Enantioconvergent carbenoid insertion into carbon−boron bonds

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Boron-mediated homologation can potentially access almost any kind of chiral centers from readily available boronates via asymmetric carbenoid insertion, followed by versatile transformations of the carbon−boron bonds. However, the current asymmetric boron homologation strategies exhibit limitations, and enantioselective insertion of diversely substituted carbenoids remains challenging. Here we report an enantioconvergent approach for direct insertion of carbon-, oxygen-, nitrogen-, sulfur-, and silicon-substituted carbenoids into carbon−boron bonds. The excellent enantioselectivity is enabled by a new class of chiral oxazaborolidines derived from inexpensive α-amino esters. Computational studies revealed that the non-C2-symmetric oxazaborolidine features a puckered geometry and the cooperative effects of multiple substituents create an asymmetric environment for effective enantioinduction. This method is scalable, and each chiral center can be independently controlled by the chiral oxazaborolidine without being influenced by nearby stereocenters. Besides forming singular chiral centers, iterative operations of this asymmetric homologation simplify synthesis of complex molecules with multiple stereocenters.

Enantioselective construction of chiral centers remains a nontrivial task for synthesis of complex organic molecules. While numerous asymmetric synthetic methods have been developed so far, a unified approach that can directly convert a common functional group (FG) to a large variety of chiral centers would be highly attractive from the strategic development viewpoint (Fig. 1a), which however has been elusive. On the other hand, boron-based homologation reactions, namely Matteson-type reactions[1-8], enable insertion of methylene or substituted methylene units to carbon−boron bonds through forming an ate-complex between a carbenoid and a boron center, followed by 1,2-metallate migration (Fig. 1b). In particular, the asymmetric Matteson-type reaction can directly introduce boron-containing C(sp^3) stereocenters from readily available boronates without relying on other existing FGs. Owing to the versatile reactivity of carbon−boron bonds, a wide range of chiral centers could in principle be accessed if diversely substituted carbenoids can be inserted[9-13]. Alternatively, the iterative homologation permitted by the Matteson-type reactions holds enormous potential for programmable stereoselective synthesis of complex molecules with multiple chiral centers[14-22].

To date, two strategies have been developed to achieve the asymmetric boron homologation. One is based on *desymmetrization* in the 1,2-boronate migration step (Fig. 1c), which involves boronate homologation with achiral carbenoid $LiCHCl_2$ followed by diastereotopic or enantiotopic displacement of one of the chlorides, enabled by either chiral auxiliaries or chiral catalysts[23-26]. The resulting chloromethylene insertion product can then react with a nucleophile

and undergo another 1,2-metallate rearrangement reaction in a separate step to introduce a new FG with stereoinversion. While the Matteson's desymmetrization approach has been successfully applied in the syntheses of several complex molecules[14-16, 21,22], it is not without limitations. First, it is a two-step procedure, and not all FGs can be introduced via the post-transformation as a nucleophile. In addition, the two most commonly used chiral auxiliaries are derived from (1*R*,2*R*)-1,2-dicyclohexylethane-1,2-diol and (+)-pinanediol; but the former is costly to prepare (expensive chiral substrates with rhodium catalysis)[27], and the latter is difficult to undergo auxiliary switch[28]. The use of a chiral Lewis acid catalyst provides an alternative choice for desymmetrization[25], albeit only with alkyl boronate substrates. The second strategy is capitalized on the use of enantioenriched carbenoids to achieve *enantiospecific* boron homologation, in which substituted methylene groups can be directly introduced in one step (Fig. 1d)[29-31]. However, there is an intrinsic dilemma about using enantioenriched carbenoids, which is the need to balance their configurational stability versus reactivity. For example, while the chiral α-chloroalkyl lithium species used in the pioneer work of Blakemore are highly reactive, their preparation often suffers from erosion of enantiopurity due to epimerization of the sulfoxide precursors[32]. On the other hand, impressive applications have been demonstrated using more stable enantioenriched Hoppe-type carbenoids[33] (i.e., lithiated carbamates/benzoates) by Aggarwal and coworkers[3], though the tradeoff is that heteroatom-substituted methylene units are challenging to be introduced[34]. In addition, the concern of practicality and tunability associated with the chiral sources employed in this approach cannot be ignored[35].

Inspired by the existing constraints of the asymmetric Matteson reactions, here we describe the development of an enantioconvergent[36-37] homologation strategy to construct diverse tertiary chiral centers using readily available racemic carbenoids, in which the stereochemical outcomes can be controlled and tuned by inexpensive chiral sources (Fig. 1e). Compared to the desymmetritive strategy, this method can directly introduce functionalized methylenes. Also, complementary to the enantiospecific approaches, various heteroatom-substituted carbenoids can be efficiently inserted through the enantioconvergent homologation.

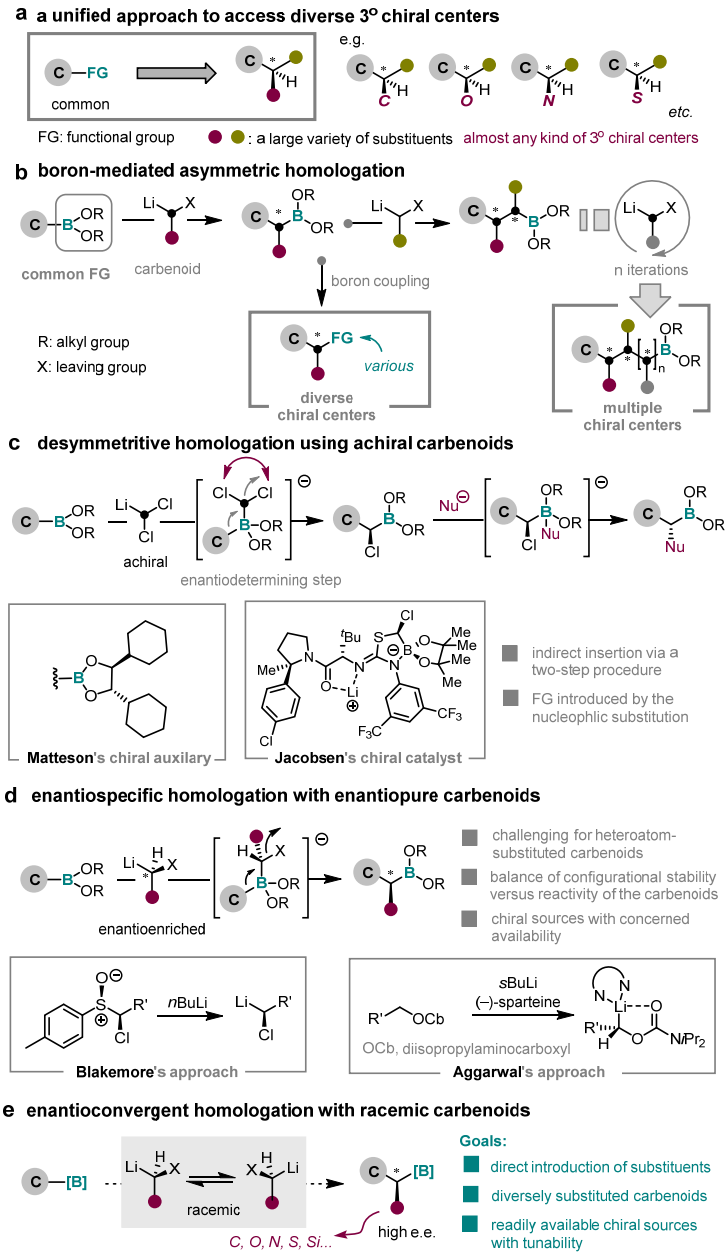

Figure 1. Strategies for asymmetric boron homologation. **a**, A unified approach to access diverse tertiary chiral centers remains to be developed. **b**, Boron-mediated asymmetric homologation reactions can potentially lead to almost any kind of tertiary chiral centers after boron coupling if various substituted carbenoids can be asymmetrically inserted. Iterative boron homologation can construct multiple chiral centers. **c**, Desymmetritive homologation using achiral carbenoids requires a two-step process. Nu, nucleophile; Me, methyl. **d**, Enantiospecific homologation with enantioenriched carbenoids is a powerful method, albeit with limitations. *n*BuLi, *n*-butyl lithium; *s*BuLi, *sec*-butyl lithium. **e**, The proposed enantioconvergent homologation uses readily available racemic carbenoids and can access diverse chiral tertiary centers.

Results and discussion

Strategy design and reaction optimization. To realize the enantioconvergent boron

homologation, it would be important to first understand why the known chiral 1,2-diol-based auxiliaries are not adequate. One can imagine that, when using racemic carbenoids as the reagent, the enantio-determining step is shifted to the addition of the carbenoid to the boron center, as the following 1,2-boronate migration is stereospecific. When chiral diols are used as the auxiliary, as depicted in Fig. 2a, the bulky substituents on the chiral backbone are too far from the boron center; thus, the chiral information is likely difficult to be relayed to the reaction site. Based on this postulation, we hypothesized that a chiral pocket near the boron center could be restored *if one oxygen substituent at the boron center is replaced by nitrogen*, i.e., based on β-amino alcohols, as the trivalent nitrogen will bring an additional substituent that can relay the steric information from the chiral backbone (Fig. 2b). When the chiral auxiliary becomes non-C2-symmetrical after introducing the nitrogen, one face of the boron could be effectively blocked while creating an asymmetric environment necessary for the desired enantioinduction. In addition, from the practicality viewpoint, both enantiomers of the β-amino alcohol-based auxiliaries can be easily accessed from the corresponding inexpensive α-amino esters. Moreover, the large chiral pool of amino acids and the flexibility of changing the *geminal* substituents on the oxygen side render great tunability of this approach.

To explore the enantioconvergent boron homologation, 2-naphthareneboronic acid was used as the model substrate, which can be smoothly converted to the corresponding oxazaborolidines via condensation with different β-amino alcohols. After careful screening of a number of β-amino alcohols and different reaction conditions (for additional optimization, see Supplementary Table 1), oxazaborolidine **1a** derived from (*S*)-*N*-(1,1-dicyclohexyl-1-hydroxy-3-methylbutan-2-yl)-4-methylbenzenesulfonamide **A1**, was efficiently homologated with $PhCH_2CH_2CHBrLi$ (generated in situ from $PhCH_2CH_2CHBr_2$ **2a** and *n*-butyl lithium at −78 °C) in tetrahydrofuran (THF) to give chiral alcohol **3a** (after peroxide oxidation) in 90% yield and 99:1 enantiomeric ratio (er) (Fig. 2c). For this substrate, the C1 cyclohexyl (Cy), C2 isopropyl (*i*Pr), and *N*-tosyl (Ts) groups are all essential for the high yield and high enantioselectivity (vide infra, computational study). For example, when a bulkier C1 substituent was used, e.g., in oxazaborolidine **S1** (changing the Cy to *i*Pr), both the yield and er dropped significantly. While changing the C1 Cy groups to cycloheptyl (**S2**) gave a similar er, the one with C1 cyclopentyl (**S3**) or phenyl (Ph) groups (**S4**) gave much lower er. The C2 substituent plays an even more important role in controlling the enantioselectivity, as simply replacing the C2 *i*Pr with ethyl (**S5**) and Ph (**S6**) groups led to low enantioselectivity. Interestingly, oxazaborolidine **S7** with phenyl groups at both C1 and C2 positions slightly favors forming the opposite enantiomer. As anticipated, the protecting group (PG) on the nitrogen has a profound impact on both reactivity and enantioselectivity. Besides Ts, other arylsulfonyl PGs (**S8** and **S9**) gave the same er with somewhat lower yield. The carbamate PG (**S10**) showed high reactivity but moderate er. In contrast, *N*-protection with urea (**S11**) and benzyl (Bn) (**S12**) PGs led to no reactivity, probably due to the reduced electrophilicity of the boron center. For comparison, the boronate substrates derived from the chiral diols used in Matteson's protocol only afforded poor enantioselectivity (**S13** and **S14**), which is consistent with the hypothesis (Fig. 2a). Notably, when the carbenoid was used as the limiting reagent, the desired product can be obtained in 81% isolated yield with 97:3 er under the same reaction condition. The high yield and high er do not suggest a kinetic resolution mechanism for this reaction, which instead

support the proposed enantioconvergent pathway.

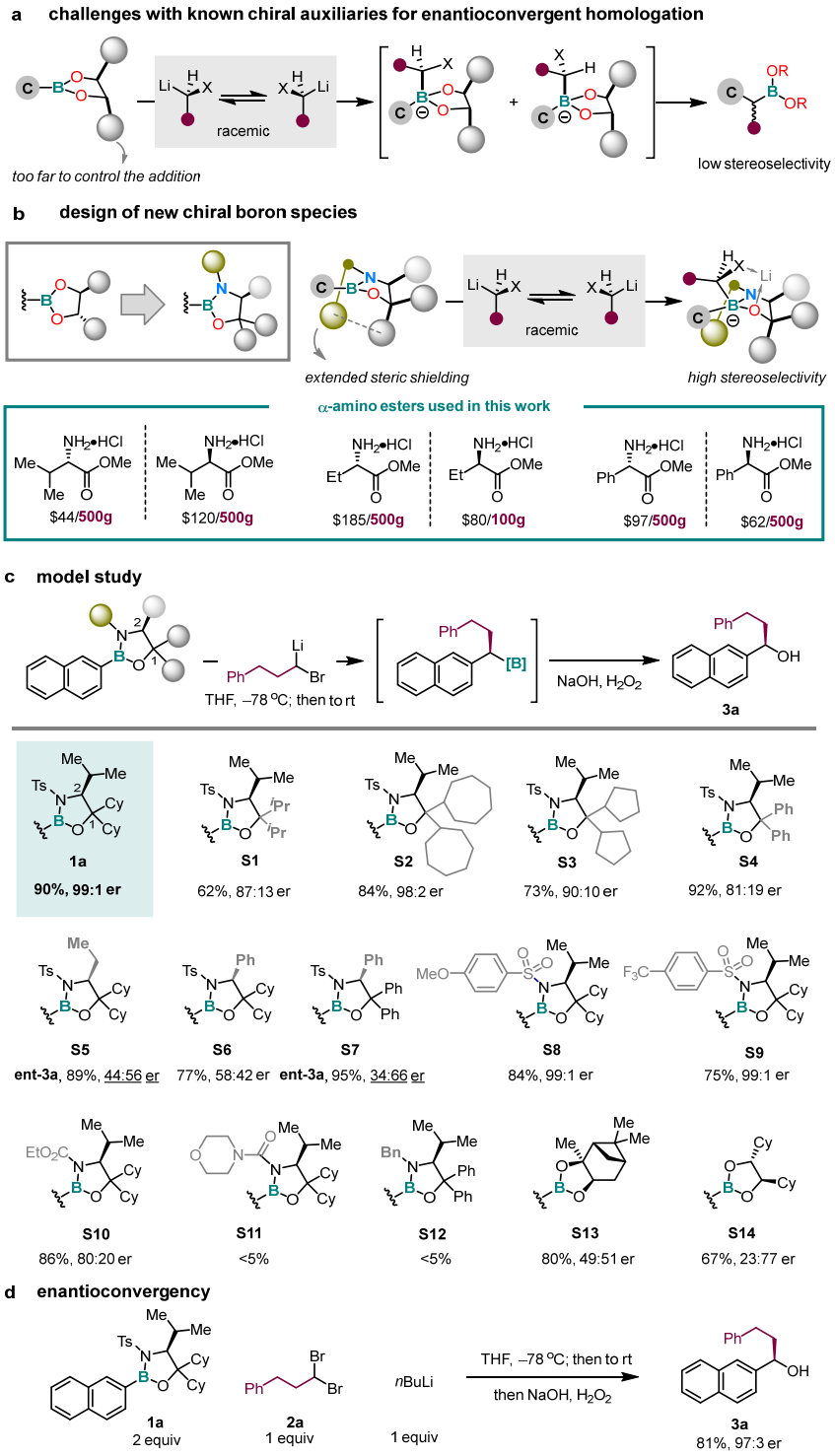

Figure 2. Design for the enantioconvergent boron homologation. a, The known chiral diol auxiliaries are challenging for enantioconvergent homologation, as the substituents on the chiral backbones are too far from the boron center. **b**, New chiral boron auxiliaries derived from inexpensive α-amino esters are designed, which can effectively provide a chiral pocket around the boron center. **c**, Model study identifies the optimal chiral auxiliary (**1a**) for the asymmetric homologation with aryl boronic substrates. **d**, The enantioconvergency of this reaction

has been examined with a limited amount of carbenoid reagent. Reaction conditions: 1) **1a** or **S** (0.1 mmol, 1.0 equiv), **2a** (0.2 mmol, 2.0 equiv), *n*BuLi (0.18 mmol, 1.8 equiv), THF (1.5 mL), –78 °C, 30 min, rt, 1 h; 2) H_2O_2 (0.25 mL, 30% aq.), NaOH (0.5 mL, 2.0 M aq.), 0 °C to rt, 1 h. Yields were determined by ^{1}H NMR (nuclear magnetic resonance) spectroscopy using $CHCl_2CHCl_2$ as an internal standard. aq., aqueous solution.

Computational study. To elucidate the origin of stereoselectivity for this reaction, we conducted computational studies using density functional theory (DFT) (Fig. 3). The computed geometries of oxazaborolidines **S1′** bearing *gem*-di-Cy groups at C1 and an *i*Pr at C2 and **S5′** with an Et in place of *i*Pr at C2 revealed a profound impact of these substituents on the conformation of the chiral auxiliary (Fig. 3a). While the five-membered ring in **S5′** is almost completely planar, **S1′** is significantly puckered by 32.1° to avoid the steric clash between C2-*i*Pr and one of the C1-Cy groups (Supplementary Figs. 1 and 2). In this puckered geometry, the Cy substituent at the (*Re*)-face is placed in a pseudoaxial position, rendering the (*Re*)-face less accessible due to the proximity of the bulky Cy group to the B center. In addition, this Cy group forms a strong C–H-π interaction with the *N*-Ts group—the lowest energy conformer without such C–H-π interaction is 2.6 kcal/mol less stable—which further restricts access to the (*Re*)-face. On the other hand, the Cy group at the (*Si*)-face of **S1′** is in a pseudoequatorial position, pointing away from the B center. The cooperative effects of the Cy, *i*Pr, and *N*-Ts substituents in **S1′** are evidenced by comparing with the geometry of **S5′**. The reduced steric interaction between Et and Cy allows the five-membered ring of **S5′** to adopt a nearly planar geometry (puckering angle = 6.6°), where the *gem*-di-Cy groups are placed nearly symmetrically at the two prochiral faces. In addition, the longer distance between the Cy and Ts groups weakens the C–H-π interaction as evidenced by the long 4.21 Å distance and a smaller energy (1.0 kcal/mol) required to place the *N*-Ts group to the opposite face of the boron. Consequently, both (*Si*)-and (*Re*)- faces of **S5′** remain accessible for carbenoid attack. The ensembles of low-energy conformers of **S1′** and **S5′** indicated that **S1′** is relatively rigid, and the puckered conformation is maintained in all conformers within 1.7 kcal/mol of the lowest-energy structure, whereas the five-membered ring of **S5′** can be planar or puckered either above or below the plane within the same energy window (Supplementary Fig. 1). This result is consistent with the substantially diminished enantioselectivity when oxazaborolidine **S5** was used in place of **1a** (Figure 2).

To investigate how the asymmetric steric environment of oxazaborolidine induces enantioselectivity in homologation, we calculated the energy profiles of the reaction of **S1′** with both enantiomers of carbenoid **C1** (Fig. 3b). Given that the carbenoid addition to form boronate anion (**Int-1a**/**Int-1b**) is highly exothermic and irreversible, and that the subsequent 1,2-migration (**TS2a**/**TS2b**) and peroxide oxidation are stereospecific, the enantioselectivity of the overall transformation is determined in the carbenoid addition step. In the most favorable carbenoid addition transition states with both (*S*)- and (*R*)-**C1** (**TS1a** and **TS1b**, respectively), the Li coordinates to the oxazaborolidine oxygen atom, while the sterically least hindered substituent (H) on the carbenoid is placed towards the oxazaborolidine ring and the methyl group points away from the oxazaborolidine to minimize steric repulsions. Therefore, the additions of (*S*)- and (*R*)-**C1** occur at the (*Si*)- and (*Re*)-faces of **S1′**, respectively (see Supplementary Fig. 3 for less stable transition state isomers). These transition state geometries highlight the importance of imposing different degrees of steric hinderance at the two prochiral faces of the oxazaborolidine. The addition of (*S*)-

C1 to the less hindered (*Si*)-face of **S1′** is 1.3 kcal/mol more favorable, which corresponds to a 97:3 er, consistent with the observed enantioselectivity favoring (*R*)-alcohol products in reactions with oxazaborolidine **1a**.

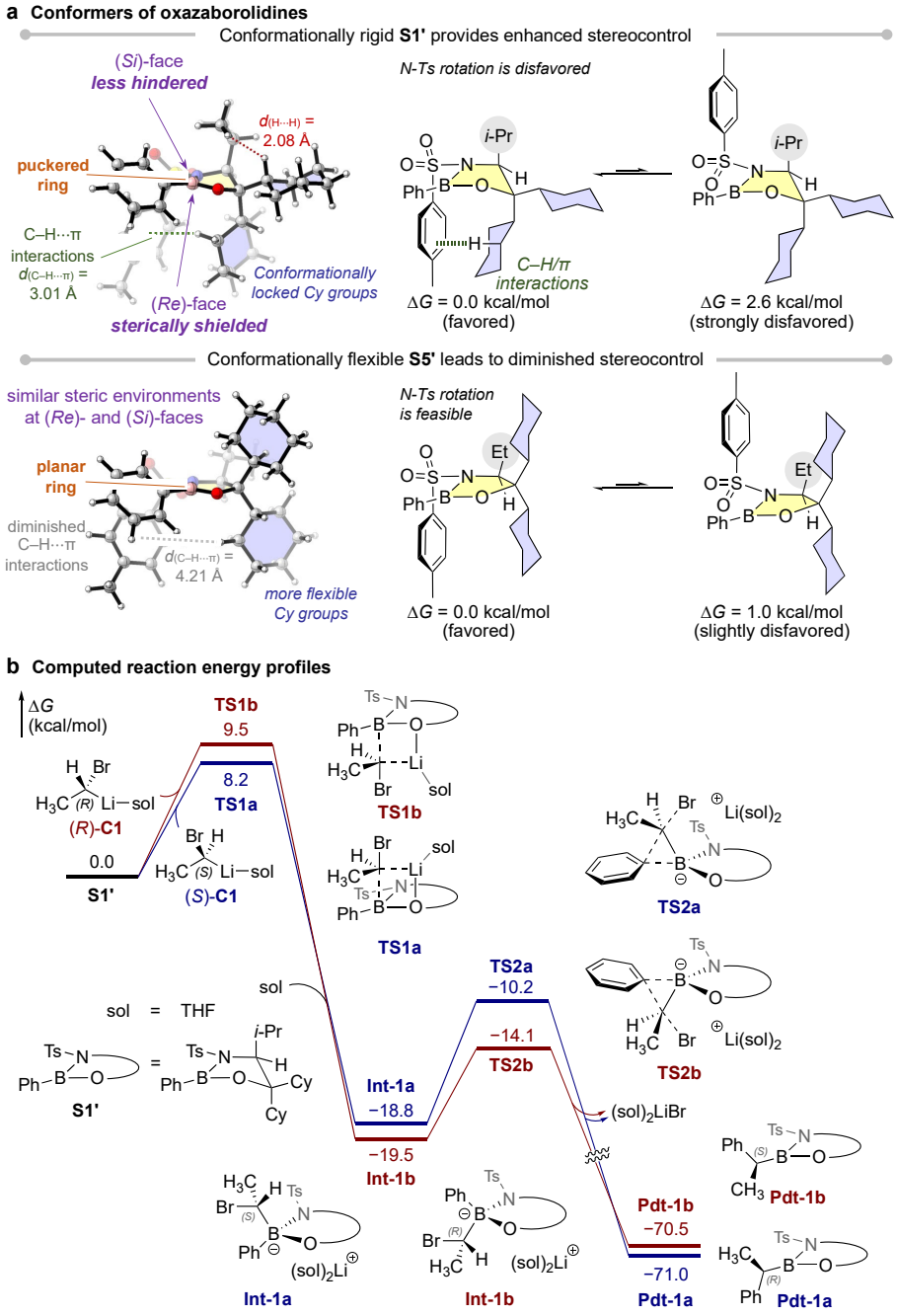

Figure 3. Computational Investigations. a, Conformers of oxazaborolidines **S1′** and **S5′** have been calculated, which show that puckered conformation is favored for oxazaborolidines **S1′** and planar conformation is favored for oxazaborolidines **S5′**. **b**, Computed reaction energy profiles of the asymmetric homologation of oxazaborolidine **S1′** with carbenoid (*S*)-**C1** and (*R*)-**C1** reveal the origin of the enantioselectivity. All calculations were performed at the M06-2X/6-311+G(d,p)/SMD(THF)//M06-2X/6-31G(d) level of theory.

Substrate scope and synthetic applications. The scope of the enantioconvergent homologation reaction was evaluated (Fig. 4). Using $PhCH_2CH_2CHBr_2$ as the carbenoid precursor, a wide range of aryl and heteroaryl boronic substrates were efficiently homologated to give the desired products in good to excellent yields and excellent er (**3a-q**, 60%-94% yields, 92:8 to >99:1 er). Substituents at para (**3c-l**), meta (**3m**), and even ortho (**3n**) positions can all be tolerated, although for the ortho substituted substrates (e.g., **3n**), using a less bulky chiral auxiliary (i.e., the one with *gem*-di-phenyl at C1 and phenyl at C2) was required to ensure high reactivity and high enantioselectivity. FGs, such as trimethylsilyl (**3e**), thiol ether (**3g**), bromo (**3h**), chloro (**3i**), fluoro (**3j**), trifluoromethyl (**3k**), and cyanide (**3l**), were tolerated. Heteroarenes including furan (**3o**), thiophene (**3p**), and carbazole (**3q**) were compatible. Notably, the enantioselectivity is somewhat sensitive to the electronic property of the arenes, as the electron-deficient substrates (**3k-l**) gave slightly lower er than electron-rich ones (**3a-g**). The reaction can be easily scaled up to 2 mmol with comparable yield and excellent er (**3f**).

For alkyl boronic substrates, using the standard (*S*)-*N*-(1,1-dicyclohexyl-1-hydroxy-3-methylbutan-2-yl)-4-methylbenzenesulfonamide-derived oxazaborolidine **A1** led to no homologation product, likely due to the increased steric demand with the sp^3 hybridized alkyl group. We therefore hypothesized that a less bulky oxazaborolidine could restore the reactivity. Indeed, after the brief survey of various chiral β-amino alcohols (see Supplementary Table 2), (*S*)-*N*-(2-hydroxy-1,2,2-triphenylethyl)-4-methylbenzenesulfonamide **A8** was found to be optimal for both primary and secondary alkyl substrates, resulting in excellent yield and er (Fig. 4, **3r-3ac**). Notably, the electrophilic primary alkyl bromide moiety can be tolerated in the substrate, giving the desired product in 80% yield and 96:4 er (**3u**). Cyclic secondary alkyl substrates with different ring sizes (**3v-z**) and caged structures (**3aa**), as well as acyclic secondary alkyl substrates (**3ab-ac**), can all smoothly undergo this transformation (74%-93% yields, 95:5 to >99:1 er). Tertiary alkyl substrates also reacted in moderate yield and good er when derived from an even less bulky β-amino alcohol (**3ad**).

The scope of carbenoids was next studied. First, carbenoids bearing a remote FG, such as γ-alkyl chloride (**3af**), alkyne (**3ag**), ketal (**3ah**), ethyl ester (**3ak**) and β-alkyl bromide (**3al**), can all efficiently undergo the desired homologation in good yields and excellent er. One can imagine that the ester-substituted carbenoid bearing acidic protons (**3ak**) would be difficult to be generated via Hoppe's deprotonation approach[33], thus unsuitable for the enantiospecific homologation. In addition, considering that carbanion nucleophiles bearing a β-bromide moiety would be highly unstable, product **3al** would be challenging to access via Matteson's desymmetritive homologation−nucleophilic substitution protocol. Bulkier carbenoids containing a secondary alkyl substituent (**3ai**) and the one derived from lithocholic acid (**3aj**) smoothly enabled the homologation with excellent stereocontrol. It is noteworthy that the carbenoid bearing an alkyl iodide moiety can also be used, though the resulting product (**3am**) contains a minor brominated side-product; however, this mixture can be easily converted to cyclic ether **4** under basic conditions.

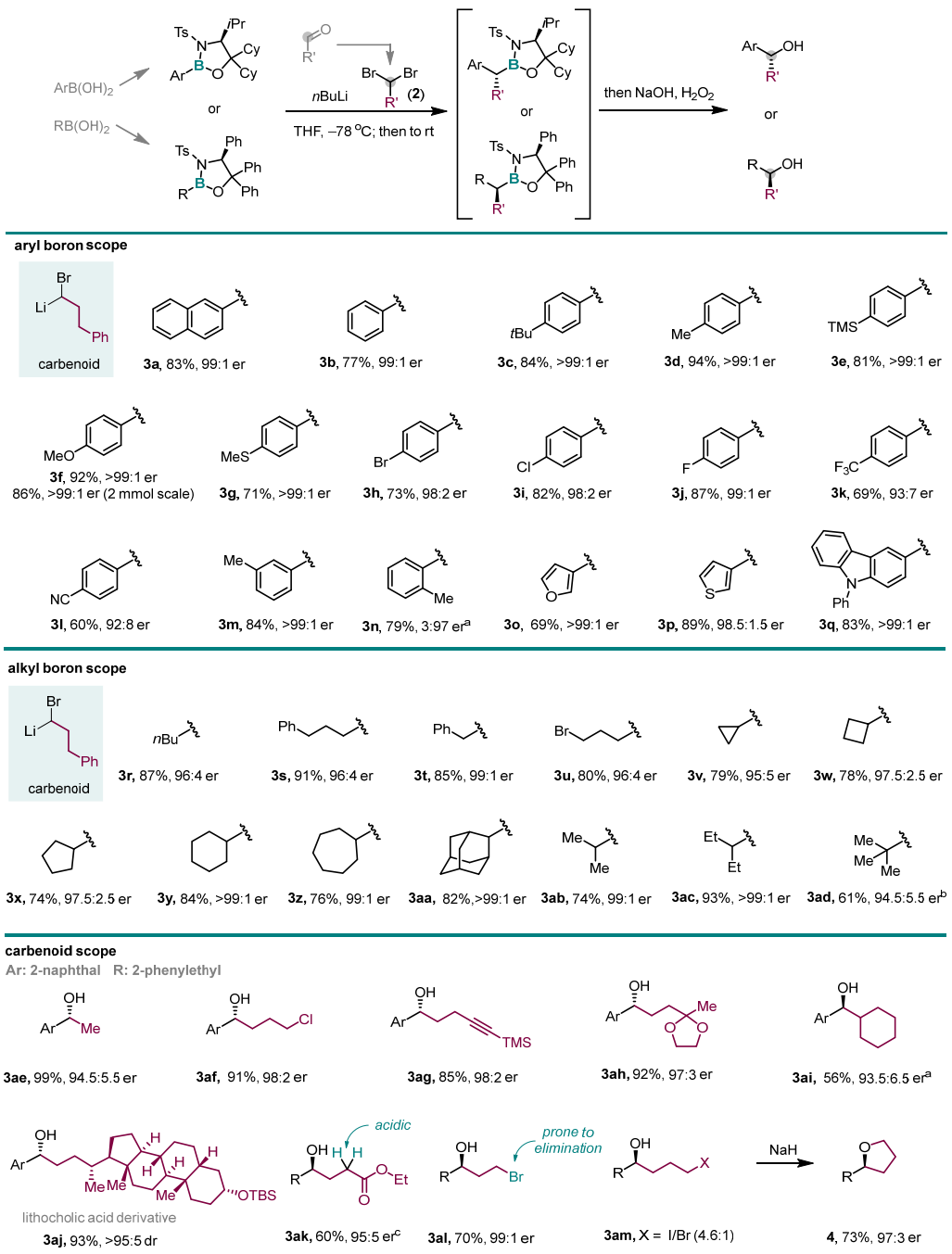

Figure 4. Scope of the enantioconvergent boron homologation with carbon-substituted carbenoids. Reaction conditions: 1) **1** (0.2 mmol, 1.0 equiv), **2** (0.4 mmol, 2.0 equiv), *n*BuLi (0.36 mmol, 1.8 equiv), –78 °C, 30 min, rt, 1 h; 2) H_2O_2 (0.5 mL, 30% aq.), NaOH (1.0 mL, 2.0 M aq.), 0 °C to rt, 1 h. rt, room temperature; TMS, trimethylsilyl; TBS, *t*-butyldimethylsilyl; Et, ethyl; dr, diastereomeric ratio. [a](*S*)-*N*-(2-hydroxy-1,2,2-triphenylethyl)-4-methylbenzenesulfonamide **A8** was used as the auxiliary. [b](*S*)-*N*-(2-ethyl-2-hydroxy-1-phenylbutyl)-4-methylbenzenesulfonamide **A13** was used as the auxiliary. [c]3 Equivalents of **2** and 3 equivalents *n*BuLi were used.

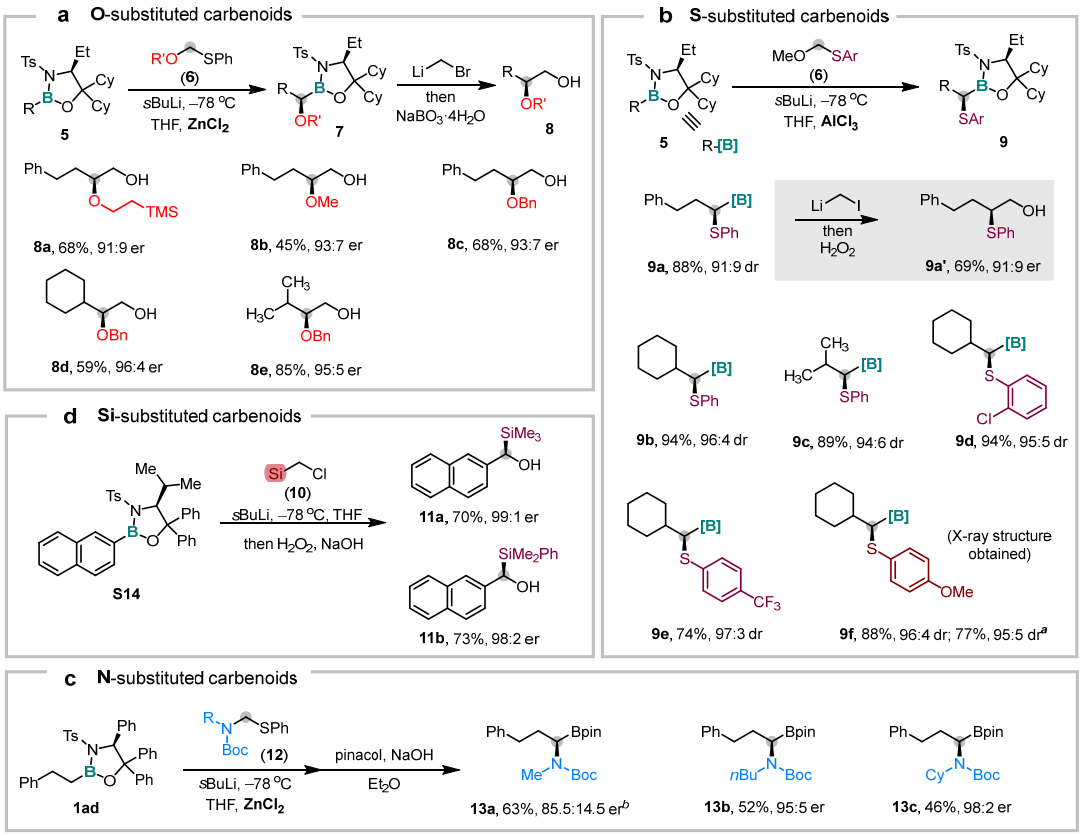

Figure 5. Asymmetric insertion of heteroatom-substituted carbenoids. a, Asymmetric insertion of oxygen-substituted carbenoids. **b**, Asymmetric insertion of sulfur-substituted carbenoids. **c**, Asymmetric insertion of nitrogen-substituted carbenoids. **d**, Asymmetric insertion of silicon-substituted carbenoids. [a]With carbenoid precursor **6** as the limiting agent. [b]**5d** as the substrate. Boc, *t*-butyloxycarbonyl; pin, pinacolato. For detailed reaction conditions, see Supplementary Information.

Besides carbon-substituted carbenoids, one advantage of this enantioconvergent method is the capability of directly inserting heteroatom-substituted carbenoids with high enantioselectivity (Fig. 5). We recently discovered that R'OCH$_2$SAr **6** can serve as an amphoteric carbenoid precursor, and by choosing different Lewis acids, selective insertion of oxygen- and sulfur-substituted methylenes can be realized[38]. When a soft Lewis acid, e.g., ZnCl$_2$, was used, alkoxy-substituted methylenes were introduced (Fig. 5a). The C1 Cy, C2 Et-derived oxazaborolidines (**5**) were found to be most effective. Due to the instability of intermediate **7** for purification, further homologation with LiCH$_2$Br followed by oxidation was carried out to give alcohol **8**. Primary (**8a-c**) and secondary (**8d-e**) alkyl boronic substrates can efficiently undergo this two-step homologation process in good yield and er. Different alkoxy groups, such as TMSCH$_2$CH$_2$O (**8a**), MeO (**8b**), and BnO (**8c**), can be introduced. When harder AlCl$_3$ was used as the Lewis acid, the same carbenoid precursor led to insertion of arylthio-substituted methylenes (Fig. 5b). The oxazaborolidine products (**9**) are stable to be directly isolated by silica gel chromatography, showing excellent yield and stereocontrol. Notably, **9f** can be obtained in 77% yield with 95:5 dr when carbenoid precursor **6** was used as the limiting agent, further supporting enantioconvergence of this reaction. The absolute stereochemistry of **9f** was

confirmed by X-ray crystallography (see Supplementary Information, section 11.1). Product **9a** can also undergo further homologation and oxidation to give β-thioalcohol **9a'** in 69% overall yield. In addition, the unprecedented asymmetric insertion of nitrogen-substituted carbenoids was also realized through the development of new carbenoid precursor **12** (Fig. 5c). The insertion products **13a-c** can be isolated in moderate yield and good to excellent enantioselectivity (85.5:14.5 to 98:2 er). Note that, the carbamate moiety is difficult to be introduced by the conventional Matteson reaction, and *the direct asymmetric insertion of oxygen-, nitrogen-, and sulfur-substituted carbenoids has not been reported by the previous approaches*. Finally, silyl-substituted carbenoids can also undergo highly enantioselective homologation with chloromethylsilanes as the carbenoid precursors (Fig. 5d, **11a-b**). It is worthy to mention that highly stereoselective insertion of simple silyl-substituted carbenoids with boronates has not been realized by the prior strategies[28, 39-40].

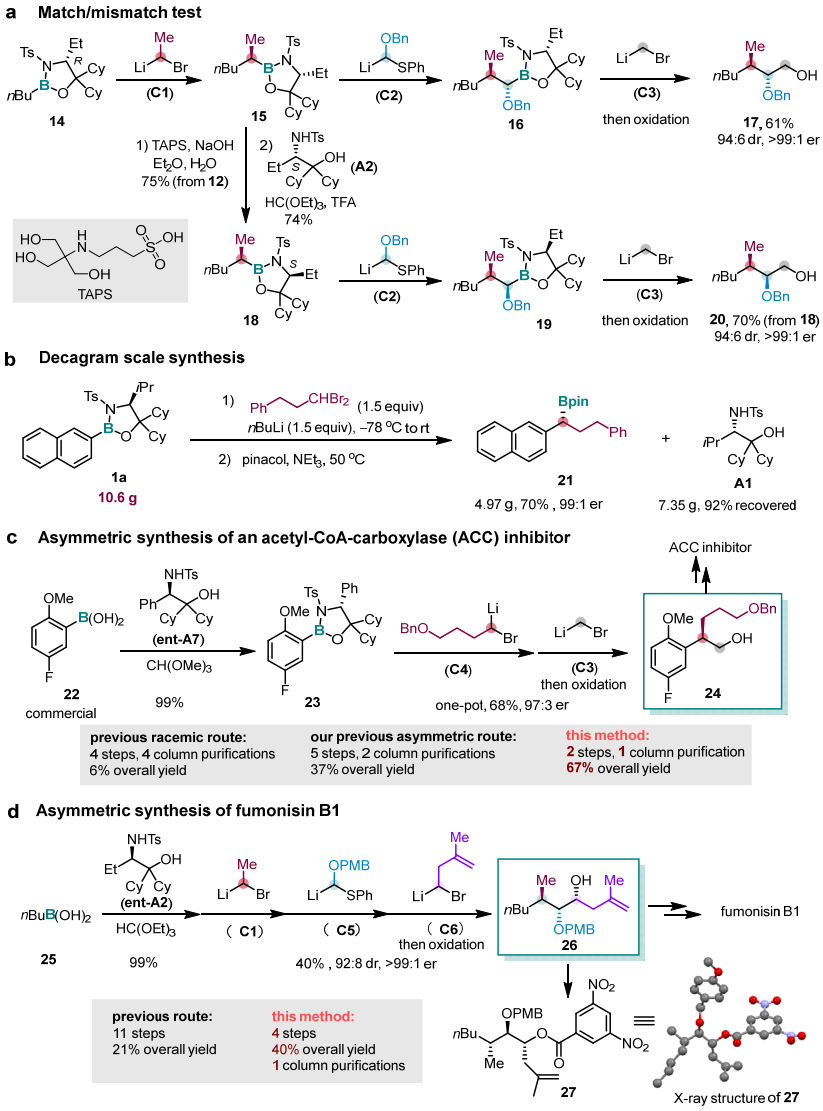

Figure 6. Synthetic utilities. a, The match/mismatch test shows that the asymmetric carbenoid insertion is not influenced by adjacent chiral centers. TAPS, *N*-[tris(hydroxymethyl)methyl]-3-aminopropanesulfonic acid. **b**, The reaction works well on a decagram scale, and the chiral auxiliary is recovered in high yield. **c**, Asymmetric formal

synthesis of an acetyl-CoA-carboxylase inhibitor is realized in 2 steps with 67% overall yield. **d**, Asymmetric formal synthesis of fumonisin B1 is realized in 4 steps with 40% overall yield. PMB, p-methoxybenzyl.

To examine whether the asymmetric carbenoid insertion is influenced by adjacent chiral centers, the match/mismatch experiments were carried out (Fig. 6a). Sequential homologation of oxazaborolidine **14** derived from the *R* enantiomer of the chiral auxiliary with carbenoids **C1**, **C2** and **C3** followed by oxidative quench afforded known compound **17** as the *anti* diastereomer in 61% yield (94:6 dr, >99:1 er)**,** whose characterization data match the literature report[41]. Meanwhile, switching the auxiliary to its enantiomer after the first homologation with **C1**[42], followed by the same remaining sequence, gave the *syn* diastereomer **20** in 70% yield, 94:6 dr and >99:1 er. These results indicate that the stereochemical outcome of each carbenoid insertion is governed by the chiral oxazaborolidine, independent from other existing stereocenters.

To show the synthetic utility of this asymmetric homologation method, a decagram-scale synthesis was carried out first. The reaction worked well with 10.6 g of **1a** as the substrate, and the homologated product **21** was isolated in 70% yield and 99:1 er after transesterification with pinacol (Fig. 6b). The chiral auxiliary **A1** can be recovered in high yield (92%). The application was next demonstrated in the asymmetric synthesis of alcohol **24**, a key intermediate to access the acetyl-CoA-carboxylase inhibitor (Fig. 6c). This compound was previously synthesized in a racemic manner with 6% overall yield after 4 steps and 4 column purifications, and chiral resolution was required to obtain the enantioenriched product[43]. Its asymmetric synthesis was recently reported by us, though 5 steps and 2 column purifications were still needed[12]. Here, capitalizing on the enantioconvergent homologation, alcohol **24** can be prepared in just two steps and one column purification in 67% overall yield and 97:3 er from commercially available boronic acid **22**. Finally, asymmetric synthesis of homoallyl alcohol **26**, a key intermediate to access sphingolipid biosynthesis inhibitor fumonisin B1[44], can be streamlined (Fig. 6d). Compound **26** bears three adjacent chiral centers, which was previously synthesized from hexanal in 11 steps with 21% overall yield. Our approach started from simple butylboronic acid **23**, and after the auxiliary installation, iterative insertion of methyl-substituted carbenoid **C1**, oxygen-substituted carbenoid **C5**, and allyl-substituted carbenoid **C6** followed by the oxidation quench rapidly delivered compound **26** in 40% overall yield with 92:8 dr and >99:1 er. The absolute stereochemistry was unambiguously determined by X-ray crystallography of its 3,5-dinitrobenoate derivative (**27**).

Conclusions

In summary, we have developed a general and robust enantioconvergent boron homologation strategy to allow asymmetric construction of diverse tertiary chiral centers. Complementary to the desymmetritive and enantiospecific homologation approaches, this enantioconvergent method uses readily accessible racemic carbenoids as building blocks and directly introduces various carbon- and heteroatom-substituted methylenes in high enantioselectivity. The stereochemical outcome of this homologation approach is not affected by existing stereocenters, making it attractive for programmable iterative synthesis of complex molecules bearing multiple chiral centers. Valuable insights gained from the computational study could have

broad implications on designing new asymmetric boron addition reactions.

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Data availability

The data supporting the findings of this study are available within the Article and its Supplementary Information. Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre (www.ccdc.cam.ac.uk/) under deposition numbers CCDC 2311818 (**9f**) and CCDC 2312263 (**25**).

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Author contributions

Q.X. and G.D. conceived of the idea and designed the experiments. Q.X. and J.L. conducted the experimental investigation. P.L. and T.H.T. conceived and designed the computational studies. T.H.T. performed the computational studies. Q.X., T.H.T., P.L. and G.D. wrote the manuscript. P.L. and G.D. directed the research.

Competing interests

The authors declare that they have no competing interests.