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Communication

# Substrate Plasticity Enables Group-Selective Transmetalation: Catalytic Stereospecific Cross-Couplings of Tertiary Boronic Esters

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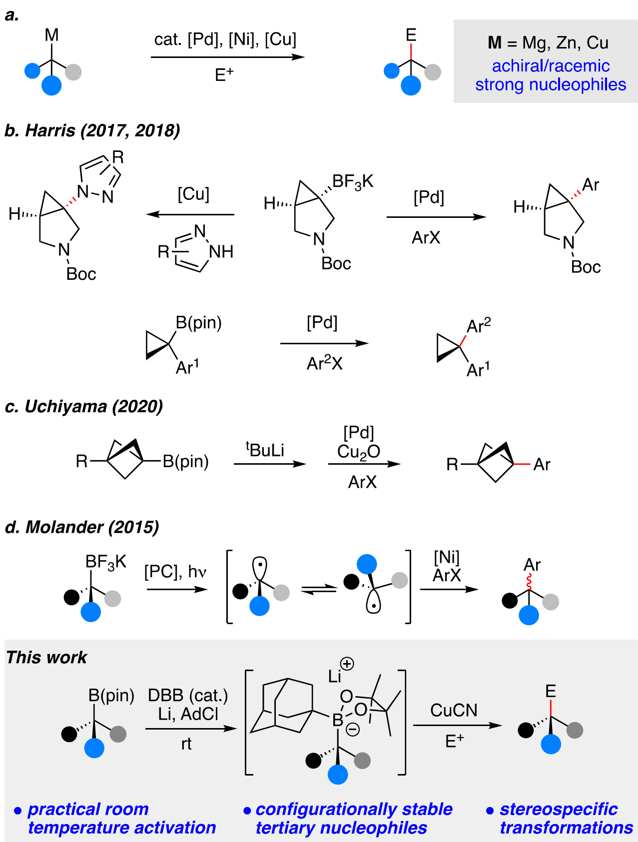
**ABSTRACT:** Activation of enantiomerically enriched tertiary alkylboronic esters with adamantyllithium generated *in situ* enables stereoretentive boron-to-copper transmetalation. The resulting alkylcopper species can undergo cross-coupling reactions with an array of electrophiles to furnish synthetically useful compounds bearing quaternary stereocenters. DFT calculations of the transmetalation process provide insights for reactivity and selectivity.



Catalytic construction of enantiomerically enriched quaternary stereocenters is a challenging and yet important task in synthetic organic chemistry.[1] In spite of impressive advances in the stereospecific cross-coupling of configurationally stable secondary nucleophiles,[2] the transmetalation of a configurationally stable tertiary alkyl group to a transition metal is nontrivial and has hampered extension of metal-catalyzed cross-coupling to the installation of quaternary centers. Most of the existing examples of transmetalation of tertiary organometallic reagents employ nucleophilic Grignard reagents,[3] organozinc reagents[4] and organocopper reagents (Scheme 1a).[3e,5] These methods are limited by the availability of nucleophiles, which can be difficult to prepare and are often configurationally unstable at room temperature. Compared with the abovementioned reagents, tertiary organoboronic esters exhibit higher configurational stability and may be prepared by a variety of efficient enantioselective synthesis methods.[6] However, these reagents are less nucleophilic and are, thus, challenging for transmetalation. Harris and co-workers utilized tertiary cyclopropyl organoboron reagents for Suzuki−Miyaura and Chan−Lam-type coupling reactions (Scheme 1b),[7] and Uchiyama et al. reported Suzuki−Miyaura cross-couplings of *tert*-butyllithium-activated bicyclo[1.1.1]-pentylboronic esters (Scheme 1c).[3e] Despite this progress, these examples are limited to strained or benzylic substrates and do not address the issue of stereospecificity. Recognizing the general challenge of coupling a tertiary nucleophile, Molander et al. established a single-electron transmetalation process[8] (Scheme 1d) in which a tertiary organoboron was first converted to a free radical, which was then trapped with a nickel complex; this sequence enabled catalytic cross-coupling with aryl halides, but the radical nature of the reaction makes it challenging to control stereochemistry.[9] In this Communication, we describe a practical catalytic method for the generation of adamantyllithium *in situ*, which then reacts with tertiary alkylboronic esters at room temperature. The resulting borate species can engage in stereospecific copper-catalyzed coupling reactions with an array of electrophiles. Insofar as we are aware, the examples presented in this manuscript represent the first that involve stereospecific

**Scheme 1. Transmetalation of Tertiary Nucleophiles in Cross-Coupling Reactions**

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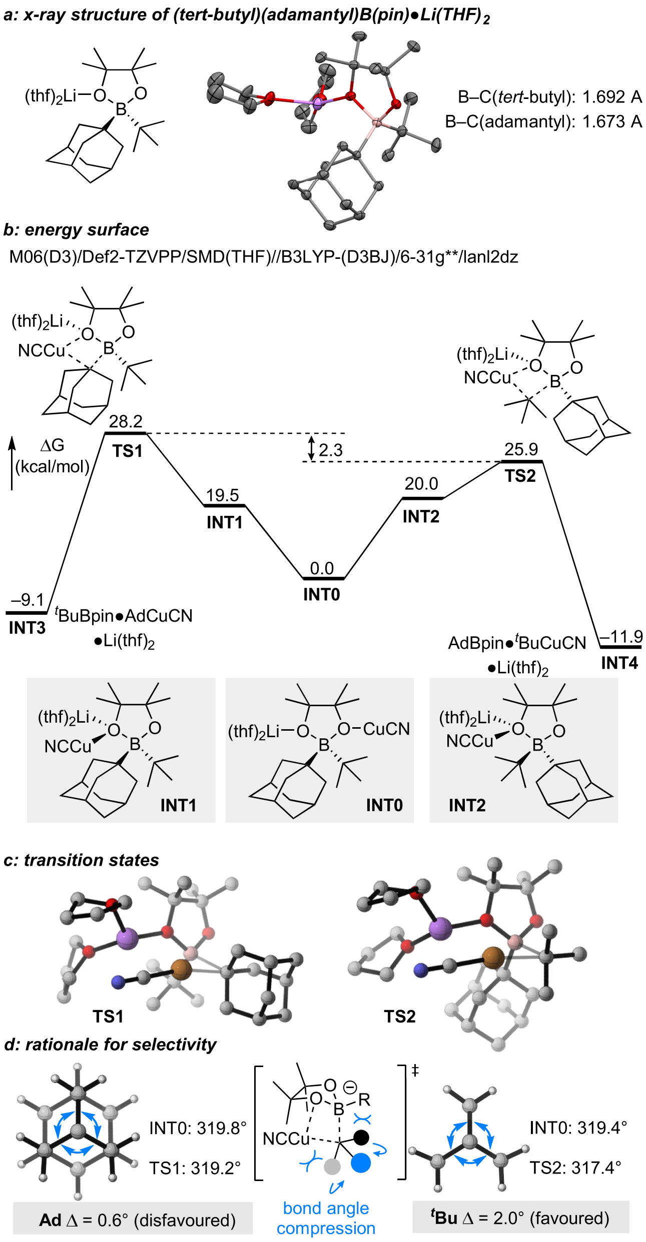
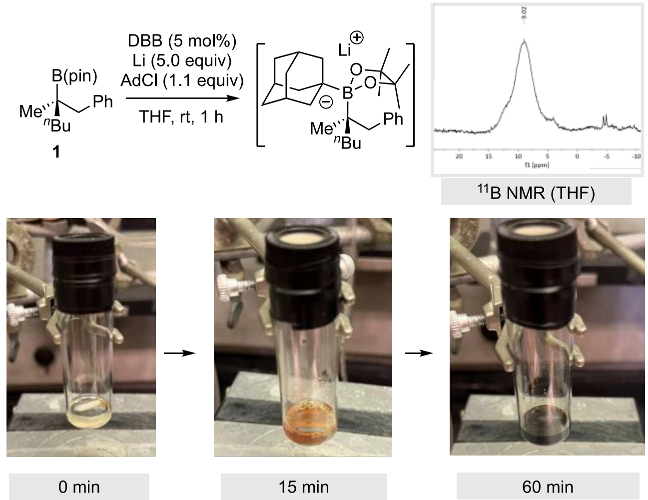



**Figure 1.** (a) X-ray structure of the (*tert*-butyl)(adamantyl)B(pin)ate complex. CCDC: 2267241. (b) DFT-calculated energy surface for boron-to-copper transmetalation of either the *tert*-butyl group or the adamantyl group. (c) Three-dimensional structure of transition state complexes. (d) Analysis of the pyramidalization changes at carbon during transmetalation.

transmetalation from a tertiary boronate to another metal. In addition to providing a useful synthesis tool, these studies shed light on features that impact transmetalation efficiency.

Recently, we demonstrated that *tert*-butyllithium-activated primary and secondary organoboronic esters can undergo stereospecific transmetalation to both copper and zinc salts, thereby enabling a broad array of cross-coupling reactions.[10] We considered that alkyllithium-activated *tertiary* alkylboronic esters might participate in similar processes. An obvious challenge would be the selectivity between transferring the activator versus transferring the substrate alkyl group. While previous activation of secondary alkylboronic esters relied on the faster transmetalation of a secondary alkyl group relative to a *tert*-butyl group, effective activation of a tertiary group would require an activator that transmetalates more slowly than the transferring tertiary alkyl substrate. We were inspired by the observation of relatively low reactivity of cyclohexyl boronic esters under *tert*-butyllithium activation and wondered if the similarly rigid and cyclic nature of an adamantyl group would preclude its transmetalation in the presence of other tertiary groups.

**Scheme 2. Activation of Tertiary Alkylboronic Esters with Adamantyllithium Generated *In Situ***




X-ray analysis of a crystal of (*tert*-butyl)(adamantyl)B(pin)·Li(THF)$_2$ (Figure 1a), obtained by slow diffusion of hexane into a THF solution of the borate, hinted at selective group transfer in transmetalation: the B–(adamantyl) bond is shorter than the B–(*tert*-butyl) bond (1.673 vs 1.692 Å), which suggests that the latter may be more reactive.[10,11] Aligned with these observations, DFT calculations (Figure 1b) indicated that the barrier for transmetalation of the adamantyl group from adamantyl(*tert*-butyl)pinacol borate to CuCN is 2.3 kcal/mol higher in energy than that for transmetalation of the *tert*-butyl group. Distortion–interaction analysis[12] revealed that the difference in energy between these two transition states arises from different energies required to distort the transmetalating group as the transition state is approached (see the Supporting Information). Analysis of the calculated transition state structures (Figure 1c) shows an increased pyramidalization in the transferring group, presumably to accommodate the increased steric encumbrance associated with a transient five-coordinated carbon center. The extent of pyramidalization as the reaction progresses from the ground state to the transition state, assessed by comparison of the sum of the three C–C–C bond angles of the transferring carbon (Figure 1d, ideal trigonal atom = 360°; ideal tetrahedron = 328.5°), was found to be greater for the *tert*-butyl group in **TS2** than the adamantyl group in **TS1** [for relevant computational experiments that calculate Δ*E* as π-orbital axis vector (POAV)[13] is varied across a series of *tertiary* alkanes, see the Supporting Information]. We postulate that in the absence of other factors (hybridization, steric effects, etc.), the plasticity of the transmetalating group can be a factor that facilitates transmetalation: the greater flexibility of the *tert*-butyl group allows it to undergo more pyramidalization than the adamantyl ligand, and yet, it requires less energy to achieve this distortion. This favors the *tert*-butyl transmetalation pathway.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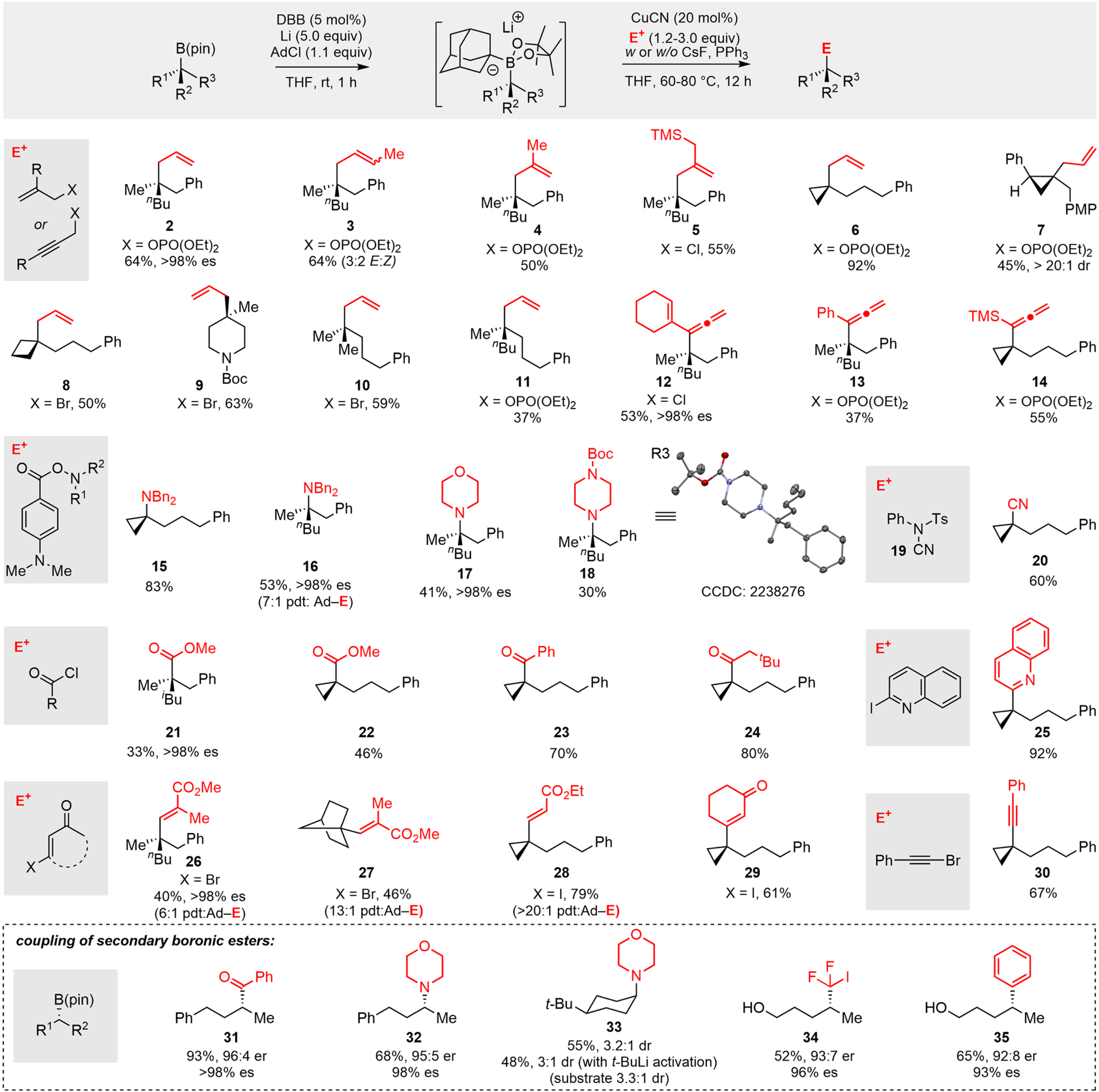

**Figure 2.** Scope of stereospecific Cu-catalyzed couplings of tertiary alkylboronic esters with electrophiles. Reactions were carried out with 0.20 mmol of alkylboronic esters. Yields are for isolated materials. Enantiomeric ratio was measured by chiral SFC analysis and had an error of ±1%. pdt:Ad−**E**, where measured, refers to the selectivity in coupling to the tertiary boronate versus coupling to the adamantyl group.

Encouraged by the results of DFT calculations, we sought a practical method for the synthesis of the corresponding adamantyl borate complexes. Adamantyllithium has been prepared by lithiation of adamantyl halides;[14] however, this reaction requires low temperature and specialized lithium alloys. Additionally, the resulting adamantyllithium is a pyrophoric reagent that is unstable in many solvents and, thus, is ill-suited for long-term storage. As an alternative, we examined a catalytic modification of a stoichiometric *in situ* lithiation described by Sumida, Hosoya, and Ohmiya et al.[15] Thus, treatment of adamantyl chloride and the tertiary boronic ester **1** (Scheme 2) with 5 mol % 4,4′-di-*tert*-butylbiphenyl (DBB) and excess lithium metal resulted in formation of the borate complex within 1 h at room temperature, as indicated by $^{11}$B NMR analysis.[16] Of note, DBB functions as both a catalyst and as an indicator for the reaction process: upon complete consumption of adamantyl chloride, the reaction mixture takes on the dark blue color of the residual Li−DBB adduct. At this stage, the borate complex can be separated from unreacted Li, the solvent removed, and the solid material stored for >1 month with little change to the $^{11}$B NMR spectrum.

With ready access to adamantyl-activated tertiary boronate complexes, their use in copper-catalyzed coupling reactions was investigated. In this process, a THF solution of the borate was added to 20 mol % copper cyanide followed by allyl



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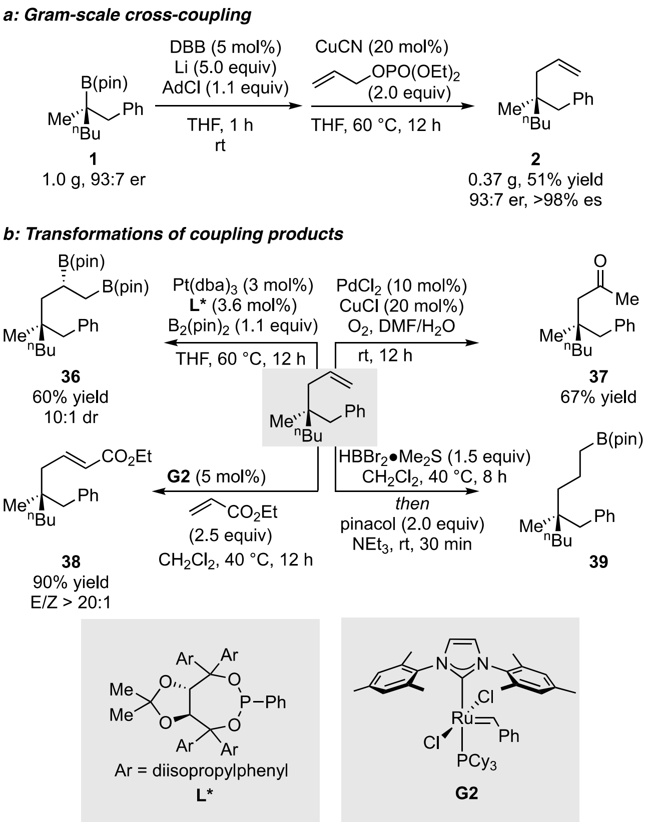
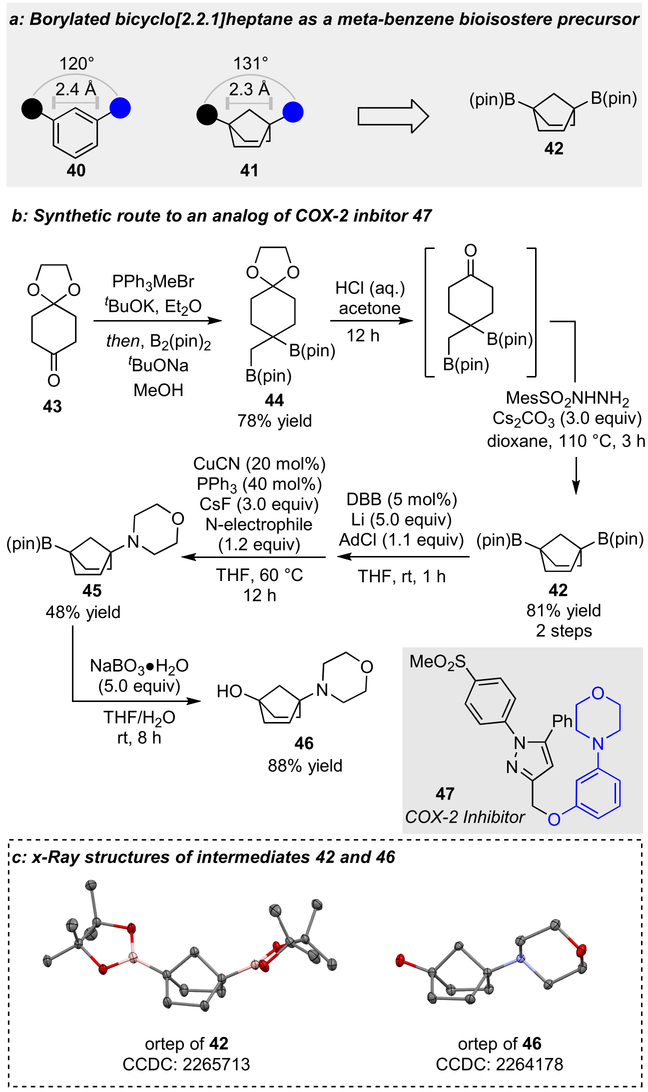
**Scheme 3. Gram-Scale Coupling and Product Derivatizations**



**Scheme 4. Synthesis of Disubstituted Bicyclo[2.2.1]heptane as *meta*-Benzene Bioisosteres**



electrophiles. For a variety of leaving groups, the desired allylation product **2** (Figure 2) was obtained in 25−60% yield (see the Supporting Information) with only trace amounts of adamantyl coupling product being observed. Depending on the nature of the leaving group, moderate to high levels of stereospecificity (54 to 98% es; es = enantiospecificity) were also observed in these reactions; however, the use of 2.0 equiv of allyldiethyl phosphate resulted in optimal yield (64%) and consistently high levels of stereospecificity.

The scope of the coupling reaction was examined with a series of different allyl and propargyl electrophiles (Figure 2), which provided moderate to good yields of alkenes and allenes containing quaternary stereocenters. For product **2** and **12**, the enantiospecificity was determined to be >98%. Of note, the Boc protecting group of product **9** survived the coupling sequence intact. Also of note, the borate species can engage in copper-catalyzed stereospecific amination reactions.[17] Thus, enantiomerically enriched amines can be prepared in moderate to good yields and good stereospecificity. The absolute configuration of **18** was assigned on the basis of X-ray crystallography, which indicated that the process occurs with retention of configuration at carbon. For less reactive electrophiles, such as acyl chlorides (products **21**−**24**), *β*-haloenones (products **26**−**29**), 2-iodopyridine (**25**), sulfonyl-cyanamide reagent **19** (product **20**), and bromoalkynes (product **30**), moderate yields can be obtained. For these electrophiles, high-yielding coupling reactions occurred when more reactive cyclopropylboronic esters were employed. For several cases with more polar electrophiles (**16** and **26**−**28**), it was possible to isolate the minor product of coupling to the adamantyl activator, and it was found that the group selectivity ranged from 3:1 to 20:1 (see Supporting Information for additional examples). Of particular interest is product **27**, where the bicyclo[2.2.1]heptyl group transfers more readily than does the adamantyl group. DFT calculations on the substrate (see the Supporting Information) show that the B−bicyclo[2.2.1]heptyl bond is shorter and presumably stronger than the B−adamantyl bond. In the ate complex, the bicycloheptyl carbon is more pyramidalized than the adamantyl carbon; however, in the transmetalation transition state structures the bicycloheptyl carbon undergoes greater pyramidalization, which suggests substrate plasticity as a more important element than bond strength in the reaction of this substrate.

A last point worth mentioning is that secondary boronic esters are suitable substrates for stereospecific adamantyl-activated couplings to provide **31**−**33** via Cu-catalyzed coupling reactions and **34**−**35** by transmetalation to Zn(II)[10b] prior to coupling with electrophiles.

To examine aspects pertaining to the synthesis utility, a gram-scale coupling reaction was conducted (Scheme 3). In this process, the desired product **2** could be isolated in 51% yield and >98% enantiospecificity. With larger quantities of coupling product, we examined transformations of the allylation adduct. It was found that the coupling product can engage in platinum-catalyzed diboration (→**36**),[18] palladium-catalyzed Wacker oxidation (→**37**), ruthenium-catalyzed olefin metathesis (→**38**), and hydroboration reactions (→**39**), which furnished synthetically useful building blocks containing a quaternary stereocenter.

To further examine the synthetic application of the coupling reactions described above, we considered a general route for the synthesis of bicyclo[2.2.1]heptane derivatives **41**. This framework has been suggested as a saturated bioisostere of *meta* disubstituted benzenes (**40**) because of the similar angle and distance of the two attachment points at the bridging carbon (Scheme 4a).[19] An obvious need for the development of this class of compound is the selective and broad-scoped installation of functional groups at the tertiary carbons. Starting from inexpensive ketone **43** (Scheme 4b), Wittig olefination, followed by diboration, provided **44** in good yield. Ketal deprotection followed by carbon insertion, as inspired by Qin et al.,[20] selectively occurs at the primary boron to provide critical diboron scaffold **42** that was characterized by X-ray crystallography (Scheme 4c). Under the standard conditions for copper-catalyzed amination of tertiary boronates described above, **45** was isolated in 48% yield. Further oxidation with sodium perborate generated **46**, which should serve as a useful starting point for the construction of COX-2 inhibitor analogs (i.e., **47**).[21]

In conclusion, a practical and mild method for activating tertiary alkylboronic esters was developed. The adamantyl-activated borate complex can engage in copper-catalyzed cross-coupling reactions with an array of electrophiles. Importantly, this reaction can be used for the construction of challenging quaternary stereocenters. Further studies on the utility of these processes are in progress.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c07129.

Procedures, characterization, and spectral data (PDF)

### Accession Codes

CCDC 2238276, 2264178, 2265713, and 2267241 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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