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Communication

Stereospecific Transformations of Alkylboronic Esters Enabled by Direct Boron-to-Zinc Transmetalation

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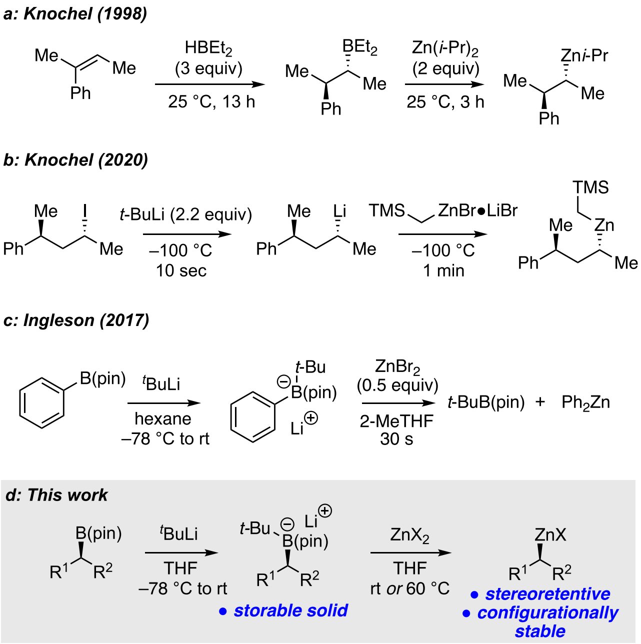
ABSTRACT: Chiral secondary organoboronic esters, when activated with *t*-butyllithium, are shown to undergo efficient stereoretentive transmetalation with either zinc acetate or zinc chloride. This reaction provides chiral secondary alkylzinc reagents that are configurationally stable under practical experimental conditions. The organozinc compounds were found to engage in stereospecific reactions with difluorocarbene, catalytic cross-couplings with palladium-based catalysts, and trifluoromethylation with a copper(III) complex. Mechanistic and computational studies shed light on the inner workings of the transmetalation event.

Enantiomerically enriched alkylboronic esters are useful building blocks in organic synthesis. They are often chemically and configurationally stable, and they can be prepared through a variety of catalytic and noncatalytic methods.[1] Moreover, alkylboronic esters undergo stereospecific transformations, allowing them to be used in the construction of a wide array of nonracemic chiral compounds.[2] These attractive features notwithstanding, alkylboronic esters are weak nucleophiles and therefore less reactive for transmetalation compared with other organometallic compounds.[3] Relative to alkylboronic esters, organozinc reagents are more nucleophilic, yet they are still configurationally stable.[4] Pioneering studies by Knochel and co-workers[5] have demonstrated that secondary alkylzinc reagents can undergo stereospecific transmetalation to copper and palladium, followed by coupling with electrophiles. Although efficient protocols have been reported for the enantioselective synthesis of α-amino,[6] α-boryl,[7] and cyclopropyl-based[8] organozinc reagents, preparation of simple enantiomerically enriched secondary alkylzinc compounds remains challenging.

Scheme 1. Stereospecific Preparation of α-Chiral Organozinc Reagents



Knochel reported that secondary organoboranes, generated by hydroboration of alkenes, can undergo stereospecific transmetalation with diisopropylzinc thereby providing a route to α-chiral organozinc reagents (Scheme 1a).[4a,9] In subsequent studies, it was found that secondary organoboronic esters could be converted to dimethylborane derivatives by treatment with methylmagnesium chloride; reaction with $(i\text{-Pr})_2Zn$ then delivers the organozinc compound.[10] Unfortunately, this latter process occurs with significant epimerization of the carbon stereocenter, likely as a consequence of metal halide salts present in the reaction mixture. More recently, Knochel reported that stereospecific lithium−iodine exchange, followed by treatment with $TMSCH_2ZnCl{\cdot}LiBr$ generates the corresponding organozinc reagent (Scheme 1b).[11] They also demonstrated that the so produced organozinc reagent can be used for stereospecific Negishi cross-coupling reactions. To expand the scope of transformations available to organoboron compounds, we considered direct transmetalation of alkyl-activated alkylboronic esters with zinc salts. Related transmetalations were examined by Ingleson during studies on zinc-catalyzed Suzuki-Miyaura reactions (Scheme 1c).[12] They found that the reaction of a PhB(pin)·*t*-BuLi adduct with zinc bromide rapidly furnished diphenylzinc. In this Letter, we describe an efficient, rapid, and stereospecific transmetalation that furnishes enantiomerically enriched secondary alkylzinc

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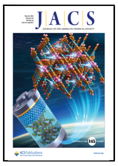

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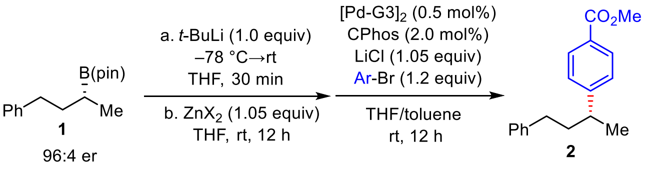
Table 1. B-to-Zn Transmetalation and Negishi Coupling



entry[a]	conditions	conversion (%)	yield (%)[b]	er (es %)[c]
1	w/o ZnX_2	<5	<5	–
2	$ZnCl_2$	92	60	21:79 (63)
3	$ZnBr_2$	70	49	29:71 (46)
4	ZnI_2	91	46	48:52 (4)
5	$Zn(OTf)_2$	>98	79	93:7 (93)
6	$Zn(OAc)_2$	>98	82	95:5 (98)
7	$Zn(OPiv)_2$	>98	67	82:18 (70)
8[d]	$Zn(OPiv)_2$	>98	72	95:5 (98)

[a] Reactions were carried out with 0.10 mmol of **1**. [b] Yields are determined by ^{1}H NMR using tetrachloroethane as internal standard. [c] Enantiomeric ratio was measured by chiral SFC analysis and have an error of ±1%. [d] Step b conducted for 1 h.

reagents from readily available pinacol-derived alkylboronic esters (Scheme 1d). We also provide insight into this transformation and demonstrate that the newly generated organozinc reagents can engage in useful stereospecific transformations.

Recently, we developed several Cu-catalyzed stereospecific transformations of organoboronic esters.[13] These reactions are believed to occur by a facile boron-to-copper transmetalation, followed by coupling to electrophiles. The success of this process relied on alkyllithium activation of otherwise unreactive alkyl boronic esters. It was of interest to determine whether similar boronic ester activation might obtain in other transmetalation processes. In spite of encouraging precedent from Falck[14] with *s*-BuLi-activated primary boronic esters, preliminary experiments in Pd-catalyzed Suzuki-Miyaura cross-coupling of secondary boronic ester **1** with *t*-BuLi activation failed to deliver product (Table 1, entry 1). On the other hand, it was found that treating the *tert*-butyllithium-activated boronic ester with zinc salts led to efficient consumption of the boron “ate” complex as determined by ^{11}B NMR (70−98% conversion, 12 h at rt) and presumably generated the corresponding organozinc reagent. Subsequent addition of a palladium catalyst[15] and an aryl halide electrophile furnished the Negishi cross-coupling product in 46−82% yield. Of note, the enantiospecificity of the reaction was found to be dependent on the identity of the zinc salt and the reaction time: zinc triflate and zinc acetate provided the product with high stereospecificity (Table 1, entries 5 and 6), while the reaction with zinc pivalate only provided high specificity if the transmetalation was conducted for short reaction periods (compare entries 7 and 8).

Racemization in the couplings described above might occur at any stage of the multistep sequence. To directly probe the stereospecificity of the boron-to-zinc exchange step, we examined the transmetalation of isotopically labeled organoboronates **3**-*syn* and **3**-*anti* by *in situ* NMR spectroscopy (Figure 1).[16] ^{11}B NMR was used to first learn about conditions needed to effect transmetalation of **3**-*syn* (Figure 1a−c). Addition of *t*-butyllithium to **3**-*syn* (δ 35 ppm) in THF furnished the boron “ate” complex (δ 10.4 ppm), cleanly (Figure 1a). Subsequent addition of zinc acetate (Figure 1b) resulted in consumption of the ate complex, as determined by reduction in the 10.4 ppm resonance, and formation of both *t*-BuB(pin) (δ 35.9 ppm) and a compound consistent with a three-coordinate borinic ester (δ 55.8 ppm).[17] Heating the reaction mixture to 60 °C for 4 h (Figure 1c) led to complete conversion of both the ate complex and the putative borinic ester to *t*-BuB(pin) and, presumably, the corresponding organozinc transmetalation product.

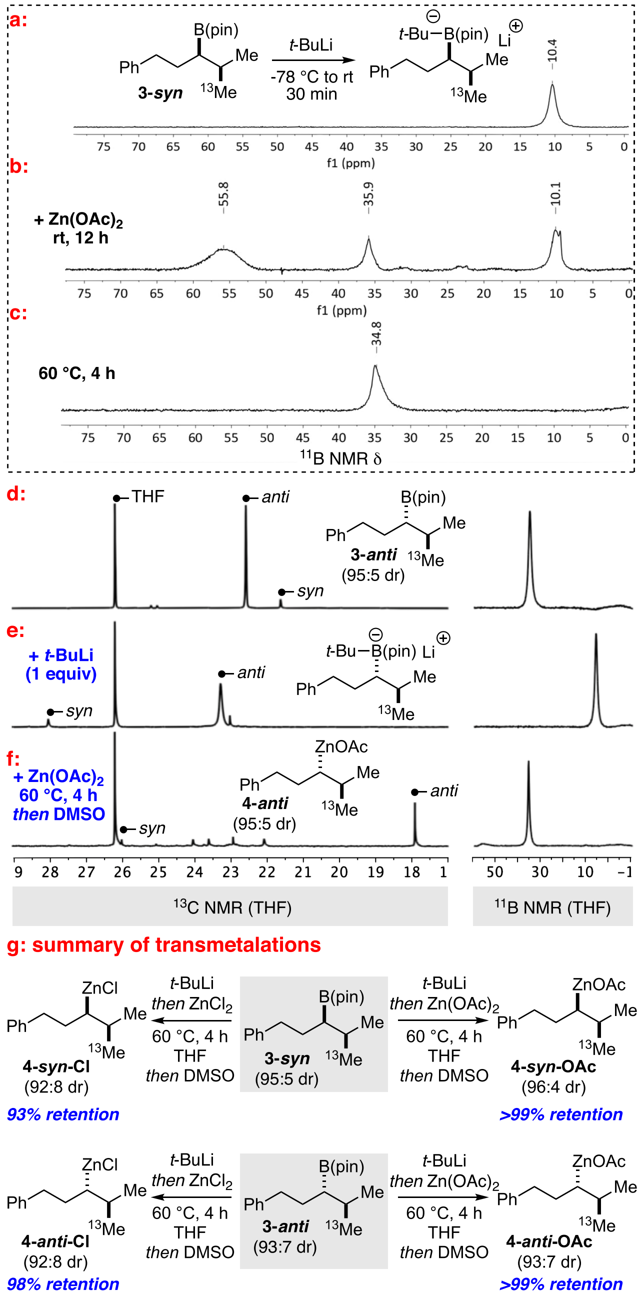


Figure 1. Probing reactivity and stereospecificity of B-to-Zn transmetalation by *in situ* ^{11}B and ^{13}C NMR. (a) ^{11}B NMR spectrum acquired after treatment of **3**-*syn* with *t*-BuLi. (b) ^{11}B NMR spectrum when **3**-*syn*·*t*-BuLi was treated with $Zn(OAc)_2$ at rt. (c) ^{11}B NMR spectrum upon heating **3**-*syn*·*t*-BuLi/$Zn(OAc)_2$ mixture to 60 °C for 4 h. (d) ^{13}C NMR analysis of **3**-*anti*. (e) ^{13}C NMR spectrum of **3**-*anti*·*t*-BuLi. (f) ^{13}C Spectrum obtained upon reaction of *t*-BuLi·**3**-*anti* with $Zn(OAc)_2$ at 60 °C for 4 h, followed by dilution with DMSO. (g) Summary of the efficiency and stereospecificity of transmetalations, as determined by ^{13}C NMR with labeled substrates.

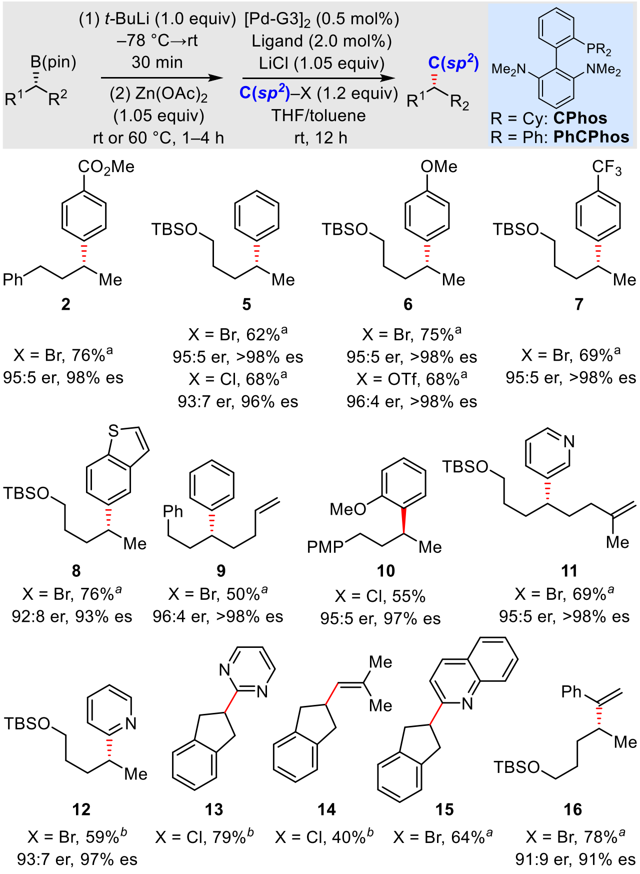


Figure 2. Stereospecific Negishi coupling of enantiomerically enriched organozinc reagents. Reactions were carried out with 0.20 mmol of an alkylboronic ester. Yields are those of purified materials. Enantiomeric ratio was measured by chiral SFC analysis and have an error of ±1%. [a]CPhos was used as a ligand. [b]PhCPhos was used as ligand.

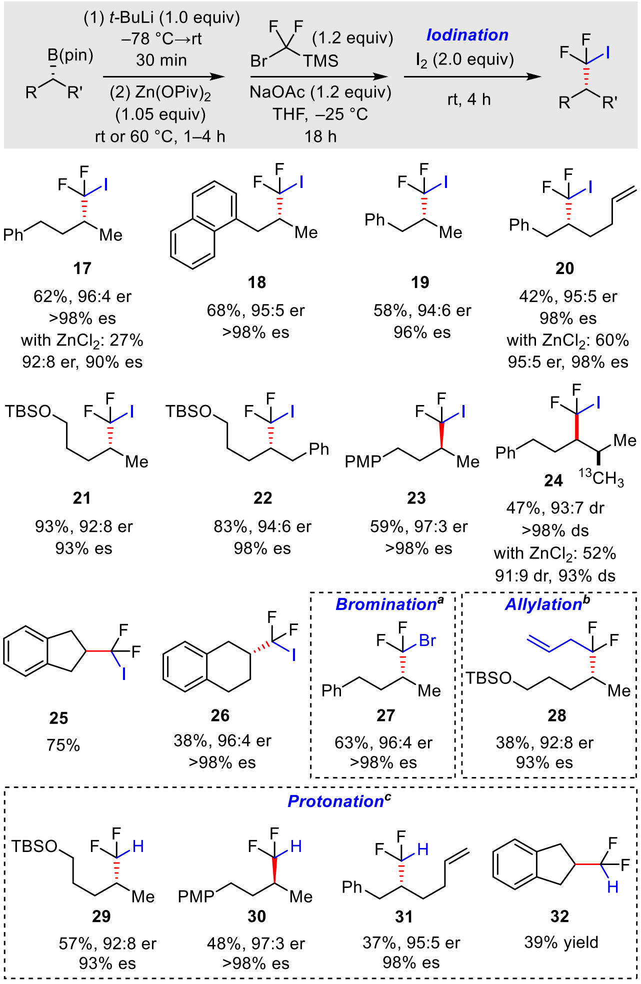


Figure 3. Reaction of difluoromethyl carbene with enantiomerically enriched organozinc reagents. Reactions were carried out with 0.20 mmol of alkylboronic ester. Yields are of purified materials. Enantiomeric ratio was measured by chiral SFC or HPLC analysis and has an error of ±1%. [a]Obtained with NBS. [b]Obtained with 10% CuI, 20% 1,10-phenanthroline, allyl bromide. [c]Obtained with acetic acid/lithium bromide.

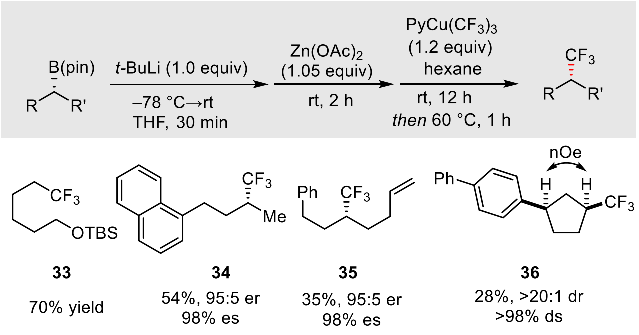


Figure 4. Stereospecific trifluoromethylation of an enantiomerically enriched organozinc. [a]Reactions were carried out with 0.20 mmol of alkylboronic ester. [b]Yields are of purified materials. [c]Enantiomeric ratio was measured by chiral SFC analysis and has an error of ±1%.

To determine the stereospecificity of the transmetalation, the reaction sequence above was analyzed by *in situ* ^{13}C NMR spectroscopy (Figure 1d–f). As shown in Figure 1d, the stereoisomer ratio of the reaction intermediates is readily measured by integrating the ^{13}C NMR resonance for the labeled carbon, and this ratio reflects the stereospecificity of each transformation as well as the configurational stability of each intermediate. Analysis of the reaction sequence showed epimerization-free conversion of the organoboronic ester (Figure 1d) to the derived ate complex (Figure 1e), however, subsequent addition of zinc acetate provided a mixture exhibiting several resonances (not shown), presumably because the alkylzinc reagents are not homogeneous and likely oligomeric.[18] Addition of DMSO (50% volume) to this solution resulted in a homogeneous mixture and cleaner spectra (Figure 1f). While a few minor resonances can be observed at the end of the sequence, the resonance corresponding to **4**-*syn* could be assigned by its independent preparation from **3**-*syn* and the data show a high level of stereospecificity for the overall process. As summarized in Figure 1g (see the Supporting Information for complete spectral data), reactions employing either zinc acetate or zinc chloride were observed to be stereospecific which suggests that racemization observed in Table 1 (i.e., entry 2) likely arises during the zinc-to-palladium transmetalation.[19] Additionally, the observations in Figure 1 suggest that the alkylzinc species themselves are configurationally stable, even at 60 °C for several hours.

With robust conditions for the boron-to-zinc transmetalation identified, the synthetic utility of this process was investigated. Stereospecific coupling of unactivated alkylbor-

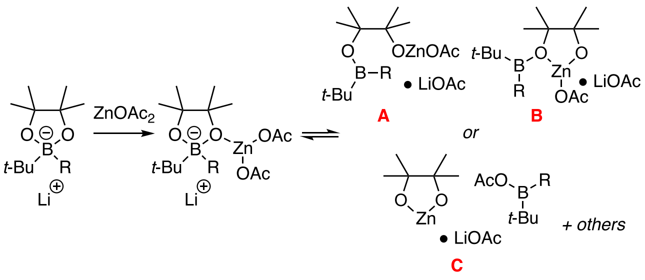


Figure 5. Plausible species involved in transmetalation of R−B(pin)·*t*-BuLi and Zn(OAc)$_2$.

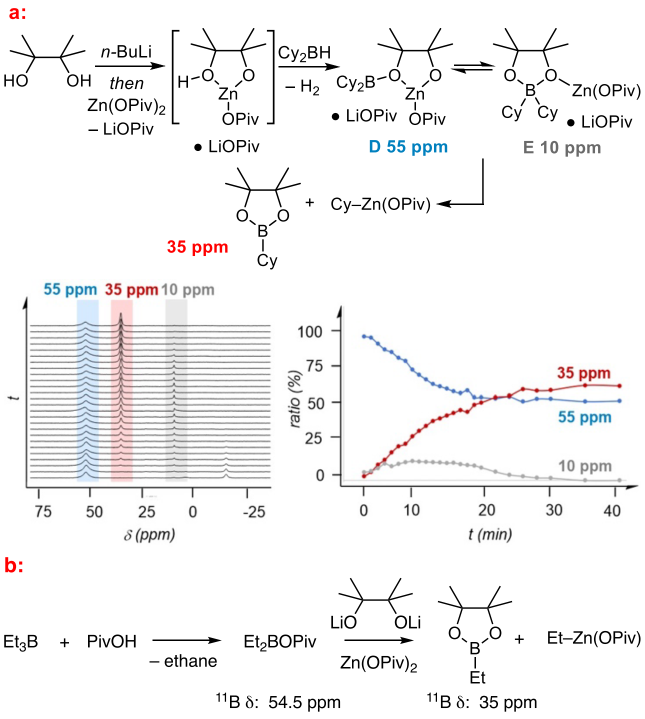


Figure 6. Identification of plausible intermediates in boron-to-zinc transmetalation. (a) Synthesis of putative borinic ester **A** from a zinc half-pinacolate and Cy$_2$BH, and analysis of the formation of Cy−B(pin) and Cy−ZnOAc by ^{11}B NMR (t = 0 at addition of Cy$_2$BH). (b) Synthesis and transmetalation of an acyloxyborane.

onic esters to C(sp^2) electrophiles is an important process.[20] Available reactions include transition-metal-free alkenylation and arylation,[21] employing alkenyl or aryllithium reagents. In addition, direct stereospecific Suzuki-Miyaura cross-coupling between nonactivated aliphatic secondary organoboron reagents and aryl halides have been reported by Biscoe and Sigman[22] (trifluoroborates) and Burke and co-workers[23] (boronic acids). Despite these advances, the current scope of these processes has been primarily explored with sterically unhindered alkylboron species (usually α-methyl substituted) and nonheterocyclic arene or alkene coupling partners. To complement these existing methods, enantiomerically enriched organozinc reagents prepared from boron-to-zinc transmetalation were examined as coupling partners for stereospecific Negishi cross-coupling reactions (Figure 2). Using Buchwald's Pd-G3 complex in conjunction with CPhos,[15] efficient coupling reactions were observed (Figure 2, 50−76% yield, 93−98% es). Challenging heterocyclic electrophiles can be employed in this reaction when PhCPhos is used as the ligand. As observed in the production of **14** and **16**, alkenyl

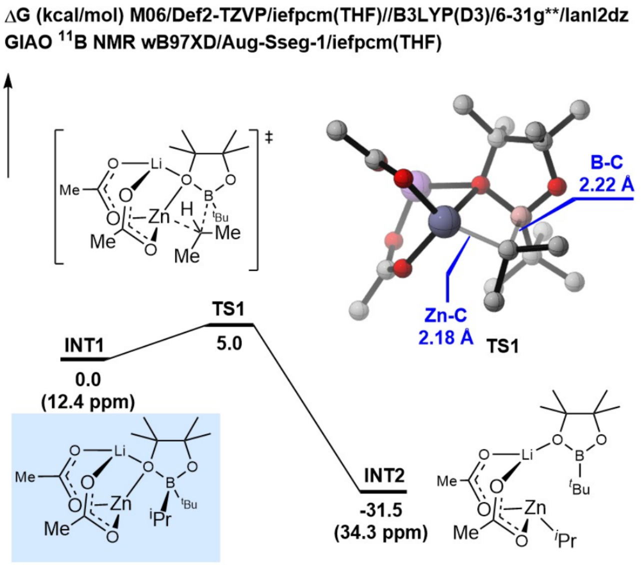


Figure 7. DFT calculated energy surface of boron-to-zinc transmetalation and GIAO-based ^{11}B chemical shifts.

halides can also be used as electrophiles. The absolute configuration of compound **10** was assigned to be (*S*) by comparing its optical rotation values with the reported data,[24] which suggests that this overall reaction is a stereoretentive process.

Racemic organozinc reagents are known to react with difluorocarbene and deliver a wide range of useful fluorinated compounds.[25] With access to enantiomerically enriched organozinc compounds as prepared above, it was of interest to determine if difluorocarbene insertion might occur in a stereospecific fashion. As shown in Figure 3, with a modification of conditions developed by Dilman and co-workers, the organozinc acetate and chloride intermediates were found to react with *in situ* generated difluorocarbene, to deliver a difluoromethylzinc intermediate; iodinolysis then produced difluoroiodomethyl derivatives with only slight erosion of enantiomeric purity. Study of the reaction conditions showed that the use of zinc pivalate in the transmetalation resulted in increased yield of the overall process (see the Supporting Information), likely by enhancing the stability of the difluoromethyl zinc intermediate. With these conditions, various secondary organoboronic esters were examined in this reaction and found to deliver the product in good yield and good enantiospecificity. Other than trapping the difluoromethyl zinc reagent with iodine to provide the difluoroiodomethyl derivative, NBS or HOAc can also be used as trapping reagent, delivering bromodifluoromethylation (**27**) and difluoromethylation[26] products (**29**−**32**), respectively. Furthermore, the difluoromethyl zinc intermediate can undergo a copper-catalyzed allylation to give difluoroalkylation product **28**. Of note, zinc chloride can also be used for this reaction (**17**, **20**, and **24**).

Stereospecific trifluoromethylation of organoboronic esters is an important objective.[27] However, our attempts to access these compounds by trapping the above-described difluoromethyl zinc intermediate with electrophilic fluorine reagents (e.g., *Selectfluor*) were unsuccessful, and only bromination product was observed (presumably, the electrophilic fluorination reagent oxidizes residual bromide to a competent electrophile). To address this problem, we considered direct trifluoromethylation of the organozinc reagent. Liu has established trifluoromethylation of primary alkylzinc and cyclohexylzinc reagents by transmetalation/reductive elimination with bench stable PyCu(III)$(CF_3)_3$.[28] In our hands, this process proceeded smoothly and delivered enantiomerically enriched CF_3-containing products (Figure 4). The use of nonpolar hexane as a solvent for the trifluoromethylation reaction provided the best results despite the poor solubility of starting materials in this system (see the Supporting Information). Both primary and secondary organoboronic esters can be used as starting materials for the transformation, however, sterically demanding or β-aryl substituted alkylboronic esters are not suitable for this reaction. In both cases, significant amount of alkene side product were generated, likely due to the β-hydrogen elimination from the corresponding alkyl copper(III) intermediate. NOESY NMR experiments with compound **36** indicated that the trifluoromethyl and aromatic groups remained *cis* after the transformation, suggesting this process is also a stereoretentive transformation.

To gain insight into the mechanism for the boron-to-zinc transmetalation, we conducted several experiments. Based on comparison to known compounds,[17] the transient ^{11}B NMR resonance observed at 55 ppm (Figure 1b) during transmetalation with $Zn(OAc)_2$ might be an intervening borinic ester, acyloxyborane,[17b] or a related compound. One plausible route to such compounds would arise from dissociation of a pinacolato oxygen atom from boron upon addition of the zinc salt. Such a process finds precedent in studies from Aggarwal,[29] and might provide either ring-opened borinic esters or derived ensembles (i.e., **A**−**C**, Figure 5).

To probe the intermediacy of species such as **A**−**C**, we examined related structures. In one experiment, pinacol was deprotonated with one equivalent of *n*-BuLi[30] and then treated with $Zn(OPiv)_2$ (Figure 6a). The presumed ligand-exchange complex was then treated with dicyclohexyborane, whereupon gas evolution was observed, and a compound immediately formed that exhibited an ^{11}B NMR resonance at 55 ppm (proposed to be **D**). Over time, the 55 ppm resonance diminished and a signal at 35 ppm appeared, suggesting that the initial species is competent for transmetalation. Interestingly, a signal at 10 ppm corresponding to a four-coordinate boron complex (**E** or related) appeared transiently during the reaction. In an alternate experiment (Figure 6b), Et_2B-(OPiv)[17b] was prepared; its resonance at 55 ppm was quickly consumed (62% conversion at 30 min) and replaced with a resonance at 35 ppm upon treatment with lithium pinacolate and zinc pivalate. While this experiment suggests that an acyloxyborane may be a participant in transmetalations, we note that the ^{11}B NMR resonance of this species is much sharper than that observed in Figure 1. Moreover, a transient 55 ppm resonance, with a similar line shape as in Figure 1, appears during transmetalations with $ZnCl_2$ (see the Supporting Information). Collectively, these experiments suggest that three-coordinate borinic esters are plausible intermediates during the course of transmetalation, but they do not rigorously establish whether these species engage in transmetalation themselves or whether they are off-cycle progenitors of reactive four-coordinate boronates.

To learn whether transmetalation is more likely from four- or three-coordinate organoboron compounds, DFT calculations were conducted for both zinc carboxylate and zinc chloride processes. While transmetalation from three-coordinate boron species was higher in energy, transmetalation of four-coordinate boronates appeared readily accessible (Figure 7, see the Supporting Information for complete details) thereby suggesting this may be the operative pathway.

In summary, we have reported a stereospecific boron-to-zinc transmetalation and show that the organozinc compounds can undergo useful stereospecific transformations. Preliminary mechanistic investigations suggest that stereospecific transfer of the alkyl group to zinc occurs from four-coordinate boronate complexes. We expect that this process may be useful for the preparation of enantiomerically enriched organozinc reagents and also extend the application scope of alkylboronic esters.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c01677.

Procedures, characterization, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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