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Enantio- and Diastereoselective Synthesis of Functionalized Carbocycles by Cu-Catalyzed Borylative Cyclization of Alkynes with Ketones

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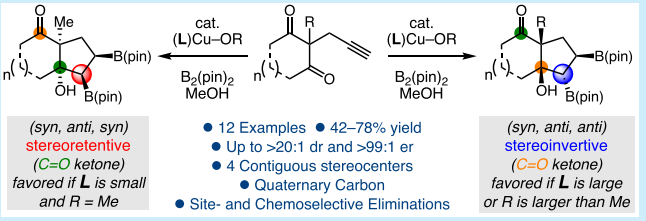
Supporting Information

ABSTRACT: A single-pot Cu-catalyzed enantio- and diastereoselective tandem hydroboration/borylative cyclization of alkynes with ketones for the synthesis of carbocycles is reported. The reaction proceeds via desymmetrization and generates four contiguous stereocenters, including an all-carbon quaternary center. The method provides rapid access to [6,5]- and [5,5]-bicycles and cyclopentane products. Catalyst-controlled diastereoselectivity by selection of bisphosphine ligand is noted. Utility of the products is demonstrated by site- and chemoselective transformations that afford valuable alkenyl and allyl organoborons.

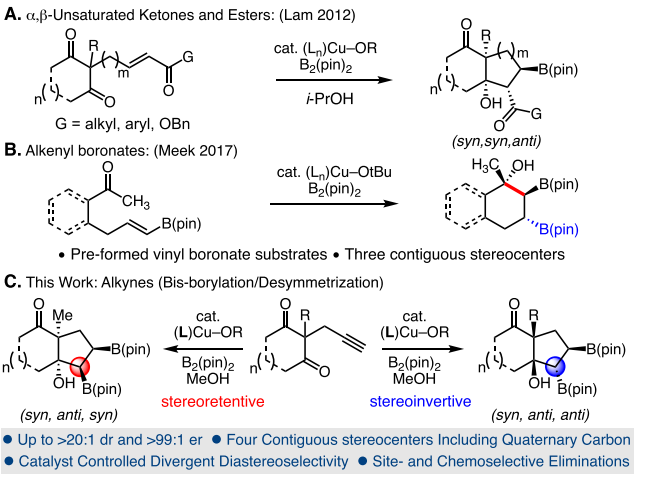


Multicomponent tandem reactions, wherein subsequent reactions occur as a result of functionality generated in a previous step, allow for the formation of several bonds in a single operation, without the need of additional reagents.[1] Such reactions minimize the economic, environmental, and labor costs associated with multistep syntheses.[1] Of particular interest are tandem catalytic reactions that stereoselectively form all-carbon quaternary stereocenters, structural motifs that remain a significant synthetic challenge in organic chemistry.[2] One strategy to generate quaternary stereocenters is through enantioselective desymmetrization processes.[3] Accordingly, incorporating an enantioselective desymmetrization step into a tandem reaction would rapidly generate stereochemical complexity in a highly efficient manner.[4] In addition to the growing importance of constructing all-carbon quaternary centers, alkyl organoborons have become important intermediates in the synthesis of pharmaceuticals and agrochemicals due to the range of stereospecific functional group transformations they undergo.[5−7]

Recently, we reported a Cu-catalyzed enantio- and diastereoselective tandem borylation/1,2-addition of alkenyl boronic esters to ketones (Scheme 1B).[8] To construct more complex structures in a simpler protocol, we sought to develop a process to efficiently construct carbocycles bearing four contiguous stereocenters.

In order to achieve these objectives, we decided to examine two changes (Scheme 1C): (1) Catalytic desymmetrization of 1,3-diketones substrates that access stereodefined, highly substituted hydrindanes, diquinanes, and cyclopentanes bearing two boronic esters. Ideally, the two C−B bonds could be sequentially functionalized, offering access to a range of stereodefined products. (2) Change from alkenyl borons to alkynes due to their ease of accessibility. Notably, alkynes pose an inherent site-selectivity challenge as hydroboration can result in α- and β-borylation isomers.[9]

Scheme 1. Enantio- and Diastereoselective Cu-Catalyzed Multicomponent Carboborylative Cyclizations



A number of studies related to Cu-catalyzed bis-borylation of alkynes have been reported; however, trapping of the resulting copper−C(sp^3) with an electrophile other than proton has not been reported to the best of our knowledge.[10] Enantioselective Cu-catalyzed bis-hydroboration of terminal alkynes and $SiMe_3$-protected alkynes have been reported.[11] Related enantioselective Cu−B(pin)-initiated carboboration reactions of olefins have also been disclosed.[12,13] In this regard, Cu-catalyzed conjugate borylation of Michael acceptors and

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subsequent aldol addition of the Cu enolate with a diketone has been shown intramolecularly (Scheme 1A).[4b]

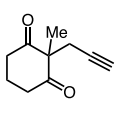
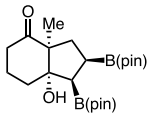
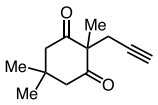
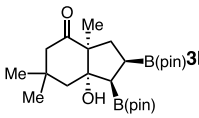
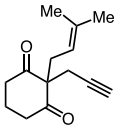
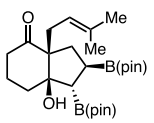
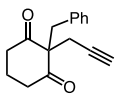
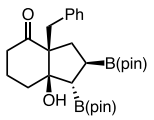
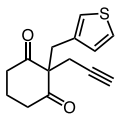
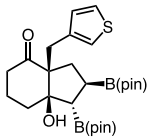
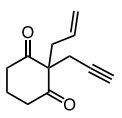
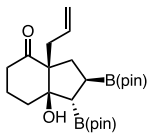
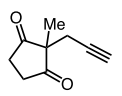
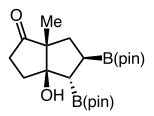
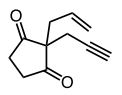
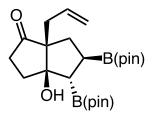
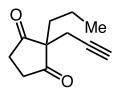
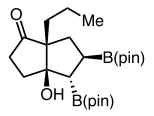
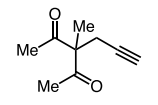
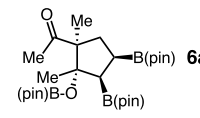
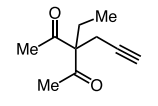
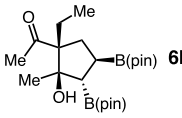
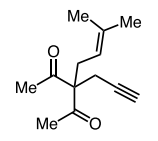
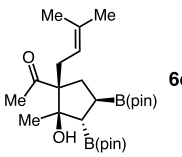
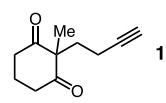
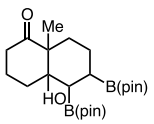
We initiated our studies by investigating the catalytic desymmetrization of cyclohexanedione **1a** to afford bis-boryl hydrindane **3a** (Table 1). Treatment of alkyne **1a** with 5 mol % of CuCl, 6 mol % of (*R*)-BINAP (**L1**), 6 mol % of KO-*t*-Bu, 2.2 equiv of $B_2(pin)_2$, and *t*-BuOH (2.0 equiv) in THF at 22 °C for 18 h afforded **3a** in 65% yield, 5:1 dr, and 99:1 er. Examination of a number of other chiral phosphine ligands (**L2**–**L6**) generated either significantly lower conversion or diastereoselectivity (Scheme 2). In contrast, it was found that employing furyl-MeO-Biphep (**L7**) greatly improved the dr while maintaining good yield and excellent enantioselectivity providing **3a** in 64% yield, 12:1 dr, and 99:1 er. Furthermore, it was found that increasing the catalyst loading to 10 mol %, and switching from *t*-BuOH to MeOH, led to an improved 78% yield of **3a** while maintaining high stereoselectivity (9:1 dr, and >99:1 er).

With conditions in hand for the alkyne desymmetrization, we next examined the substrate scope of the tandem reaction (Table 1). In general, the yields are moderate to good, and enantio- and diastereoselectivity are generally excellent. Product **3a** was isolated in 70% yield, 13:1 dr, and >99:1 er. Additional substitution on the 6-membered ring was tolerated (**3b**) (the X-ray structure of **3b** was obtained (see Scheme 5A) (vide infra)). Prenyl-containing substrate **1c** was found to cyclize to **3c** with lower diastereoselectivity (5:1 dr) but in excellent enantioselectivity (98:2 er, and >99:1 er). Incorporation of benzyl (**1d**) and thiophene (**1e**) substituents led to **3d** and **3e** in 60% (>20:1 dr) and 65% (3:2 dr), respectively. Notably, upon isolation, the minor diastereomer of **3e** decomposes affording a single diastereomer (>20:1 dr, and 94:6 er). Terminal alkenes are also tolerated, and bis-boron **3f** is isolated in 46% yield, 17:1 dr, and in 88:12 er; the lower er is possibly due to coordination of the unhindered alkene to the catalyst.

For [5,5]-fused carbocycles (entries 7–9), however, **L1** was found to be a slightly better ligand compared to **L7**. Methyl-substituted diquinane **5a** is formed in 69% yield, 2:1 dr, and 90:10 er.[14] Increasing the size of the group on the quaternary center to an allyl (**1h**) or *n*-propyl group (**1i**) provided products **5b** and **5c** in 57% yield (>20:1 dr, 89:11 er) and 64% yield (>20:1 dr, 94:6 er), respectively. Diquinane **5c** could be recrystallized once to 97.5:2.5 er. For cyclopentane products **6a**–**c**, yields again were moderate, but reactions proceeded with generally excellent enantio- and diastereoselectivities (Table 1). For example, product **6a**, formed in 56% NMR yield, was isolated as the tris-boronate (>20:1 dr, > 99:1 er).[15] Simply switching from Me to Et provided tertiary alcohol bis-boronate **6b** in 42% yield as a single stereoisomer (>20:1 dr, > 99:1 er). Prenyl-substituted diketone **1l** was found to undergo smooth cyclization to afford **6c** in 17:1 dr (>99:1 er) when compared to the [6,5]-prenyl **3c** formed in 5:1. The alkyne cyclization strategy was also tested for the generation of 6-membered rings to form decalins (entry 13, Table 1). Unfortunately, large amounts of double hydroboration are observed (<2% conversion to **7**); starting from the vinyl boronic ester failed to improve the reaction (see the SI for details).

Next, in order to determine the efficiency of the alkyne hydroboration and carboboration steps, we undertook a brief comparison of the catalytic reaction starting from the preformed alkenyl boronic esters versus alkyne (Scheme 3).

Table 1. Reaction Scope[a,b]

entry	starting material		product		result
1		**1a**		**3a**	with **L7**: 70% yield, 13:1 dr *>99:1 er*
2		**1b**		**3b**	with **L7**: 54% yield, >20:1 dr *>99:1 er*
3		**1c**		**3c**	with **L7**: 49% yield, 5:1 dr *98:2 er, >99:1 er*
4		**1d**		**3d**	with **L7**: 60% NMR yield 32% yield, >20:1 dr *96:4 er*
5		**1e**		**3e**	with **L7**: 65% NMR yield, 3:2 dr 25% yield, >20:1 dr *94:6 er*
6		**1f**		**3f**	with **L7**: 46% yield, 17:1 dr 88:12 er
7		**1g**		**5a**	with **L1**: 69% yield, 2:1 dr *74:26 er, 90:10 er*
8		**1h**		**5b**	with **L1**: 57% yield, >20:1 dr *89:11 er*
9		**1i**		**5c**	with **L1**: 64% yield, >20:1 dr *94:6 er* [recryst: 97.5:2.5 er]
10		**1j**		**6a**	with **L7**: 56% NMR yield 37% yield, >20:1 dr *>99:1 er*
11		**1k**		**6b**	with **L7**: 42% yield, >20:1 dr *>99:1 er*
12		**1l**		**6c**	with **L7**: 48% yield, 17:1 dr *>99:1 er*
13		**1m**		**7**	with **L1** or **L7**: <2% conv

[a]Same conditions and analytical methods as in Scheme 2; see the SI for details. [b]Yields of purified hydroxyl bis-boronate products.

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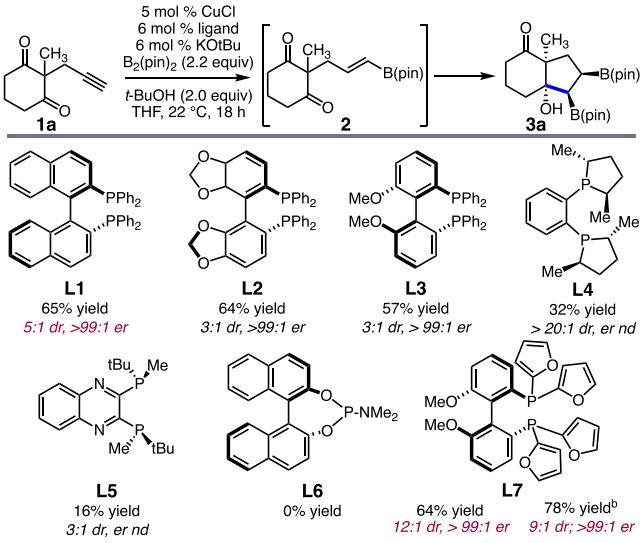
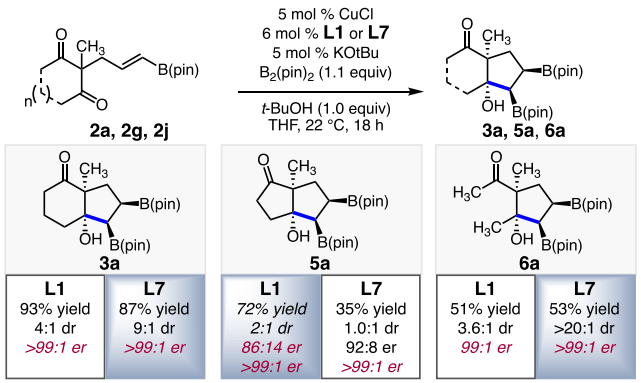
Scheme 2. Reaction Optimization[a]



[a]Reactions performed under N_2 atmosphere. Yield and diastereomeric ratios (dr) determined by analysis of 400, 500, or 600 MHz ^{1}H NMR spectra of crude reactions with hexamethyldisiloxane as internal standard. Enantiomeric ratios (er) determined by HPLC or SFC analysis; see the SI for details. nd = not determined. [b]CuCl (10 mol %), **L7** (11 mol %), KO*t*Bu (10 mol %), MeOH (2.0 equiv).

Scheme 3. Comparison to Alkenyl Boronic Esters in Ketone Desymmetrization[a]

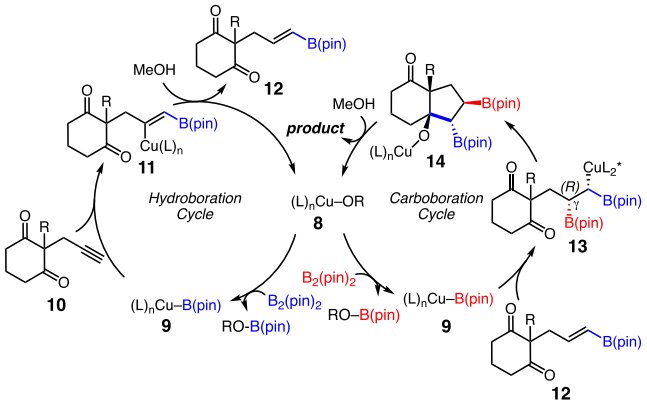


[a]Same conditions and analytical methods as in Scheme 2; see the SI for details.

The reactions of the three vinyl boronic esters **2a**, **2g**, and **2j** were examined, and the results are illustrated in Scheme 3. With 1.1 equiv of $B_2(pin)_2$ and 1.0 equiv of *t*-BuOH, cyclization to cyclopentane products **3a**, **5a**, and **6a** resulted in only a marginal improvement in yield compared to starting from the corresponding alkynes, indicating efficient alkyne hydroboration.

A proposed mechanism for the Cu-catalyzed tandem alkyne cyclization method is shown in Scheme 4, which depicts dual catalytic cycles that proceed contemporaneously.[9,10] Accordingly, a Cu-catalyzed alkyne boryl−protonation cycle occurs followed by a carboboration cycle. In the hydroboration cycle, transmetalation of (L)Cu−OR **8** with $B_2(pin)_2$ generates (L)Cu−B(pin) complex **9**. Regioselective *syn* migratory insertion of **9** across alkyne **10** is followed by protonation of alkenyl copper **11** by MeOH to liberate *trans*-*β*-vinyl boronic

Scheme 4. Proposed Dual Catalytic Cycles



ester **12**. In the carboboration cycle, migratory insertion of **9** across vinyl boronic ester **12** sets the absolute stereochemistry, which is followed by diastereoselective cyclization (**13** → **14**). Protonation of Cu-bound product **14** releases the product and regenerates catalyst **8**.

As noted previously, the X-ray structure of tertiary alcohol **3b** was obtained (Scheme 5A). The structure shows a *cis* [6,5] ring juncture, with the B(pin) *anti* to the hydroxyl group.[16] Importantly, borylation of the *E*-alkenyl boron with (*R*)-furyl-biphep-derived catalyst results in *R* stereochemistry (e.g., in **13**). The *syn* relationship between the two B(pin) moieties in **3b** can be explained by a stereoretentive mode of addition by the (L)Cu-alkyl to the ketone. A result rationalized by use of the small furylphosphine ligand in combination with a methyl group on the substrate, which results in a sterically accessible (L)Cu−alkyl (e.g., **13**).

Later in our study, surprisingly, we found that when alkyne **1a** is cyclized with BDPP (**L8**), *syn,anti,syn*- diastereomer **15** is formed instead in 97% yield and 11:1 dr (Scheme 5B). With other [6,5] products, we found that **L8** afforded the *same* diastereomers (e.g., **3f**) as **L7** and **L1** in >20:1 dr. These unexpected results encouraged us to further investigate the stereochemistry. The X-ray structure of **3f** was obtained (Scheme 5A). Remarkably, the stereochemistry of three of the stereocenters was different compared to **3b**. As the stereochemistry of the boronic ester *γ* to the hydroxyl is set in the initial hydroboration, we assigned this stereocenter as *R* for all substrates based on the absolute configuration of **3b**. The *anti* boronic esters of **3f** indicate a stereoinvertive cyclization, observed in previous work by our group and others.[8,17] To account for this, we propose that the cyclization occurs invertively for R substituents larger than Me (e.g., **3f**) due to increased steric repulsion between the R group and the PAr_2 phosphine ligand, which prevents coordination of Cu to the ketone (Scheme 5C). The change in stereochemistry at the ring junction is due to cyclization on the other diastereotopic ketone due to unfavorable B(pin)↔R steric interaction. The stereochemistry of the [5,5] products was confirmed as *syn,anti,anti* on the basis of the X-ray structure of **5b** (Scheme 5A). Since reactions with **L1**, **L7**, and **L8** result in increasing dr for methyl and with high dr for larger substituents, all [5,5] products predominantly arise from a stereoinvertive cyclization pathway.[18] Cyclopentane products **6a**−**c** have been assigned by analogy: **6a** as stereoretentive *syn,anti,syn* and **6b,c** as stereoinvertive *syn,anti,anti*. This is also supported by the decrease in dr for **6a** going from **L7** to **L1**.[19]

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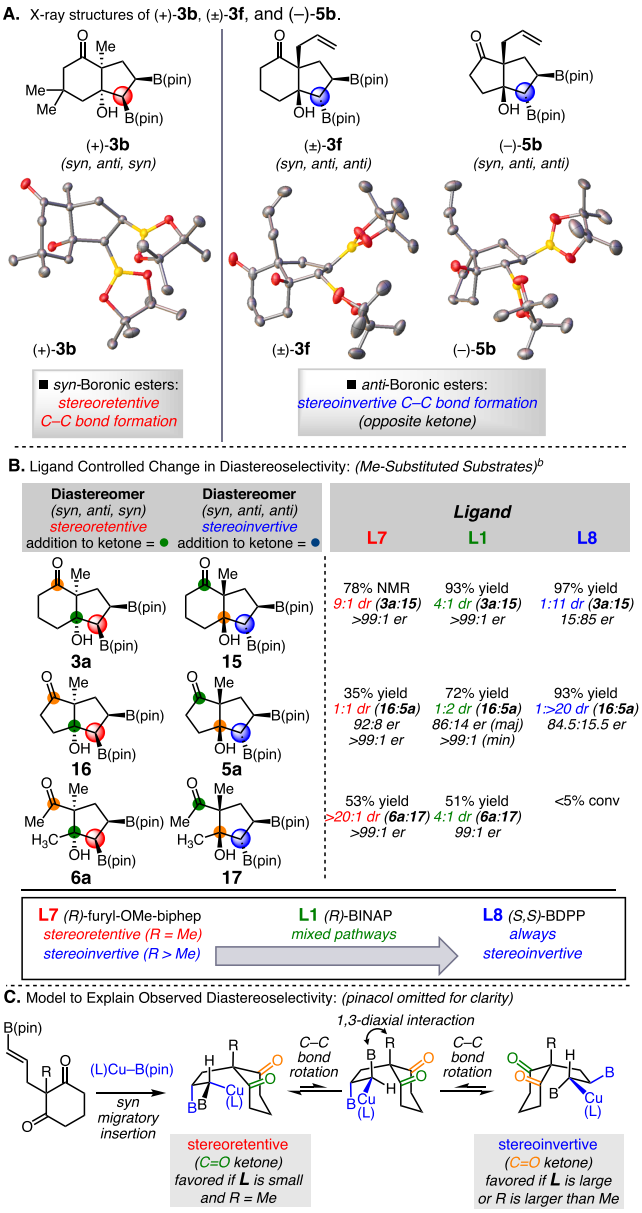
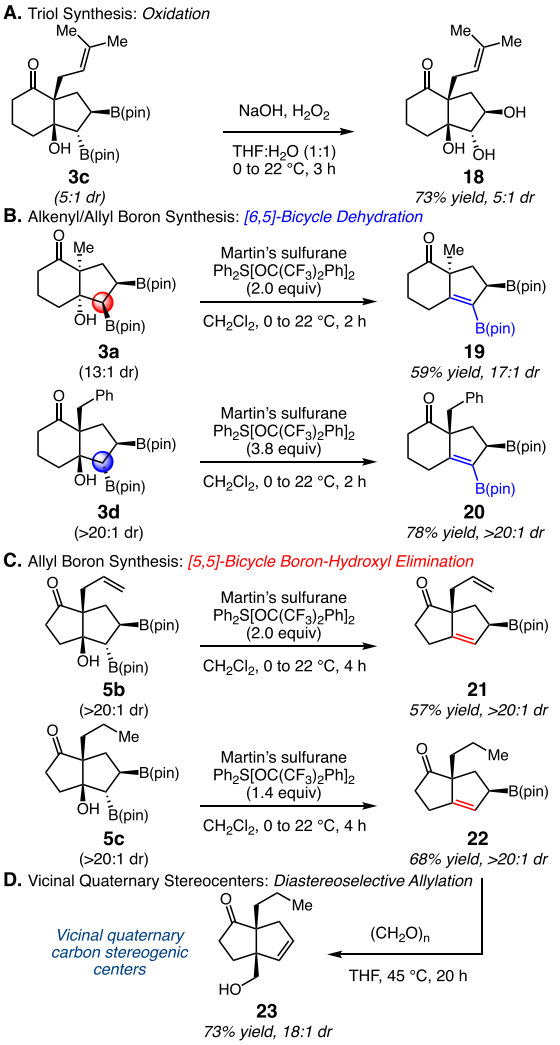
Scheme 5. Stereochemical Analysis and Ligand-Controlled Diastereoselectivity[a]



[a]See the SI for details. [b]Data given in Scheme 5B refer to NMR yields.

Scheme 6. Utility of Bis-boronate Products[a]



[a]See the SI for details.

The synthetic utility of organodiboron carbocycles accessible through the tandem Cu-catalyzed bis-borylation/cyclization protocol is highlighted through several site- and chemoselective transformations depicted in Scheme 6. (1) Oxidation of **3c** with H_2O_2/NaOH affords triol **18** in 73% yield (Scheme 6A). (2) Exposure of the tertiary alcohol products to Martin's sulfurane[20] results in site- and chemoselective eliminations that are dependent on the hydrocarbon bicycle. For example, treatment of [6,5]-product **3a** with Martin's sulfurane effects a site-selective dehydration to afford alkenyl boron **19** in 59% yield (Scheme 6B). Subjecting benzyl derivative **3d** to the same reaction conditions also provides dehydrated alkenyl boron product **20** in 78% yield, despite the change in relative stereochemistry. This is in direct contrast to [5,5]-bicycles, which when treated with Martin's sulfurane result in an *anti* boron−hydroxyl elimination (Scheme 6C). For example, allyl borons **21** and **22** are generated in 57% and 68% isolated yield from **5b** and **5c**, respectively. We believe the divergence in reactivity arises from the σ_{C-B} aligning better with the carbocation p-orbital in the more planar [5,5]-bicycle versus the σ_{C-H}. To the best of our knowledge, this reactivity is the first time an *anti* boron−hydroxyl elimination has been reported for a tertiary alcohol and is the first example of Martin's sulfurane used in transformation of an organoboron.[21] Further transformation of allyl boronic ester **22** to alcohol **23** was accomplished by a stereospecific allylation with formaldehyde, generating vicinal all-carbon quaternary stereocenters in 73% yield and 18:1 dr (Scheme 6D).

In conclusion, we present a catalytic tandem enantio- and distereoselective method for the preparation of borylated carbocycles. We demonstrate the formation of four contiguous stereocenters, including an all-carbon quaternary center, in good yield and selectivity (up to >98:2 dr, and >99:1 er). Stereoinvertive and stereoretentive cyclization pathways were found to be operative and dependent on ligand and substrate. Site- and chemoselective eliminations with Martin's sulfurane highlight valuable alkenyl and allyl organoborons accessible through the method. Development of additional catalytic

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carboboration methods continues to be investigated in these laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01769.

Experimental procedures and spectral and analytical data for all products (PDF)

Accession Codes

CCDC 1916345−1916346 and 1922369 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(18) **L8** was tested for products **3c**,**d**,**f**, **5a**, **6a**, and **6b**, and it affords the same diastereomers as **L1** and **L7** *in all cases* (except **6a**,**b**, <5% conversion observed).

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