

The Stereochemical Course of Pd-Catalyzed Suzuki Reactions Using Primary Alkyltrifluoroborate Nucleophiles

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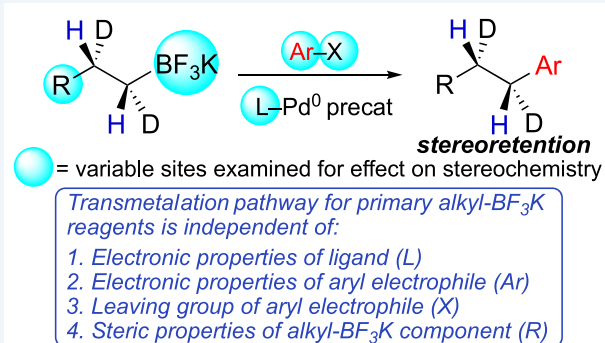
Supporting Information

ABSTRACT: Using deuterium-labeled stereochemical probes, we show that primary alkyltrifluoroborate nucleophiles undergo transmetalation to palladium exclusively via a stereoretentive pathway and that the resulting stereospecificity is broadly independent of electronic and steric effects. This stands in stark contrast to the stereochemical course of transmetalation for secondary alkyltrifluoroborates, which varies between net stereoretention and net stereoinversion depending upon the electronic properties of the supporting phosphine ligand, the electronic properties of the aryl electrophile, and the steric properties of the alkylboron nucleophile. In this study, we additionally show that the stereochemical course of transmetalation for secondary alkylboron reagents can be under reagent steric control, while no such steric control exists for analogous primary alkylboron nucleophiles. The combined study reveals fundamental mechanistic differences between transmetalations of primary and secondary alkylboron reagents in Pd-catalyzed Suzuki reactions.

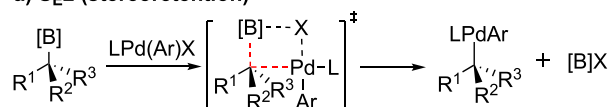
KEYWORDS: Suzuki coupling, palladium, transmetalation, alkylboron, stereochemistry

Over recent decades, the emergence of Pd-catalyzed cross-coupling reactions has revolutionized our modern approach to organic synthesis. Oxidative addition, transmetalation, and reductive elimination constitute the fundamental steps in the standard catalytic cycle of cross-coupling reactions proceeding via a Pd(0)–Pd(II) redox couple.¹ Although oxidative addition and reductive elimination processes are mechanistically well understood, the prevailing mechanistic pathway of transmetalation can be less clear.^{2,3} This is especially true for Suzuki cross-coupling reactions involving alkylboron nucleophiles.⁴ In principle, transmetalation of an alkylboron nucleophile can occur with retention (Figure 1a) or inversion (Figure 1b) of the absolute configuration. As such, the stereochemical outcome of Suzuki cross-coupling reactions involving enantioenriched alkylboron compounds is often difficult to predict.

The Biscoe/Sigman laboratories⁴ and the Burke laboratory⁵ have each reported approaches toward stereospecific Pd-catalyzed Suzuki reactions using unactivated enantioenriched secondary alkyltrifluoroborates (i.e., without α -heteroatom substitution, α -C(sp²) substitution, or remote coordinating groups).^{6–9} Our study resulted in the development of a stereodivergent Suzuki process in which the preferred stereochemical course was intimately tied to the electronic properties of the supporting phosphine ligand (Figure 2a). In these cross-coupling reactions, the bulky electron-deficient ligand bis-CF₃PhXPhos¹⁰ (1) promoted a stereoretentive transmetalation pathway, whereas bulky electron-rich ligands



a) S_E2 (stereoretention)



b) S_E2 (stereoinversion)

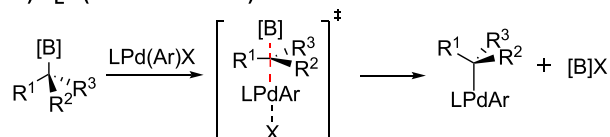


Figure 1. Putative mechanistic pathways for stereoretentive and stereoinvertive transmetalation of alkylboron nucleophiles.

P^tBu₃ and PAd₃ (2)¹¹ promoted a stereoinvertive transmetalation pathway. This study also revealed that the electronic properties of the aryl electrophile can bias the transmetalation pathway. In contrast to our observation, Molander and Dreher (Figure 2b) have shown that 2-

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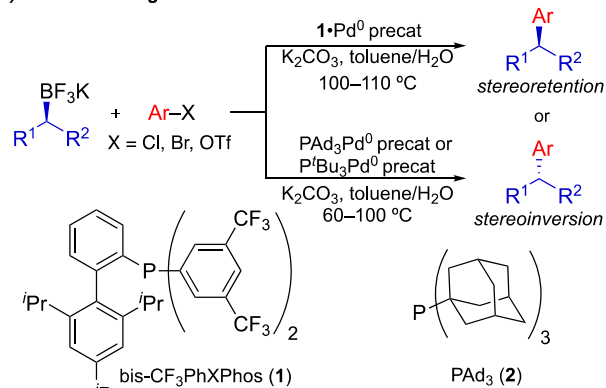
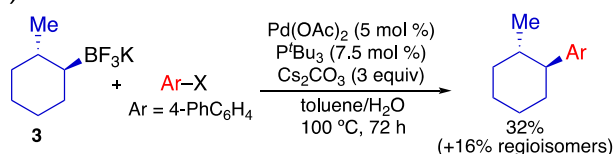
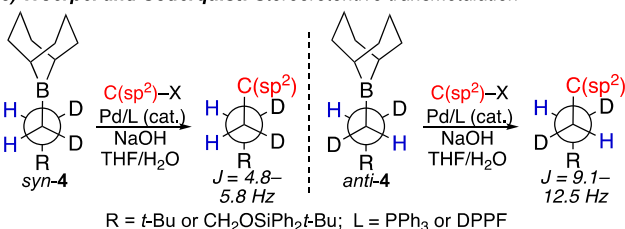
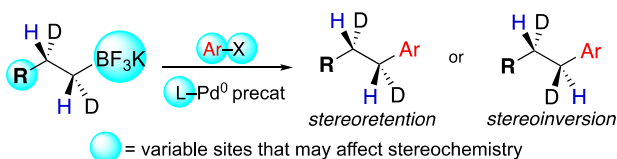
a) **Biscoe and Sigman:** Stereoretentive or stereoinvertive transmetalationb) **Molander and Dreher:** Stereoretentive transmetalationc) **Woerpel and Soderquist:** Stereoretentive transmetalationd) **This work:** Evaluation of electronic, ligand, and steric effects on stereochemical course of transmetalation

Figure 2. Stereospecific Pd-catalyzed Suzuki cross-coupling reactions using unactivated nucleophiles: (a) ligand-controlled stereodivergent Suzuki reactions; (b) stereoretentive transmetalation of **3**; (c) previous use of isotopically labeled alkyl-9-BBN nucleophiles as stereochemical probes; (d) investigation of the stereochemical course of alkylboron transmetalation described in this study.

methylcyclohexyltrifluoroborate (**3**) undergoes stereoretentive arylation using the bulky electron-rich ligand P^tBu_3 .¹² These seemingly conflicting stereochemical outcomes suggest that the steric effects of **3** preclude transmetalation via the stereo-invertive pathway (see Figure 7 within for a model). Thus, steric properties can potentially override ligand properties in dictating the stereocontrol of transmetalation. Collectively, these results suggest that the electronic properties of the phosphine ligand and electrophilic coupling partner, as well as the steric properties of the alkylboron nucleophile, can independently bias the stereochemical outcome of *B*-alkyl Suzuki reactions. Hence, the factors influencing the prevailing pathway of alkylboron transmetalation are much more nuanced than were previously appreciated.

Using the Whitesides protocol for probing the stereochemical course of organometallic reactions,^{13,14} Woerpel¹⁵ and Soderquist¹⁶ conducted seminal mechanistic investigations

of primary alkylboron transmetalation to palladium. In these studies, vicinally deuterated primary alkyl-9-BBN nucleophiles (*syn*-**4** and *anti*-**4**) were employed in Suzuki cross-coupling reactions, with the vicinal J_{H-H} coupling constant being indicative of the stereochemistry of the resulting product (Figure 2c). The investigations showed that transmetalation of primary alkyl-9-BBN nucleophiles to palladium proceeds with retention of configuration for alkylboron nucleophile **4**. Though these studies provided an important foundation on which to build our mechanistic understanding of alkylboron transmetalation, recent transmetalation studies using enantioenriched secondary alkyltrifluoroborate nucleophiles imply that primary alkylboron transmetalation might likewise proceed through competing mechanisms that are highly sensitive to ligand, electronic, and steric effects.^{4,5,12} Additionally, because alkyl-9-BBN reagents exhibit nucleophilicity more comparable to that of alkylzinc reagents, it is unclear how the stereochemical course of their transmetalation relates to that of less reactive alkyltrifluoroborates, boronic acids, or boronic esters. Herein we report on the stereochemical course of transmetalation for Suzuki cross-coupling reactions involving primary alkyltrifluoroborate nucleophiles.¹⁷ Using vicinally deuterated alkyltrifluoroborate reagents as stereochemical probes, we have conducted studies to deconvolute potential stereochemical effects arising from electronic, steric, and ligand effects within the reaction components. Through careful evaluation of these effects, we have determined that, unlike the transmetalation of secondary alkyltrifluoroborates, the transmetalation of primary alkyltrifluoroborates proceeds preferentially via a stereoretentive pathway that is independent of electronic, steric, and ligand perturbations.

Starting from *tert*-butylacetylene, we successfully prepared the vicinally deuterated alkyltrifluoroborate compounds *syn*-**6** and *anti*-**6** as stereochemical probes of transmetalation to palladium (Figure 3). Unlike previously employed alkyl-9-BBN

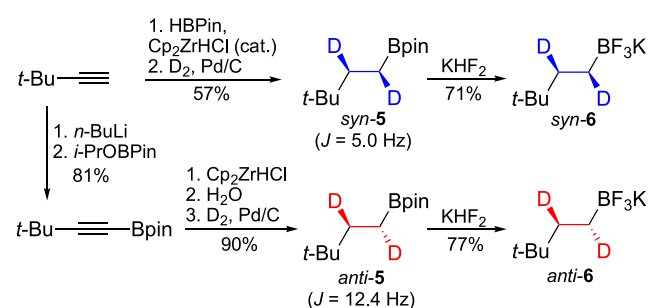


Figure 3. Synthetic routes to deuterated stereochemical probes *syn*-**6** and *anti*-**6**.

reagents,^{15,16} alkylBPIn compounds *syn*-**5** and *anti*-**5** are isolable and are easily characterized. An examination of the vicinal J_{H-H} coupling constants from their 2H -decoupled 1H NMR spectra supports their stereochemical assignments (Figure 4a). Representative cross-coupling products *syn*-**7c** and *anti*-**7c** are shown in Figure 4b. As with *syn*-**5** and *anti*-**5**, the relative stereochemistry of *syn*-**7c** and *anti*-**7c** is easily established using the vicinal J_{H-H} coupling constants from their 2H -decoupled 1H NMR spectra. Because we sought to determine the dominant transmetalation mechanism while also investigating the possibility of competitive transmetalation pathways, it was important that we obtained clearly resolved quantifiable signals indicative of *syn* or *anti* stereochemistry. An

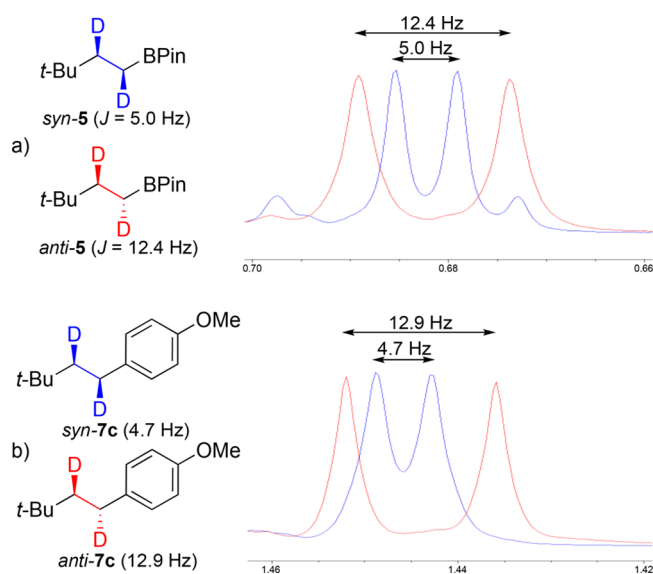


Figure 4. ^2H -decoupled ^1H NMR (800 MHz) spectra showing vicinal $J_{\text{H-H}}$ coupling constants for deuterium-labeled (a) alkyltrifluoroborates *syn*-5 and *anti*-5 (0.66–0.70 ppm range shown) and (b) cross-coupling products *syn*-7c and *anti*-7c (1.42–1.46 ppm range shown). Minor peaks appearing in (a) alongside *syn*-5 arise from isotopic impurities (e.g., *t*-BuCH₂CHD-BPin and/or *t*-BuCHDCH₂-BPin—see refs 14 and 16).

800 MHz NMR instrument was thus employed to ensure that trace impurities from the preparation of deuterated probes or from the coupling reactions could be clearly identified and not mistaken as products arising from a minor transmetalation pathway. Accordingly, because *anti*-5 showed greater isotopic purity in comparison to *syn*-5, the use of *anti*-5 and *anti*-6 as stereochemical probes enabled a clearer evaluation of the stereochemical course of transmetalation.

Our discovery that the stereochemical course of transmetalation of secondary alkyltrifluoroborates to $\text{LPd}(\text{Ar})\text{X}$ complexes is dictated by the electronic properties of the supporting phosphine ligand (L) as well as by the electronic properties of the aryl unit (Ar) suggested that the mechanism of primary alkylboron transmetalation may likewise proceed via competing stereoretentive and stereoinvertive pathways depending on the specific components of the cross-coupling reaction.⁴ Accordingly, *anti*-6 was employed in cross-coupling reactions using bis- $\text{CF}_3\text{PhXPhos}$ (**1**), which has been to shown to promote the stereoretentive transmetalation of secondary alkyltrifluoroborates, and using P^tBu_3 , which has been shown to promote the stereoinvertive transmetalation of secondary alkyltrifluoroborates (Table 1). Because we have observed that the use of electron-rich aryl electrophiles can bias the transmetalation of secondary alkyltrifluoroborates toward the stereoinvertive pathway, reactions of primary alkyltrifluoroborates were conducted using electron-deficient, electron-neutral, and electron-rich electrophilic coupling partners. The use of electronically differentiated electrophiles thus enabled an assessment of the effect of subtle electronic changes on the net stereochemical course of transmetalation. For all such reactions of *anti*-6, only the stereoretentive transmetalation pathway was observed.¹⁸ The use of *syn*-6 also provided stereochemical data consistent with stereoretention, though the presence of isotopic impurities in *syn*-6 complicated its use as a mechanistic probe (see the Supporting Information for a complete study using *syn*-6). No stereochemical variance

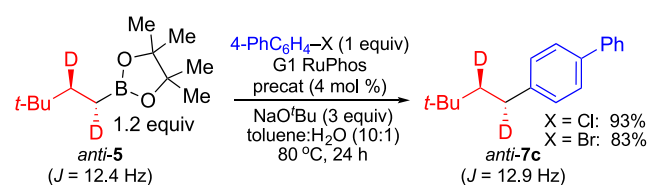
resulted when the phosphine ligand was changed from bis- $\text{CF}_3\text{PhXPhos}$ (**1**) to P^tBu_3 or when the aryl electrophile was varied. To assess the possibility that transmetalation is influenced by the identity of the leaving group on the aryl electrophile, we also investigated the use of aryl bromides and triflates in analogous reactions. These reactions, likewise, resulted in exclusive formation of the cross-coupling products from stereoretentive alkylboron transmetalation. Finally, the direct use of the alkyl pinacol boronate probe *anti*-5 was employed to determine the preferred transmetalation pathway for pinacol boronate nucleophiles, which undergo slower transmetalation to palladium in comparison to their corresponding trifluoroborate and boronic acids.^{3a} Though cross-coupling conditions developed by our group for use with alkyltrifluoroborates failed for *anti*-5,¹⁹ reaction conditions developed by Liu, Marder, and Steel^{17k} specifically for use with primary alkyl pinacol boronates successfully generated the cross-coupling product *anti*-7c (Figure 5), again via a stereoretentive transmetalation pathway. Together, these results suggest that, unlike transmetalation of unactivated secondary alkyltrifluoroborates, the transmetalation mechanism of unactivated primary alkylboron nucleophiles proceeds exclusively through a stereoretentive pathway that is insensitive to the electronic properties of both the phosphine ligand and aryl electrophile.²⁰

Though the data presented in Table 1 suggest that the mechanism of transmetalation of unactivated primary alkyltrifluoroborates is broadly independent of electronic effects, we were concerned that the steric properties of the *tert*-butyl substituent of *anti*-6 might override electronic effects from the phosphine ligand and aryl electrophile, resulting in a sterically controlled pathway of transmetalation. Indeed, the Whitesides protocol for stereochemical analysis using vicinal coupling constants requires the presence of such a bulky β substituent to bias conformational preference toward the *anti* conformer (Figure 2c). Additionally, a report from Molander and Dreher (Figure 2b) demonstrating stereoretentive transmetalation of *trans*-2-methylcyclohexyltrifluoroborate (**3**) using P^tBu_3 as the supporting phosphine contrasts with our observation that P^tBu_3 promotes stereoinvertive transmetalation of unhindered and unactivated secondary alkyltrifluoroborates (Figure 2a). To gain general insight into the potential steric effects on alkylboron transmetalation and the divergent stereochemical outcomes using P^tBu_3 , we prepared a *cis*/*trans* (ca. 5/1) mixture of 4-*tert*-butylcyclohexyltrifluoroborate (**9**) for use as a probe of alkylboron transmetalation. Though **3** is capable of conformation equilibration through ring inversion, which complicates mechanistic and kinetic analysis, **9** strongly favors a conformation that places the *tert*-butyl group in the equatorial position, which greatly simplifies an assessment of the stereochemical course of transmetalation. Using P^tBu_3 as a ligand, Suzuki coupling of *cis*-**9** occurs rapidly (half-life of approximately 10 min) and exclusively generates *trans*-**10** with clean stereoinvertive transmetalation. In contrast, Suzuki coupling of *trans*-**9** proceeds very slowly (half-life of approximately 2 h) and occurs with stereoretentive transmetalation, also generating *trans*-**10** as the exclusive reaction product (Figure 6).²¹ These results are easily rationalized, as *cis*-**9** freezes the boron group in an axial position from which the stereoinvertive $\text{S}_{\text{E}}2$ pathway of transmetalation is readily accessed, while *trans*-**9** freezes the boron substituent in an equatorial position from which the stereoinvertive $\text{S}_{\text{E}}2$ pathway of transmetalation is hindered by axial repulsions (Figure 6,

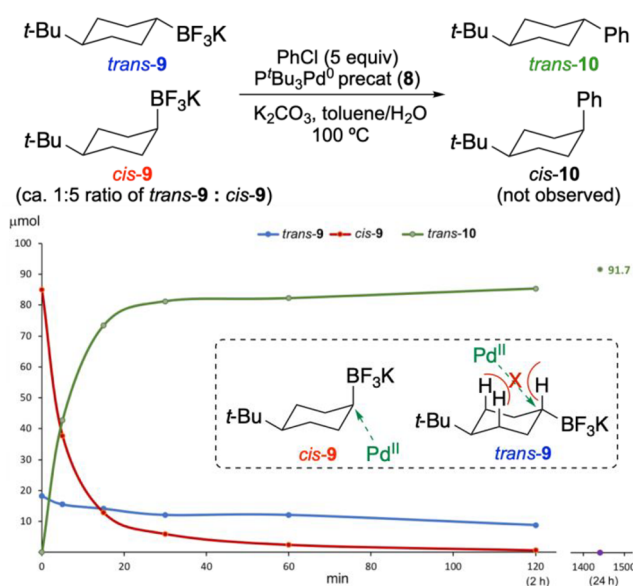
Table 1. Pd-Catalyzed Suzuki Cross-Coupling Reactions of Vicinally Deuterated *anti*-6 Using the Electron-Rich Ligand P^tBu₃ and the Electron-Deficient Ligand 1

Entry	Ar-X	Ligand	Product	Yield ^b (%)	J value (Hz)
1		P ^t Bu ₃		76	12.8
2		P ^t Bu ₃		52	12.9
3		P ^t Bu ₃		84	12.9
4		P ^t Bu ₃		82	12.9
5		P ^t Bu ₃		22	12.9
6		1		90	12.8
7		1		74	12.9
8		1		75	12.9
9		1		87	12.9
10		1		98	12.9

^aVicinal $J_{\text{H-H}}$ coupling constant of alkylBPIn derivative 5. ^bCalibrated GC yields (average of two runs).

**Figure 5.** Pd-catalyzed Suzuki cross-coupling reaction of vicinally deuterated pinacol boronate *anti*-5 using the conditions of ref 17k.

inset). Because *trans*-9 cannot undergo stereoinvertive transmetalation, the slow stereoretentive S_E2 pathway emerges as the only viable option. The comparative kinetics of these reactions, alongside the exclusive formation of *trans*-10 from both reactions, is consistent with sterically controlled transmetalation for *trans*-9. On the basis of these results, we propose that the stereoretentive Suzuki reaction of 3, which was demonstrated by Molander and Dreher using P^tBu₃, arises from steric control of the transmetalation pathway (Figure 7a). Stereoinvertive transmetalation of conformer 3a is impeded by axial repulsions, while stereoinvertive transmetalation of conformer 3b is impeded by its lower abundance at equilibrium as well as potential steric effects arising from the β -anti-methyl group. Thus, it is vital that potential steric effects also be considered when predicting or rationalizing the stereochemical course of alkylboron transmetalation.

**Figure 6.** Relative reaction rates of *cis*-9 and *trans*-9 in Pd-catalyzed Suzuki reactions using P^tBu₃ as a ligand.

In order to minimize the potential steric effect on the stereochemistry of transmetalation using primary alkyltrifluoroborates, we redesigned our stereochemical probe. In our new

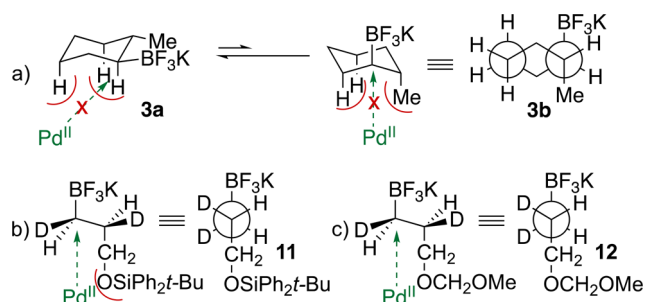


Figure 7. Models depicting (a) proposed sterically controlled transmetalation of **3**, (b) hindered stereoinvertive transmetalation of **11**, and (c) minimally hindered stereoinvertive transmetalation of **12**.

approach, we employed a CH₂OSiPh₂t-Bu group as the bulky β substituent, which enables an assessment of *syn* and *anti* stereochemistry in the cross-coupling products, as shown by Woerpel (Figure 7b,c).¹⁵ However, following preparation of vicinally deuterated alkylBPIn compound **13**, the bulky silyl group was removed and replaced with a much smaller CH₂OMe (MOM) protecting group on the alkylboron probe (**12**) (Figure 8). Thus, the mechanism for stereoinvertive

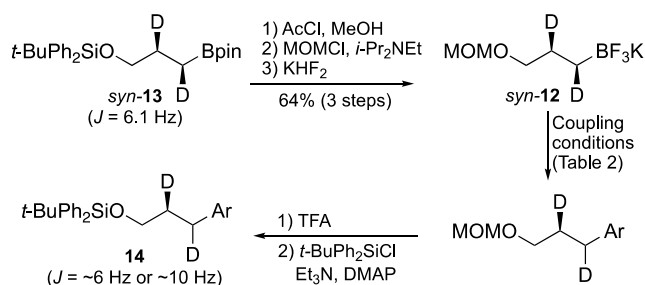


Figure 8. Reaction sequence used to establish the stereospecificity of Pd-catalyzed Suzuki reactions using *syn*-**12**.

transmetalation of **12** should be significantly less sensitive in comparison to **11** to the steric properties of the β substituent (Figure 6b,c). Following the use of **12** in cross-coupling reactions, the bulky silyl group was reinstalled to enable differentiation of *syn*- and *anti*-**14**. When cross-coupling reactions were performed using **12**, the stereoretentive pathway of transmetalation was again observed, independent of the ligand and the electronic properties of the aryl electrophile (Table 2).²² These results strongly suggest that the general stereochemical course of transmetalation for primary alkylboron nucleophiles proceeds via a stereoretentive mechanism and that the stereospecificity is not influenced by steric perturbations of the alkylboron nucleophile or by the electronic properties of the phosphine ligand and aryl electrophile. These results stand in stark contrast to the mechanism of transmetalation of secondary alkylboron nucleophiles, which is strongly influenced by subtle electronic and steric properties of the supporting ligand and coupling partners.

In summary, we have shown that primary alkyltrifluoroborate nucleophiles undergo transmetalation to palladium exclusively via a stereoretentive pathway and that the resulting stereospecificity is broadly independent of electronic and steric effects. This contrasts with the pathway of transmetalation for secondary alkyltrifluoroborates, which varies between net stereoretention and net stereoinversion depending upon the

Table 2. Pd-Catalyzed Suzuki Cross-Coupling Reactions of Vicinally Deuterated *syn*-**12** Using the Electron-Rich Ligand P^tBu₃ and Electron-Deficient Ligand **1**

Reaction scheme: **syn-13** (MOM-protected, BF₃K) reacts with 8 (5 mol %), K₂CO₃ (3 equiv), Ar-Cl in toluene:H₂O (2:1) at 100 °C for 24 h to yield **syn-14** (t-BuPh₂SiO-protected).

Entry	Ligand	Product	Yield ^a (%)	J value (Hz)
1	P ^t Bu ₃	syn-14a (Ar = CO ₂ Et)	25	6.3
2	P ^t Bu ₃	syn-14b (Ar = Ph)	34	6.4
3	1	syn-14a (Ar = CO ₂ Et)	36	6.3
4	1	syn-14b (Ar = Ph)	51	6.4

^aIsolated yield over three steps (average of two runs).

electronic properties of the supporting phosphine ligands, the electronic properties of the aryl electrophile, and the steric properties of the alkyltrifluoroborate nucleophile. During these studies, sterically controlled transmetalation of secondary alkylboron nucleophiles was also demonstrated for the first time, which highlights the importance of considering steric effects in attempting to predict or rationalize the stereochemistry of secondary alkyl Suzuki reactions. The insensitivity of the stereochemical course of primary alkylboron transmetalation to electronic (ligand and substrate) and steric properties indicates that the mechanisms of transmetalation for primary and secondary alkylboron nucleophiles are mutually distinct and underscores the intrinsic complexity of alkylboron transmetalation. These mechanistic insights should help to guide the future design of new strategies for Pd-catalyzed B-alkyl Suzuki cross-coupling reactions involving primary and secondary alkylboron reagents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscatal.0c04325>.

Procedural details, compound characterization, and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) *Metal-Catalyzed Cross-Coupling Reactions and more*; de Meijere, A.; Bräse, S.; Oestreich, M., Eds.; Wiley-VCH: Weinheim, Germany, 2014.
- (2) For reviews of cross-coupling reactions involving alkyl nucleophiles, see: (a) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. The *B*-Alkyl Suzuki-Miyaura Cross-Coupling Reaction: A Versatile C–C Bond-Forming Tool. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544–4568. (b) Jana, R.; Pathak, T. P.; Sigman, M. S. Advances in Transition Metal (Pd, Ni, Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-Organometallics as Reaction Partners. *Chem. Rev.* **2011**, *111*, 1417–1492. (c) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. Enantioselective and Enantiospecific Transition-Metal-Catalyzed Cross-Coupling Reactions of Organometallic Reagents to Construct C–C Bonds. *Chem. Rev.* **2015**, *115*, 9587–9652. (d) Wang, C.-Y.; Derosa, J.; Biscoe, M. R. The Use of Stable, Optically Active Organometallic Nucleophiles in Cross-Coupling Reactions. *Chem. Sci.* **2015**, *6*, 5105–5113. (e) Rygus, J. P. G.; Crudden, C. M. Enantiospecific and Iterative Suzuki-Miyaura Cross-Couplings. *J. Am. Chem. Soc.* **2017**, *139*, 18124–18137. (f) Sandford, C.; Aggarwal, V. K. Stereospecific Functionalizations and Transformations of Secondary and Tertiary Boronic Esters. *Chem. Commun.* **2017**, *53*, 5481–5494.
- (3) (a) Carrow, B.; Hartwig, J. F. Distinguishing between Pathways for Transmetalation in Suzuki–Miyaura Reactions. *J. Am. Chem. Soc.* **2011**, *133*, 2116–2119. (b) Amatore, C.; Jutand, A.; Le Duc, G. Kinetic Data for the Transmetalation/Reductive Elimination in Palladium-Catalyzed Suzuki–Miyaura Reactions: Unexpected Triple Role of Hydroxide Ions Used as Base. *Chem. - Eur. J.* **2011**, *17*, 2492–2503. (c) Thomas, A. A.; Denmark, S. E. Pre-Transmetalation Intermediates in the Suzuki-Miyaura Reaction Revealed: The Missing Link. *Science* **2016**, *352*, 329–332. (d) Thomas, A. A.; Wang, H.; Zahrt, A. F.; Denmark, S. E. Structural, Kinetic, and Computational Characterization of the Elusive Arylpalladium(II)boronate Complexes in the Suzuki–Miyaura Reaction. *J. Am. Chem. Soc.* **2017**, *139*, 3805–3821. (e) Thomas, A. A.; Zahrt, A. F.; Delaney, C. P.; Denmark, S. E. Elucidating the Role of the Boronic Esters in the Suzuki-Miyaura Reaction: Structural, Kinetic, and Computational Investigations. *J. Am. Chem. Soc.* **2018**, *140*, 4401–4416.
- (4) (a) Li, L.; Zhao, S.; Joshi-Pangu, A.; Diane, M.; Biscoe, M. R. Stereospecific Pd-Catalyzed Cross-Coupling Reactions of Secondary Alkylboron Nucleophiles and Aryl Chlorides. *J. Am. Chem. Soc.* **2014**, *136*, 14027–14030. (b) Zhao, S.; Gensch, T.; Murray, B.; Niemeyer, Z. L.; Sigman, M. S.; Biscoe, M. R. Enantiodivergent Pd-Catalyzed C–C Bond Formation Enabled through Ligand Parameterization. *Science* **2018**, *362*, 670–674.
- (5) Lehmann, J. W.; Crouch, I. T.; Blair, D. J.; Trobe, M.; Wang, P.; Li, J.; Burke, M. D. Axial Shielding of Pd(II) Complexes Enables Perfect Stereoretention in Suzuki-Miyaura Cross-Coupling of Csp³ Boronic Acids. *Nat. Commun.* **2019**, *10*, 1263.
- (6) For stereospecific Pd-catalyzed cross-coupling reactions involving benzylic organoboron nucleophiles, see: (a) Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. Cross-Coupling Reactions of Chiral Secondary Organoboronic Esters with Retention of Configuration. *J. Am. Chem. Soc.* **2009**, *131*, 5024–5025. (b) Ohmura, T.; Awano, T.; Sugimoto, M. Stereospecific Suzuki-Miyaura Coupling of Chiral α -(Acylamino)benzylboronic Esters with Inversion of Configuration. *J. Am. Chem. Soc.* **2010**, *132*, 13191–13193. (c) Awano, T.; Ohmura, T.; Sugimoto, M. Inversion of Retention? Effects of Acidic Additives on the Stereochemical Course in Enantiospecific Suzuki-Miyaura Coupling of α -(Acetylamino)-benzylboronic esters. *J. Am. Chem. Soc.* **2011**, *133*, 20738–20741. (d) Matthew, S. C.; Glasspoole, B. W.; Eisenberger, P.; Crudden, C. M. Synthesis of Enantiomerically Enriched Triarylmethanes by Enantiospecific Suzuki-Miyaura Cross-Coupling Reactions. *J. Am. Chem. Soc.* **2014**, *136*, 5828–5831.
- (7) For stereospecific Pd-catalyzed cross-coupling reactions involving allylic organoboron nucleophiles, see: (a) Partridge, B. M.; Chausset-Boissarie, L.; Burns, M.; Pulis, A. P.; Aggarwal, V. K. Enantioselective Synthesis and Cross-Coupling of Tertiary Propargylic Boronic Esters Using Lithiation-Borylation of Propargylic Carbamates. *Angew. Chem., Int. Ed.* **2012**, *51*, 11795–11799. (b) Chausset-Boissarie, L.; Ghazati, K.; LaBine, E.; Chen, J. L.-Y.; Aggarwal, V. K.; Crudden, C. M. Enantiospecific, Regioselective Cross-Coupling Reactions of Secondary Allylic Boronic Esters. *Chem. - Eur. J.* **2013**, *19*, 17698–17701. (c) Ding, J.; Rybak, T.; Hall, D. G. Synthesis of Chiral Heterocycles by Ligand-Controlled Regiodivergent and Enantiospecific Suzuki-Miyaura Cross-Coupling. *Nat. Commun.* **2014**, *5*, 5474. (d) Rybak, T.; Hall, D. G. Stereoselective and Regiodivergent Allylic Suzuki-Miyaura Cross-Coupling of 2-Ethoxydihydropyranyl Boronates: Synthesis and Confirmation of Absolute Stereochemistry of Diospongin B. *Org. Lett.* **2015**, *17*, 4156–4159. (e) Potter, B.; Edelstein, E. K.; Morken, J. P. Modular, Catalytic Enantioselective Construction of Quaternary Carbon Stereocenters by Sequential Cross-Coupling Reactions. *Org. Lett.* **2016**, *18*, 3286–3289. (f) Rubial, B.; Collins, B. S. L.; Bigler, R.; Aichhorn, S.; Noble, A.; Aggarwal, A. K. Enantiospecific Synthesis of Ortho-Substituted 1,1-Diaryllkanes by a 1,2-Metalate Rearrangement/*anti*-S_N² Elimination/Rearomatizing Allylic Suzuki-Miyaura Reaction Sequence. *Angew. Chem., Int. Ed.* **2019**, *58*, 1366–1370.
- (8) For stereospecific Pd-catalyzed cross-coupling reactions involving α -heteroatom-substituted organoboron nucleophiles, see: (a) Lee, J. C. H.; McDonald, R.; Hall, D. G. Enantioselective Preparation and Chemoselective Cross-Coupling of 1,1-Diboron Compounds. *Nat. Chem.* **2011**, *3*, 894–899. (b) Molander, G. A.; Wisniewski, S. R. Stereospecific Cross-Coupling of Secondary Organotrifluoroborates: Potassium 1-(Benzyloxy)-alkyltrifluoroborates. *J. Am. Chem. Soc.* **2012**, *134*, 16856–16868. (c) Feng, X.; Jeon, H.; Yun, J. Regio- and Enantioselective Copper(I)-Catalyzed Hydroboration of Borylalkenes: Asymmetric Synthesis of 1,1-Diborylalkanes. *Angew. Chem., Int. Ed.* **2013**, *52*, 3989–3992. (d) Malova Krizkova, P.; Hammerschmidt, F. On the Configurational Stability of Chiral Heteroatom-Substituted [D₁]Methylpalladium Complexes as Intermediates of Stille and Suzuki-Miyaura Cross-

coupling Reactions. *Eur. J. Org. Chem.* **2013**, 2013, 5143–5148. (e) Sun, C.; Potter, B.; Morken, J. P. A Catalytic Enantiotopic-Group-Selective Suzuki reaction for the Construction of Chiral Organo-boronates. *J. Am. Chem. Soc.* **2014**, 136, 6534–6537. (f) Ohmura, T.; Miwa, K.; Awano, T.; Sugino, M. Enantiospecific Suzuki-Miyaura Coupling of Nonbenzylic α -(Acylamino)alkylboronic Acid Derivatives. *Chem. - Asian J.* **2018**, 13, 2414–2417.

(9) For stereospecific Pd-catalyzed cross-coupling reactions involving organoboron nucleophiles bearing remote coordinating groups, see: (a) Sandrock, D. L.; Jean-Gerard, L.; Chen, C.-Y.; Dreher, S. D.; Molander, G. A. Stereospecific Cross-Coupling of Secondary Alkyl β -Trifluoroboroamides. *J. Am. Chem. Soc.* **2010**, 132, 17108–17110. (b) Daini, M.; Sugino, M. Palladium-Catalyzed, Stereoselective, Cyclizative Alkenylboration of Carbon-Carbon Double Bonds through Activation of a Boron-Chlorine Bond. *J. Am. Chem. Soc.* **2011**, 133, 4758–4761. (c) Blaisdell, T. P.; Morken, J. P. Hydroxyl-Directed Cross-Coupling: A Scalable Synthesis of Debromohamigeran E and Other Targets of Interest. *J. Am. Chem. Soc.* **2015**, 137, 8712–8715. (d) Hoang, G. L.; Yang, Z.-D.; Smith, S. M.; Pal, R.; Miska, J. L.; Perez, D. E.; Pelter, L. S. W.; Zeng, X. C.; Takacs, J. M. Enantioselective Desymmetrization via Carbonyl-Directed Catalytic Asymmetric Hydroboration and Suzuki-Miyaura Cross-Coupling. *Org. Lett.* **2015**, 17, 940–943. (e) Hoang, G. L.; Takacs, J. M. Enantioselective γ -Borylation of Unsaturated Amides and Stereoretentive Suzuki-Miyaura Cross-Coupling. *Chem. Sci.* **2017**, 8, 4511–4516.

(10) The structurally related ligand JackiePhos has been shown to promote stereoretentive Stille reactions of enantioenriched secondary alkylstannanes. See: (a) Li, L.; Wang, C.-Y.; Huang, R.; Biscoe, M. R. Stereoretentive Pd-Catalyzed Stille Cross-Coupling Reactions of Secondary Alkyl Azastannatranes and Aryl Electrophiles. *Nat. Chem.* **2013**, 5, 607–612. (b) Zhu, F.; Rouke, M. J.; Yang, T.; Rodriguez, J.; Walczak, M. A. Highly Stereospecific Cross-Coupling Reactions of Anomeric Stannanes for the Synthesis of C-Aryl Glycosides. *J. Am. Chem. Soc.* **2016**, 138, 12049–12052. (c) Wang, C.-Y.; Ralph, G.; Derosa, J.; Biscoe, M. R. Stereospecific Pd-Catalyzed Acylation of Alkylcarbostannatranes: A General Alternative to Asymmetric Enolate Reactions. *Angew. Chem., Int. Ed.* **2017**, 56, 856–860. (d) Ma, X.; Zhao, H.; Binayeva, M.; Ralph, G.; Diane, M.; Zhao, S.; Wang, C.-Y.; Biscoe, M. R. A General Approach to Stereospecific Cross-Coupling Reactions of Nitrogen-Containing Stereocenters. *Chem.* **2020**, 6, 781–791.

(11) Chen, L.; Ren, P.; Carrow, B. P. Tri(1-adamantyl)phosphine: Expanding the Boundary of Electron-Releasing Character Available to Organophosphorus Compounds. *J. Am. Chem. Soc.* **2016**, 138, 6392–6395.

(12) Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. Efficient Cross-Coupling of Secondary Alkyltrifluoroborates with Aryl Chlorides – Reaction Discovery Using Parallel Microscale Experimentation. *J. Am. Chem. Soc.* **2008**, 130, 9257–9259.

(13) Bock, P. L.; Boschetto, D. M.; Rasmussen, J. R.; Demers, J. P.; Whitesides, G. M. Stereochemistry of Reactions at Carbon-Transition Metal α Bonds. $(\text{CH}_3)_3\text{CCHDCHDFe}(\text{CO})_2\text{C}_5\text{H}_5$. *J. Am. Chem. Soc.* **1974**, 96, 2814–2825.

(14) (a) Taylor, B. L. H.; Jarvo, E. R. Stereochemistry of Transmetalation of Alkylboranes in Nickel-Catalyzed Alkyl-Alkyl Cross-Coupling Reactions. *J. Org. Chem.* **2011**, 76, 7573–7576. (b) Wilsily, A.; Tramutola, F.; Owston, N. A.; Fu, G. C. New Directing Groups for Metal-Catalyzed Asymmetric Carbon–Carbon Bond-Forming Processes: Stereoconvergent Alkyl-Alkyl Suzuki Cross-Couplings of Unactivated Electrophiles. *J. Am. Chem. Soc.* **2012**, 134, 5794–5797.

(15) Ridgway, B. H.; Woerpel, K. A. Transmetalation of Alkylboranes to Palladium in the Suzuki Coupling Reaction Proceeds with Retention of Stereochemistry. *J. Org. Chem.* **1998**, 63, 458–460.

(16) Matos, K.; Soderquist, J. A. Alkylboranes in the Suzuki-Miyaura Coupling: Stereochemical and Mechanistic Studies. *J. Org. Chem.* **1998**, 63, 461–470.

(17) For Pd-catalyzed cross-coupling reactions involving unactivated primary alkyl boronic acids, boronate esters, and trifluoroborates, see: (a) Sato, M.; Miyaura, N.; Suzuki, A. Cross-Coupling Reaction of Alkyl- or Arylboronic Acid Esters with Organic Halides by Thallium(I) Salts and Palladium-Catalyst. *Chem. Lett.* **1989**, 18, 1405–1408. (b) Kirchhoff, J. H.; Netherton, M. R.; Hills, I.; Fu, G. C. Boronic Acids: New Coupling Partners in Room-Temperature Suzuki Reactions of Alkyl Bromides. Crystallographic Characterization of an Oxidative-Addition Adduct Generated under Remarkably Mild Conditions. *J. Am. Chem. Soc.* **2002**, 124, 13662–13663. (c) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. Air Stable, Sterically Hindered Ferrocenyl Dialkylphosphines for Palladium-Catalyzed C–C, C–N, and C–O Bond-Forming Cross-Coupling. *J. Org. Chem.* **2002**, 67, 5553–5566. (d) Molander, G. A.; Yun, C.-S.; Ribagorda, M.; Biolatto, B. B-Alkyl Suzuki-Miyaura Cross-Coupling Reactions with Air-Stable Potassium Alkyltrifluoroborates. *J. Org. Chem.* **2003**, 68, 5534–5539. (e) Molander, G. A.; Vargas, F. β -Aminoethyltrifluoroborates: Efficient Aminoethylations via Suzuki-Miyaura Cross-Coupling. *Org. Lett.* **2007**, 9, 203–206. (f) Molander, G. A.; Jean-Gerard, L. Scope of the Suzuki-Miyaura Aminoethylation Reaction Using Organotrifluoroborates. *J. Org. Chem.* **2007**, 72, 8422–8426. (g) Molander, G. A.; Ham, J.; Seapy, D. G. Palladium-Catalyzed Cross-Coupling Reaction of Alkenyl Bromides with Potassium Alkyltrifluoroborates. *Tetrahedron* **2007**, 63, 768–775. (h) Molander, G. A.; Sandrock, D. L. Orthogonal Reactivity in Boryl-Substituted Organotrifluoroborates. *J. Am. Chem. Soc.* **2008**, 130, 15792–15793. (i) Molander, G. A.; Sandrock, D. L. Utilization of Potassium Vinyl Trifluoroborate in the Development of a 1,2-Dianion Equivalent. *Org. Lett.* **2009**, 11, 2369–2372. (j) Dreher, S. D.; Lim, S.-E.; Sandrock, D. L.; Molander, G. A. Suzuki-Miyaura Cross-Coupling Reactions of Primary Alkyltrifluoroborates with Aryl Chlorides. *J. Org. Chem.* **2009**, 74, 3626–3631. (k) Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. Alkylboronic Esters from Copper-Catalyzed Borylation of Primary and Secondary Alkyl Halides and Pseudohalides. *Angew. Chem., Int. Ed.* **2012**, 51, 528–532.

(18) The use of PdAd_3 results in stereoselectivity identical with that of P^tBu_3 for Suzuki reactions of the primary alkyltrifluoroborate *anti*-6 (see the Supporting Information). For coupling products of *anti*-6, the ^2H -decoupled doublets were baseline-separated, which would enable a clear observation of the doublets corresponding to the *syn* product from stereoinvertive transmetalation (see doping studies on page S99 of the Supporting Information). On the basis of these data, we can estimate that <10% of *syn* product forms in all of these reactions.

(19) Using ligand **1**, a <20% calibrated GC yield was observed for the coupling of *anti*-5 and 4- $\text{PhC}_6\text{H}_4\text{Cl}$. However, isolation of this product did show stereoretentive transmetalation (see the Supporting Information).

(20) In our study, the use of bulky monodentate ligands enables the direct comparison of primary alkyl transmetalation to secondary alkyl transmetalation. In Woerpel's original study,¹⁵ use of a bidentate phosphine ligand also resulted in net-stereoretentive transfer of a primary alkyl group in Pd-catalyzed Suzuki reactions. However, we have been unable to effect successful transmetalation of secondary alkyltrifluoroborates using analogous bidentate ligands.

(21) Using ligand **1**, which promotes stereoretentive transmetalation, the opposite behavior was observed. *trans*-9 exhibits a half-life of 50 min, while *cis*-9 exhibits a half-life of 18 h. With a 1/5 ratio of *trans*-9/*cis*-9 as the starting materials, a ca. 4/1 ratio of *trans*-10/*cis*-10 was observed after complete consumption of *cis*-9 (see the Supporting Information for details).

(22) For coupling products of *syn*-12, ^2H -decoupling alongside homonuclear ^1H decoupling of the neighboring methylene enables deconvolution of the coupling constants. However, the smaller difference in coupling constants for *syn* and *anti* products (relative to *syn* and *anti* products from coupling reactions of *anti*-6) creates the possibility of greater error (see doping studies on page S180 of the Supporting Information). On the basis of these data, we can estimate that <15% of *anti* product forms in these reactions.