ar = Ph, R = Et) was subjected to standard Matteson homologation with $ClCH_2Li$ and then to oxidation, the desired product **4a** (Ar = Ph, R = Et) was obtained in 71% yield along with the tertiary alcohol derived from **3a** (**B** = OH) in 20% yield. Monitoring of the reaction by ^{11}B NMR spectroscopy indicated the formation of **8** by O migration in the borate generated from **3** and $ClCH_2Li$ (Scheme 3).[8] Aggarwal and co-workers envisioned that a

Scheme 3. Proposed mechanism for C and O migration.

borate bearing a bulky and less polar leaving group would prefer a conformation suitable for C migration to one for O migration, as in the case with a bromide group as the leaving group X. Thus, when **3a** was treated with $BrCH_2Li$[9] and then with H_2O_2/NaOH, the yield of **4a** increased to 83%, and the yield of the tertiary alcohol diminished to 5% (Scheme 2). As *tert*-butyl and thexyl groups in boronates are reportedly reluctant to undergo 1,2-migration, the smooth homologation with complete chirality transfer is remarkable.

Next, the Zweifel vinylation protocol (treatment with one equivalent of $H_2C=CHMgBr$ and then I_2 and NaOMe) was applied to **3a**. However, **5a** (Ar = Ph, R = Et) was formed in only 26% yield. ^{11}B NMR spectroscopic analysis of the reaction mixture provided insight into the unusual outcome: trivinylborate **10** was formed instead of the expected borate **9**, and a large amount of **3a** remained unreacted. This observation led Aggarwal and co-workers to use four equivalents of $H_2C=CHMgBr$, which resulted in the complete consumption of **3a** and a much higher yield of **5a** (Scheme 2). The modified procedure was general for boronates **3**. Since it is reasonable to assume that the iodonium salt **11** is generated upon the

addition of I_2, the good yield of **5** indicates that the migratory aptitude of an ArMeRC moiety is higher than that of a vinyl group. The synthetic utility of the vinylation reaction was demonstrated by the concise and highly enantioselective synthesis of (+)-(S)-sporochnol,[10] a natural product isolated from a Caribbean marine alga (Scheme 4).

Scheme 4. Synthesis of (+)-(S)-sporochnol.

The homologation of **3a** with 1-chloroallyllithium was found to occur smoothly to give **6** in good yield with high diastereoselectivity and perfect stereospecificity (Scheme 2). Since 1-chloroallyllithium was generated from allyl chloride and lithium diisopropylamide as a racemic mixture, the excellent stereochemical outcome implied that the dynamic kinetic resolution of the carbenoid with **3** was effective.

The study by Aggarwal and co-workers clearly demonstrates the versatility of *tert*-alkyl boronates as reagents for the enantioselective construction of quaternary carbon centers. At present, the presence of an aryl group at the stereogenic carbon atom is inevitable when **3** is prepared by the homologation of **1**.[4] Alternatively, Hoveyda and co-workers recently carried out copper-catalyzed asymmetric boryl addition/substitution reactions with α,β-unsaturated (thio)esters and allylic carbonates. These reactions provided not only boronates of type **3** but also non-arylated boronates **12** and **13** with a high enantioselectivity (Scheme 5).[11] It

Scheme 5. Copper-catalyzed asymmetric synthesis of *tert*-alkyl boronates **12** and **13**. NHC = N-heterocyclic carbene.

would be intriguing to apply the transformations described herein to non-arylated boronates to widen the substrate scope and also investigate whether the presence of an aryl group in **3** significantly influences the stereochemical outcome of the homologation and olefination reactions.

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