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Stereospecific Csp^3 Suzuki–Miyaura Cross-Coupling That Evades β-Oxygen Elimination

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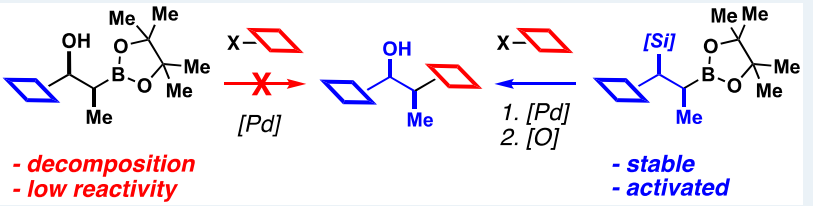

ABSTRACT: Stereospecific Csp^3 Suzuki–Miyaura cross-coupling could transform stereochemically complex small molecule synthesis into a simple and broadly accessible process. However, most current methods are not compatible with complex building blocks that represent densely packed, multistereogenic center-containing motifs commonly found in natural products and other complex targets. Here, we report a method that enables the α-methyl-β-hydroxyl motif, which is found in >18 000 natural products as well as other Csp^3-rich organic fragments, to be embedded within stereochemically defined secondary alkyl boronic ester building blocks that are readily cross-coupled in a stereospecific manner. The steric effect-mediated decrease in reactivity toward transmetalation and deleterious side reactions associated with the cross-coupling of β-oxygen-containing Csp^3 boronic esters are concomitantly addressed using β-aryloxysilyl groups as dual-purpose transmetalation-promoting groups and stable β-oxygen surrogates. Mechanistic studies including real-time HPLC analysis show that a five-membered pinacol siloxaborolate generated in situ is then hydrolyzed to a dihydroxysiloxaborolate that acts as an activated transmetalation partner in a stereospecific process that proceeds with retention of configuration.

KEYWORDS: *cross-coupling, Csp3, alkyl, Suzuki–Miyaura, stereospecific, palladium, siloxaborolate*

INTRODUCTION

Since Crudden's first demonstration of stereospecific Suzuki–Miyaura cross-coupling of acyclic chiral nonracemic Csp^3 boronates in 2009,[1] many important advances in this space have been made.[2] This substantial and accelerating progress suggests that a simple, generalized, and broadly accessible Lego-like process for making stereochemically complex Csp^3-rich small molecules may be within reach.[3] However, application of stereospecific Csp^3 Suzuki–Miyaura cross-coupling in densely packed, natural-product-like settings remains rare (Figure 1A).[2k,m,t,3d,4] We are only aware of one example of a linear, secondary alkyl boronic ester with a neighboring stereogenic center undergoing stereospecific cross-coupling, and this required a doubly activated substrate with a γ-hydroxyl group on one alkyl terminus, and a β-pinacol boronic ester group on the other.[2m,4c]

With increasing evidence that stereospecific cross-coupling could broadly simplify the synthesis of complex Csp^3-rich small molecules, we asked whether a classic motif found in more than 18 000 polyketide and other types of natural products,[5] the α-methyl-β-hydroxyl stereodiad (Figure 1B), could be preprogrammed into organoboron building blocks for installation via stereospecific Csp^3 Suzuki–Miyaura cross-coupling. This required the cross-coupling of secondary alkyl pinacol boronic esters with β-oxygen functionality. When we synthesized β-hydroxy boronic ester **1** and submitted it to Suzuki–Miyaura conditions, we observed only trace formation of the desired product **2** as well as 50% yield of alkene byproduct **3** generated via base-promoted boron-Wittig elimination[6] and/or palladium(II)-mediated β-heteroatom elimination (Figure 1C).[7] Changing reaction conditions to those reported by Fu and co-workers[8] in the coupling of a primary pinacol boronic ester with a β-hydroxyl group still yielded only trace product and only somewhat mitigated elimination, likely via deprotonation of the alcohol group by potassium *tert*-butoxide. Running the same two reaction conditions except with 2.0 equiv of **1** only allowed for low yields of product (<5% and 15%, respectively) and significantly increased the quantity of elimination byproduct **3** that we observed. We hypothesize that the slower transmetalation rate

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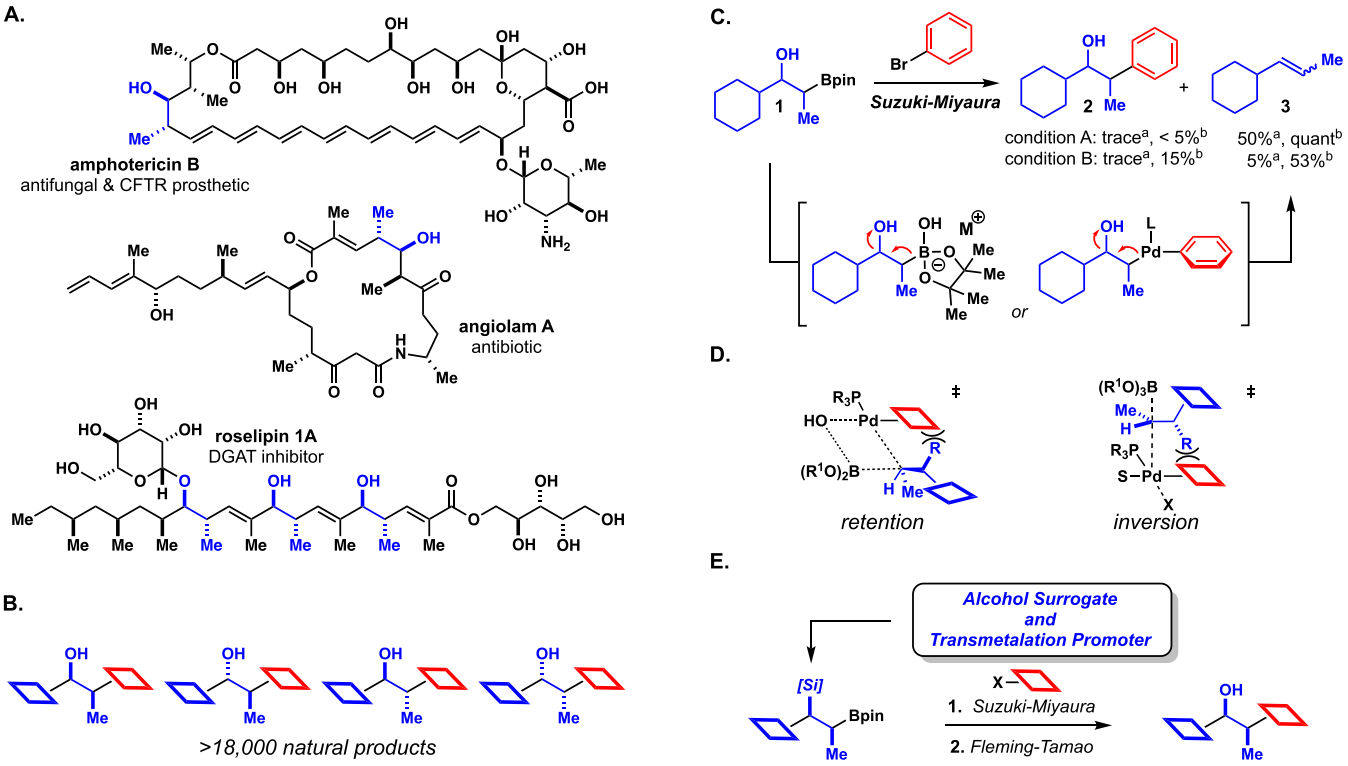

Figure 1. Pre-encoding natural product stereochemistry into building blocks for stereospecific Suzuki−Miyaura cross-coupling. (A) α-Methyl-β-hydroxyl stereodiad in natural products. (B) Programming stereochemical complexity into building blocks. (C) β-Hydroxy boronic ester nucleophiles are poor coupling partners. Condition A: RuPhos Pd G4 (10 mol %), RuPhos (10 mol %), CsOH·H_2O (3.0 equiv), PhBr (1.0 equiv), (a) **1** (1.0 equiv) or (b) **1** (2.0 equiv), DMSO/H_2O, 80 °C, 24 h. Condition B: Pd_2dba_3 (5 mol %), RuPhos (7 mol %), KO*t*Bu (3.0 equiv), PhBr (1.0 equiv), (a) **1** (1.0 equiv) or (b) **1** (2.0 equiv), THF/toluene/H_2O, 70 °C, 24 h. Yields calculated relative to bromobenzene. Pd RuPhos G4 = Buchwald RuPhos fourth generation palladacycle. Yields obtained by gas chromatography and comparison to internal standard and independently synthesized product standards. (D) Highly hindered transmetalation mechanisms of secondary alkyl organoboron nucleophiles to Pd(II). (E) β-Silyl groups as alcohol surrogates and transmetalation promoters.

of secondary boronic esters, especially when substituted with proximal functional groups, renders undesired decomposition pathways faster than the desired transmetalation step (Figure 1D). Overcoming these challenges via the design of a hyperactive and stable surrogate for the α-methyl-β-hydroxyl motif would represent an important step toward harnessing the substantial but currently untapped potential for stereospecific cross-coupling to broadly simplify the synthesis of complex Csp^3-rich compounds.

RESULTS AND DISCUSSION

To overcome both the steric hindrance and competitive decomposition pathways associated with cross-coupling β-hydroxyl-substituted boronic esters, we sought an alcohol surrogate that could simultaneously promote the high-energy transmetalation step while resisting undesired elimination pathways (Figure 1E). Silanes have been utilized as masked alcohols as early as 1984 as they are easily converted to the latter via stereospecific Fleming−Tamao oxidation.[9] Encouragingly, Yun and co-workers have reported the successful cross-coupling of a primary alkyl pinacol boronic ester with a β-phenyldimethylsilyl substituent,[10] and recently Ito and co-workers employed a cyclopropyl variant.[11] Using a route developed by Suginome and co-workers to vicinal silylboronic esters (Figure 2A),[9] we generated a secondary alkyl pinacol boronic ester with a β-phenyldimethylsilyl substituent (**4**) and submitted it to cross-coupling conditions but observed none of the desired product (Figure 2B), potentially due to the low reactivity of this highly hindered nucleophile. To overcome this, we drew inspiration from previous reports by Morken,[2m] Suginome,[2a,c,f,r] Molander,[2b,h] Hall,[2e,k] and Takacs,[2n,p] demonstrating that proximal Lewis basic functional groups can promote transmetalation of secondary alkyl boronates. We thus hypothesized that installation of Lewis basic functionality on the silyl group could have an activating effect thereby increasing the reactivity of the sterically hindered nucleophile toward transmetalation.

Adding an additional step to Suginome's route,[12,13] we were able to affect late-stage conversion of the phenyldimethylsilyl group to various oxygen substituted silyl groups (Figure 2A). Submission of β-methoxydimethylsilyl boronic ester **5** to the coupling conditions followed by Tamao oxidation afforded desired product **8** in 40% yield, suggesting that the Lewis basic substituent could provide an activating effect. β-Phenoxydimethylsilyl boronic ester **6** underwent cross-coupling with bromobenzene and then oxidation to yield **8** in 57% yield, and β-(2,6-dimethoxyphenoxy)dimethylsilyl boronic ester **7** provided **8** with the highest isolated yield of 73% (Figure 2B). This optimized aryloxysilyl group was selected for further exploration.

A range of β-(2,6-dimethoxyphenoxy)dimethylsilyl boronic esters were tested in this cross-coupling/oxidation sequence and were found to be competent coupling partners with various aryl halides (Figure 2C). Modification of the nucleophile by replacing the phenyl ring with an *n*-alkyl chain retained reactivity to form **10**; thus, an aryl ring is not

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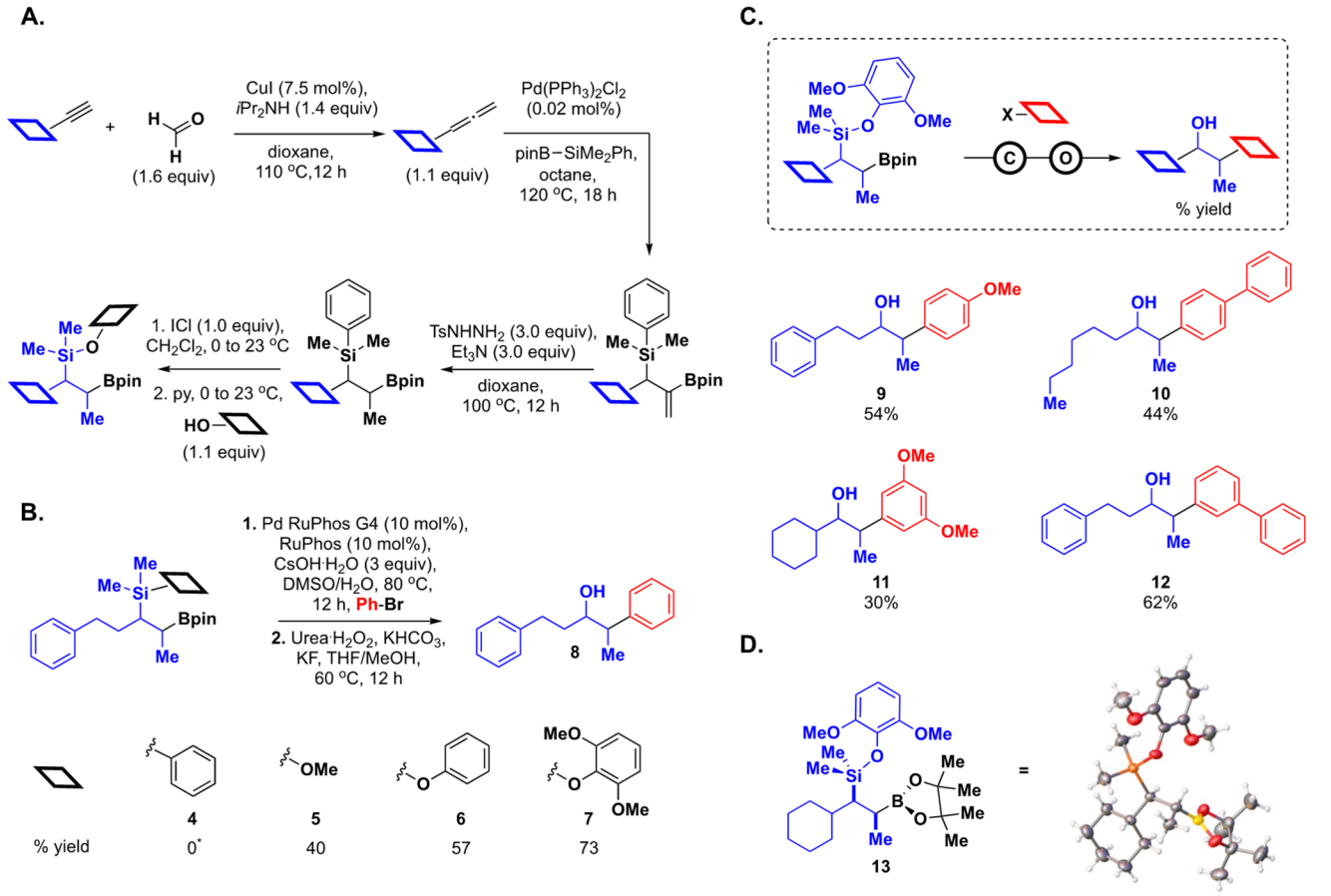

Figure 2. *β*-Alkoxysilyl groups as alcohol surrogates. (A) Synthesis of *β*-alkoxysilyl boronic esters. (B) Silyl activating group screen. *Not oxidized. Reactions run on a 0.1 mmol scale with 1.0 equiv of aryl halide and 2.0 equiv of boronic ester. (C) Cross-coupling of *β*-aryloxysilyl boronic esters. Reaction conditions same as in part B, but on a 0.2 mmol scale; cross-couplings run for 16 h, and oxidations run for 14 h. Yield represents mass of product purified by silica gel column chromatography. Compounds **9**−**11** generated with aryl bromide; compound **12** generated with aryl chloride. (D) X-ray crystal structure of *β*-aryloxysilyl boronic ester **13**.

required in the nucleophile. The X-ray crystal structure of *γ*-cyclohexyl-*β*-aryloxysilyl boronic ester **13** (Figure 2D) highlights the sterically hindered nature of the nucleophilic carbon atom. Successful cross-coupling of **13** with 1-bromo-3,5-dimethoxybenzene demonstrates the reactivity of this system. Aryl chloride electrophile, 3-chloro-1,1′-biphenyl, also proved to be a competent coupling partner, generating product **12**.

To investigate the stereochemical course of the reaction, we required a general route to enantio- and diastereomerically enriched *β*-(2,6-dimethoxyphenoxy)dimethylsilyl boronic esters. Thus, a novel and scalable route to these compounds was developed (Figure 3A). Starting from pinacol boronic ester **14**, key steps including Morken's Pt-catalyzed enantioselective hydrosilylation,[14] Aggarwal's lithiation borylation,[9e,15] and ICl conversion of the phenyldimethylsilyl substituent to an electrophilic chlorodimethylsilyl group followed by substitution with 2,6-dimethoxyphenol formed **7-*syn*** with ≥94:6 dr. We found that this route is easily applied to the synthesis of **7-*anti*** by simply changing the enantiomer of the ligand used for enantioselective hydrosilylation.[14] This flexible route allows for the synthesis of all four possible stereoisomers, and dr can be further enriched by chromatography.

Submission of stereoisomerically enriched *β*-aryloxysilyl boronic ester **7-*syn*** to our cross-coupling/oxidation sequence with various aryl bromides revealed that the transmetalation is highly stereoretentive, yielding homobenzylic alcohol products with >99% ds in most cases (Figure 3B). When **7-*anti*** was submitted to the cross-coupling/oxidation sequence, we again observed near perfect stereoretention to yield **8-*anti*** (98% ds). We observed a slight decrease in dr from starting material to products for **7-*anti***, and a slight increase in dr for **7-*syn***, which may be attributable to kinetic resolution with starting materials containing small amounts of diastereomeric coupling partners (*vide infra*). Product dr can be further enhanced by chromatography.

Compounds **20-*syn*** and **20-*anti*** were prepared bearing a terminal ethyl group. This modification somewhat decreases reaction yield, likely due to increased steric hindrance and/or *β*-hydride elimination, but stereospecificity is maintained. Interestingly, the reaction yielding **20-*syn*** also generated **21** with the phenyl ring appended to the C5 position likely via a rate-competitive post-transmetalation *β*-hydride elimination−hydropalladation−reductive elimination sequence (Figure S1).

We attempted the cross-coupling of **7-*syn*** with a natural-product-inspired activated vinyl bromide and obtained product **24** with near perfect diastereospecificity and a modest yield. While further optimization is required, it is notable that the 7-carbon motif found in **24** appears in many different natural products, including angiolam A (Figure 1A).

A series of experiments were carried out to clarify the role of the *β*-aryloxysilyl substituent. Unactivated secondary alkyl pinacol boronic ester **25** was shown to be unreactive under the

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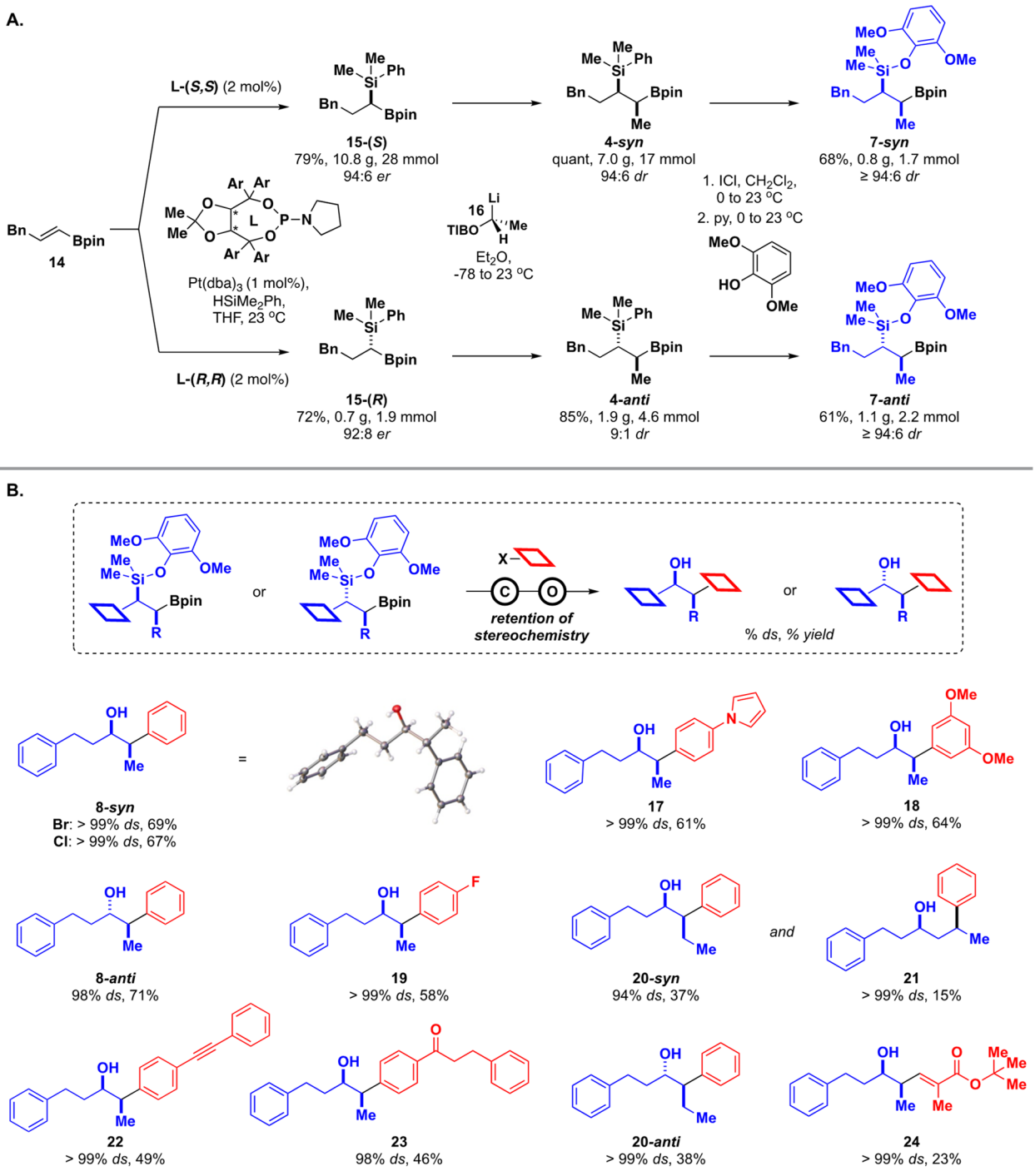

Figure 3. Synthesis and cross-coupling of stereoisomerically enriched secondary alkyl β-aryloxysilyl pinacol boronic esters. (A) Synthetic route to stereoisomerically enriched secondary alkyl β-aryloxysilyl boronic esters. Ar = 3,5-diethoxyphenyl. (B) Stereospecific cross-coupling of stereoisomerically enriched secondary alkyl β-aryloxysilyl boronic esters. Reactions run on 0.2 mmol scale of aryl halide and purified by silica gel column chromatography. Yield represents mass of purified product over two steps. Diastereomeric ratios determined by GC of crude reaction mixtures. Cross-coupling reaction conditions (C): 0.2 mmol of halide, 0.4 mmol of boronic ester, RuPhos Pd G4 (10 mol %), RuPhos (10 mol %), $CsOH{\cdot}H_2O$ (3.0 equiv), 1:1 DMSO:H_2O (0.2 M), 80 °C, 16 h. (O): $KHCO_3$ (6.0 equiv), KF (11.0 equiv), urea·H_2O_2 (10.0 equiv), 1:1 THF:MeOH (0.05 M), 60 °C, 12−14 h.

cross-coupling conditions, demonstrating that the β-aryloxysilyl group increases reactivity (Figure 4A). As mentioned above, β-phenyldimethylsilyl pinacol boronic ester **4** was not a competent coupling partner, demonstrating that an oxygen substituent on the silyl group is critical (Figure 2B). Analysis of cross-coupling reaction mixtures suggested hydrolysis of the silyl ether and formation of a tetracoordinate boronate species (Figure 4B).[2t,9e,16] We suspected that 5-membered pinacol siloxaborolate **27-*syn*** (Figure 4C), analogous to an alkenyl variant reported by Suginome,[16] could form in situ. To test this, **27-*syn*** was independently synthesized and submitted to cross-coupling and oxidation conditions, in absence of additional base, and yielded product **8-*syn*** in 52% yield and

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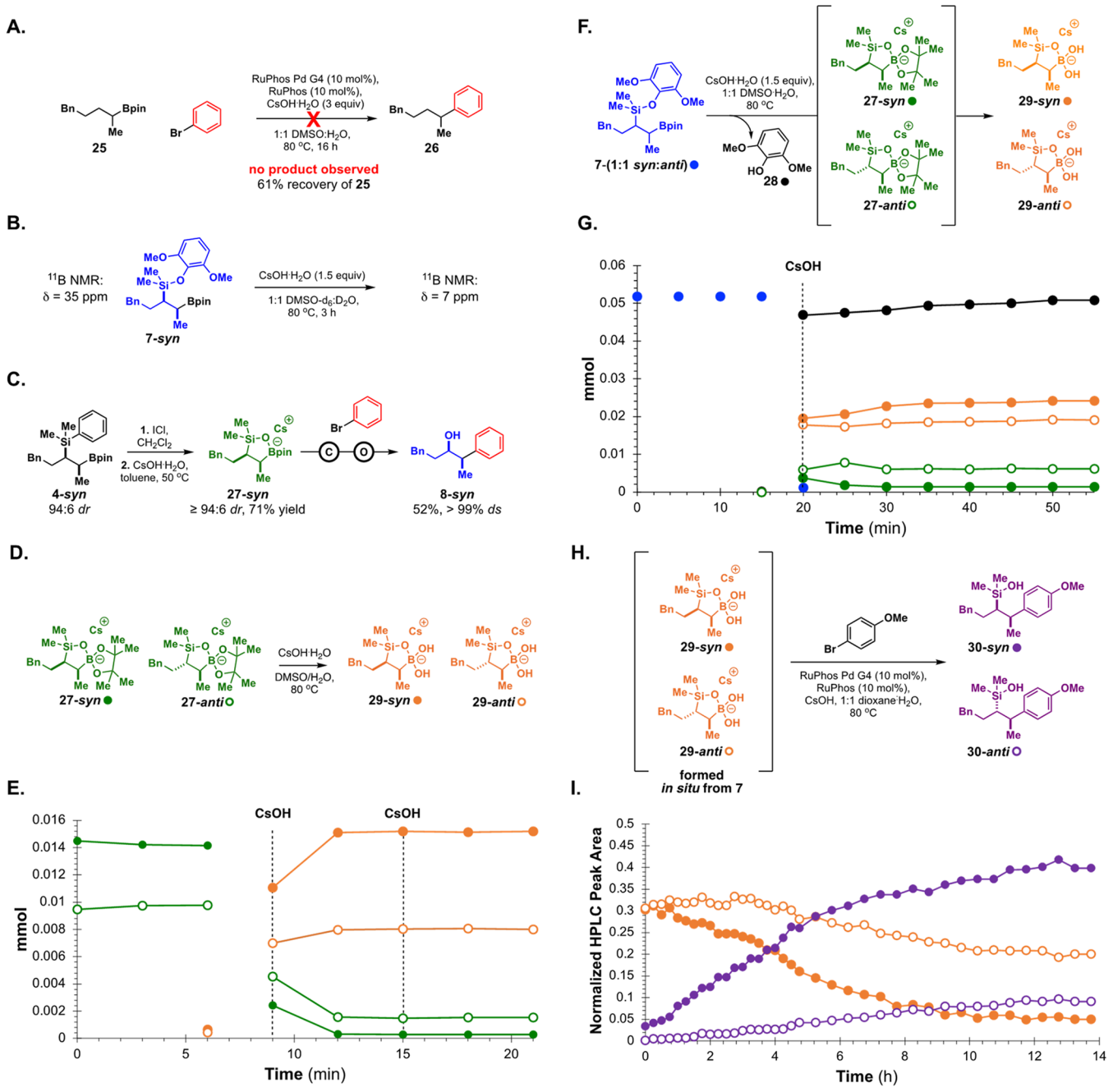

Figure 4. Mechanistic studies. (A) Secondary alkyl pinacol boronic esters are unreactive. (B) *In situ* formation of a boronate species. (C) Synthesis and cross-coupling of a pinacol siloxaborolate. (D) Pinacol siloxaborolate hydrolysis under aqueous basic conditions. (E) Real-time HPLC analysis of experiment described in part D. 0.5 equiv of CsOH per addition. (F) *β*-Aryloxysilyl boronic ester hydrolysis pathway. (G) Real-time HPLC analysis of experiment described in part F. (H) Cross-coupling reaction scheme. (I) Real-time HPLC analysis of experiment described in part H (phenol **28** not shown). Dioxane was used to increase the homogeneity of the solution allowing for more reproducible sampling.

>99% ds, suggesting that **27-*syn*** could be a competent intermediate.

Although secondary alkyl pinacol ester **25** proved to be remarkably stable under aqueous basic cross-coupling conditions, we asked whether a pinacol siloxaborolate could undergo further hydrolysis facilitated by intramolecular activation by the silanolate group (Figure 4D). Interrogating the speciation of boronates under our reaction conditions proved challenging by NMR due to minimal deviation in ^{11}B and ^{1}H chemical shifts, so we turned to reaction monitoring via direct injection HPLC to provide real-time reaction progress.[17]

A diastereomeric mixture of **27** was dissolved in DMSO, and aqueous CsOH solution was dosed in while monitoring via real-time HPLC (Figure 4E). Immediately upon the first addition of aqueous CsOH solution we observed almost complete disappearance of **27-*syn*** and **27-*anti*** and formation of two new compounds tentatively assigned as dihydroxy siloxaborolate salts **29-*syn*** and **29-*anti***. Independent synthesis and isolation of these materials support this assignment, as ^{11}B NMR confirms the presence of a single tetracoordinate pyramidalized borate; ^{1}H NMR supports the loss of the pinacol ester fragment, and HRMS characterization of the

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mixture is consistent with expected molecular weights (SI, pages 73−74). While **27-*syn*** is fully consumed to generate the corresponding **29-*syn***, the conversion of **27-*anti*** to **29-*anti*** appears to arrest at ∼80% even after addition of another 0.5 equiv of CsOH solution, suggesting that the diastereomeric pinacol boronates **27-*syn*** and **27-*anti*** may possess different relative stability and rates of hydrolysis.

Next, we asked whether pinacol siloxaborolates **27-*syn*** and **27-*anti*** were observed upon hydrolysis of β-aryloxysilyl boronic ester **7**, or if dihydroxy siloxaborolates **29-*syn*** and **29-*anti*** were formed directly (Figure 4F). Addition of 1.5 equiv of aqueous CsOH solution to a DMSO solution of **7** yielded instantaneous disappearance of silyl ether **7** and appearance of 2,6-dimethoxyphenol **28** (Figure 4G). **27-*syn*** and **27-*anti*** were concomitantly formed and observed as transient intermediates before succumbing to rapid hydrolysis to generate **29-*syn*** and **29-*anti***. The rapid hydrolysis of pinacol esters from siloxaborolates **27-*syn*** and **27-*anti*** is in stark contrast to simple alkyl pinacol esters (Figure 4A), suggesting that the oxysilyl group may play a critical role in both the hydrolysis of the pinacol boronic ester in addition to its intended purpose as a mediator of transmetalation. The diastereomeric pinacol esters again displayed different relative stabilities, with **27-*syn*** showing complete conversion to **29-*syn***, with only 83% of **27-*anti*** being converted to **29-*anti*** indicating a diastereoselective hydrolysis mechanism. Furthermore, the near immediate and quantitative conversion of silyl ether **7** to the dihydroxy siloxaborolates suggests that **29-*syn*** and **29-*anti*** are the active transmetalation partners in the Csp^3 coupling reaction.

Finally, we executed a reaction progress investigation of the Suzuki coupling using a diastereomeric mixture of silyl ether **7** and bromoanisole (Figure 4H). Disappearance of **29-*syn*** occurred at a notably faster rate than **29-*anti***. Likewise, cross-coupling product **30-*syn*** is formed at an accelerated rate relative to the diastereomeric counterpart **30-*anti*** (Figure 4I). This observation clarifies the stereochemical outcomes observed in Figure 3B. While **7-*syn*** was found to undergo diastereomeric enrichment over the course of our cross-coupling/oxidation sequence, **7-*anti*** displayed a slight erosion of dr. The reaction progress data (Figure 4I) supports a stereospecific reaction mechanism whereby small changes in the observed dr are attributable to kinetic resolution of **29-*syn*** and **29-*anti***.

An additional role of the β-silyl group could be to promote transmetalation via formation of a Si−O−Pd linkage and simultaneous activation of the boronate via an intramolecular silanolate base (Figure S2). This hypothesis is further supported by pinacol siloxaborolate **27-syn** not requiring exogenous base for cross-coupling (Figure 4C). It is also consistent with studies from the Denmark lab illuminating the remarkable stability of Si−O−Pd(II) pretransmetalation intermediates, and that Suzuki−Miyaura cross-couplings employing silanolate bases can proceed efficiently via a boronate transmetalation mechanism.[18]

CONCLUSIONS

In summary, we have developed a strategy that enables complex, natural-product-like, α-methyl-β-hydroxyl-containing compounds to be prepared in a Lego-like fashion via stereospecific Csp^3 Suzuki−Miyaura cross-coupling. The steric challenges and deleterious side reactions associated with the cross-coupling of β-oxygen-containing boronic esters were overcome using β-aryloxysilyl groups as dual-purpose activating groups and alcohol surrogates. State-of-the-art online HPLC analytical techniques were critical to uncovering the complex organoboron speciation pathway that is at play during this reaction. We expect that similar intramolecular-coordination-promoted hydrolysis mechanisms of otherwise hydrolytically stable boronic esters may be operative in other Csp^3 Suzuki−Miyaura reactions.[2a,m] Ongoing studies in our laboratories aim to more fully elucidate the mechanism of this reaction and expand reactivity to currently inaccessible electrophiles, including unactivated vinyl as well as acyl halides/surrogates, to enable automated Lego-like synthesis of a wide range of polyketide-like and other natural products and derivatives.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.2c03245.

Experimental procedures and characterization data for all new compounds (PDF)

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Author Contributions

A.J.L. and M.D.B. conceived the project. A.J.L. developed the reaction, completed optimization and substrate scope, and performed the synthesis of all molecules. Y.S. performed the real-time HPLC experiments with supervision from J.E.H. A.J.L. and M.D.B. wrote the manuscript with input from Y.S. and J.E.H.

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Notes

The authors declare no competing financial interest.

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