JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

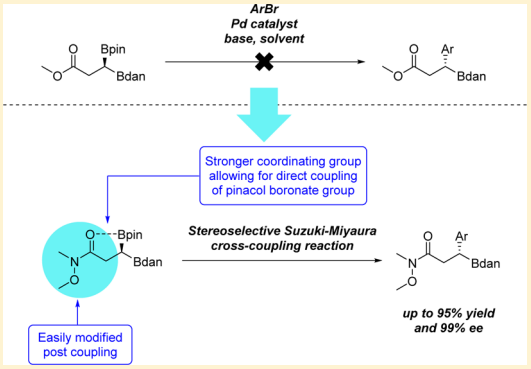
Optimization of Reaction and Substrate Activation in the Stereoselective Cross-Coupling of Chiral 3,3-Diboronyl Amides

Jack Chang Hung Lee, Ho-Yan Sun, and Dennis G. Hall*

Department of Chemistry, Centennial Centre for Interdisciplinary Science, University of Alberta, 11227 Saskatchewan Drive, Edmonton, Alberta T6G 2G2, Canada

Supporting Information

ABSTRACT: A method has been developed for the chemo- and stereoselective Suzuki–Miyaura cross-coupling of optically enriched *gem*-diboronyl compounds with various aryl bromides. Experimental evidence suggests that the Lewis acidity of the second boron group in these substrates plays a significant role in facilitating these otherwise challenging cross-coupling processes. β-Diboronyl esters may be successfully cross-coupled in excellent yield and enantiomeric excess with prior conversion of the pinacol boronate to the corresponding trifluoroborate salt. In contrast, a substrate bearing a Weinreb amide can undergo direct coupling of the Bpin moiety, likely due to the stronger coordination of the more basic amide carbonyl group. The resulting optically enriched secondary boronate may be used in a second enantioselective cross-coupling to afford pharmaceutically relevant diarylmethane products. The use of a Weinreb amide substrate allows for facile postcoupling modification, as demonstrated by a transformation to the corresponding ketone.



INTRODUCTION

The realm of cross-coupling reactions to access synthetically valuable organic compounds by forming new carbon–carbon bonds has dramatically expanded over the past few decades. In addition to its widespread use in synthetic organic chemistry, applied fields such as medicinal chemistry, chemical biology, materials, and nanotechnology have all used these prevalent cross-coupling methods for the preparation of new and valuable compounds.[1] The Suzuki–Miyaura reaction, among all cross-coupling reactions, is especially important because one of the coupling partners, the organoboron counterpart, is generally more readily available and environmentally friendlier than most other available organometallics.[2] Moreover, organoboron reagents such as boronic acids exhibit moisture, air, and heat stability, thus allowing cross-couplings to be performed under convenient reaction conditions. Traditionally, cross-couplings have been restricted to various partners with sp^2 carbon centers, while couplings between sp^3 carbon centers were relatively sparse due to several mechanistic issues: difficult oxidative addition, slow transmetalation, and undesired side reactions such as protodehalogenation, protodeboronation, and β-hydride elimination.[1,2p] These issues become even more complicated when stereoselective cross-coupling is desired with either optically enriched alkyl halides or alkyl organoboronates. Due to the development of efficient novel ligands and new coupling conditions, however, many challenges associated with cross-coupling chemistry have been overcome over the past decade. For example, cross-couplings of chiral alkyl halides with different organoboron partners can now be conducted stereoselectively.[3] Moreover, the Fu group has developed elegant stereoconvergent methods to cross-couple racemic electrophiles stereoselectively through the usage of chiral ligands.[4]

On the other hand, cross-couplings of optically enriched organoboron partners have also become achievable over the past few years. Crudden and co-workers first reported stereoretentive cross-couplings between chiral benzylic boronates with aryl halides, affording various chiral diarylmethanes stereoselectively (eq 1, Figure 1).[5] The Suginome group reported two separate cross-couplings of chiral alkyl boronates and organohalides with retention of stereochemistry.[6] The first case involves the cross-coupling of alkyl boroxoles (eq 2, Figure 1),[6a] while the second report involves the cross-couplings of chiral α-amido benzylic boronates with aryl halides (eq 3, Figure 1).[6b] In 2012, Molander and co-workers reported cross-couplings of 1-(alkoxy)alkyltrifluoroborates with aryl halides that proceed with retention of stereochemistry (eq 4, Figure 1).[7] The stereochemical outcome of these cross-couplings possibly results from the four-membered transition state **1**, as originally proposed by the Soderquist and Woerpel groups.[8]

In addition to these stereoretentive cross-couplings, there have been a number of recent examples of Suzuki–Miyaura cross-couplings that proceed with inversion of stereochemistry. In 2010, Suginome and co-workers reported cross-couplings of chiral α-amido benzylic boronates with aryl halides with

Received: May 3, 2015
Published: June 19, 2015

DOI: 10.1021/acs.joc.5b00991
J. Org. Chem. 2015, 80, 7134–7143

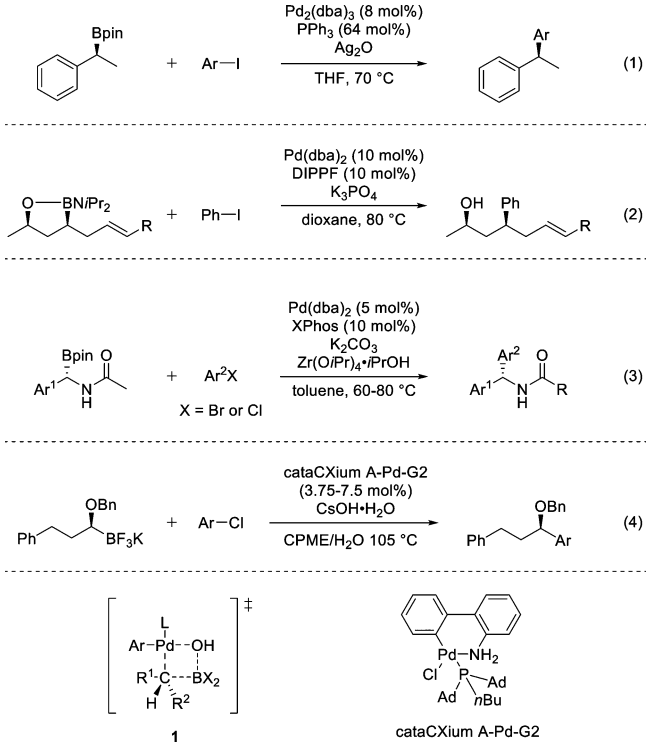


Figure 1. Stereoretentive cross-couplings of chiral alkyl boronates.

inversion of stereochemistry.[9] It was suggested that the reported inversion of stereochemistry is caused by the internal coordination of the carbonyl oxygen to the boron atom (such as in **2**), which prevents the four-membered transition state (described above) required for stereoretentive transmetalation (eq 5, Figure 2). A similar approach was employed by Molander and co-workers, where they successfully conducted

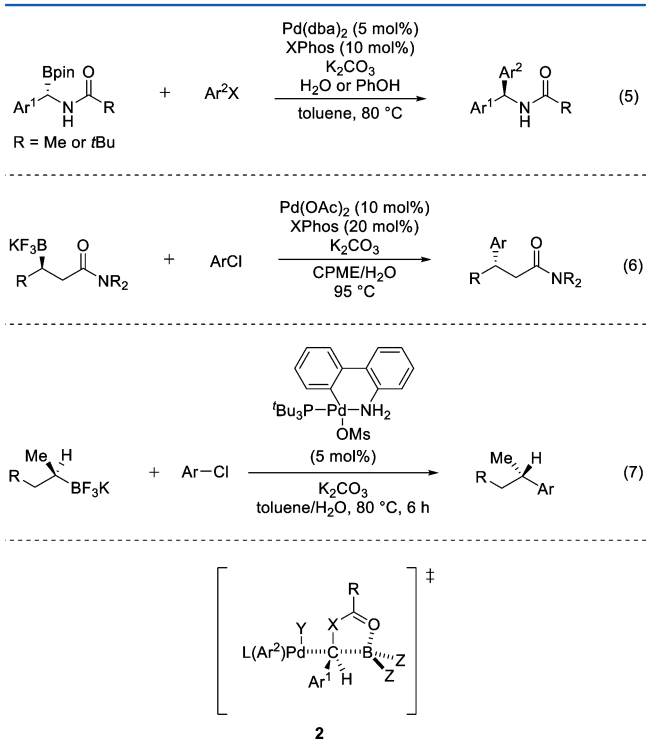


Figure 2. Stereoinvertive cross-couplings of chiral alkyl boronates.

one example of a stereoinvertive cross-coupling between a nonbenzylic chiral secondary alkyl trifluoroborate and an aryl halide (eq 6, Figure 2).[10] Due to the intramolecular coordination of the amide oxygen to the boron atom, the transmetalation again proceeds with inversion of stereochemistry. More recently, a stereoinvertive cross-coupling of chiral secondary alkyl trifluoroborates was reported by Biscoe and co-workers (eq 7, Figure 2).[11] Remarkably, this cross-coupling process occurs without the need for any boron-coordinating group, nor is it restricted to benzylic boronate substrates.

Recently, a report by the Shibata group demonstrated that 1,1-diboronyl compounds possess unique reactivity, allowing chemoselective mono-cross-coupling to be conducted at room temperature.[12,13] Based on DFT calculations and experimental observations, the authors proposed that the second boronyl unit of the same carbon serves not only to facilitate borate formation but also to facilitate the transmetalation step by stabilizing the resultant α-boronyl–Pd(II) intermediate. Based on this result and previous reports that intramolecular coordination is necessary for cross-couplings of secondary alkyl boronates (vide supra), our group recently reported the stereoselective cross-couplings of optically pure chiral alkyl *gem*-diboronyl compounds with various aryl or alkenyl bromides to afford the corresponding chiral alkyl boronates in high optical purity.[14] Herein, a detailed account of the discovery of the current cross-coupling manifold and a new complementary cross-coupling system where boron pinacolates can be cross-coupled directly with aryl halides in a stereoselective manner is presented (Figure 3).

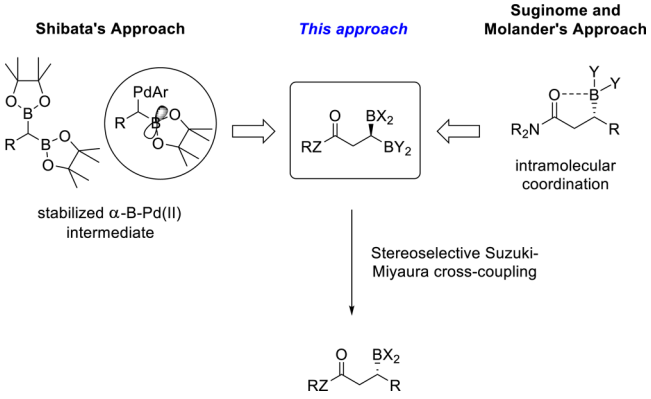


Figure 3. Proposed approach to expand stereoselective cross-couplings of optically enriched *gem*-diboronyl compounds.

RESULTS AND DISCUSSION

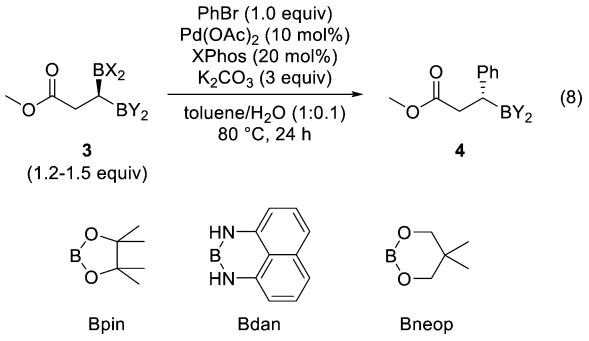
Based on the reports from the groups of Suginome and Molander,[9,10] it is apparent that the efficiency of invertive cross-couplings depends heavily on an intramolecular coordination between the carbonyl oxygen and the boron atom of the substrate (cf. Figure 3). As a result, we hypothesized that a proper evaluation of the Lewis acidity of the boron atom and the Lewis basicity of the carbonyl group could help expand the scope of this diboronyl cross-coupling system to a variety of other coupling partners.

Variation of Lewis Acidity of the Boronyl Unit. In order to increase the Lewis acidity of the boron atom, we aimed to employ Shibata's approach outlined above.[12] Due to the empty p orbital of the second boron atom, the formal borate anion

DOI: 10.1021/acs.joc.5b00991
J. Org. Chem. 2015, 80, 7134–7143

generated with the base could be greatly stabilized, thus facilitating borate formation and the subsequent cross-coupling reactions. Based on this premise, different 3,3-diboronyl compounds were prepared and tested in a model cross-coupling reaction with bromobenzene under previously published conditions.[14] In spite of its enhanced Lewis acidity in comparison to that of the monoboronyl species, 3,3-diboronyl bis(pinacolate) **3a** failed to convert to product, returning the starting material (entry 1, Table 1). Turning one

Table 1. Suzuki–Miyaura Cross-Coupling Reactions of 3,3-Diboronyl Propanoate Esters Bearing Different Boronyl Units



(8)

entry	substrate	BX_2	BY_2	yield (%)
1	**3a**	Bpin	Bpin	no conversion
2	**3b**	Bpin	Bdan	no conversion
3	**3c**	Bneop	Bdan	protodeboronation side product obtained
4	**3d**[a]	BF_3K	Bdan	89 (99)[b]

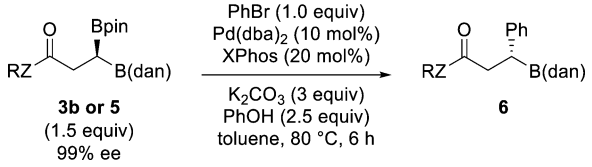
[a]Substrate used had an ee of 99%. [b]Value of ee (%) of the product in parentheses was determined by enantioselective HPLC.

of the pinacol boronates to a 1,8-diaminonaphthalene-protected boronate (Bdan)[15] allowed for the possibility of stereoselective cross-coupling, but unfortunately, the compound failed to undergo cross-coupling, as well (entry 2, Table 1). Neopentyl glycol is known to be a readily hydrolyzable protecting group with a steric constraint smaller than that of a pinacolate unit, and therefore, the boron atom should possess a higher Lewis acidity. The corresponding neopentyl glycol boronate **3c**, however, was found to be prone to undergo protodeboronation, as indicated in Table 1 (entry 3). Boronic acids are smaller than the corresponding esters and, thus, are generally more readily accessible to Lewis bases under cross-coupling conditions. However, alkyl boronic acids are known to be less stable than boronic esters and are prone to undergo side reactions such as oxidation and protodeboronation.[2] Recently, a strategy that involves a slow release of boronic acids in situ from protected forms of boronic acids such as trifluoroborates and *N*-methyliminodiacetic acid (MIDA)-protected boronates has become popular as a way to limit the concentration of free boronic acids in solution and thus minimize any possible side reactions (eq 9).[2o,16] Realizing that this approach could be applicable to diboronyl **3**, the corresponding trifluoroborate salt **3d** was prepared and tested. Indeed, after optimization, the desired cross-coupling reaction could be performed in good yield with inversion of stereochemistry (entry 4), demonstrating that the ready accessibility of the boronic acid by base is indeed influencing the efficiency of the cross-coupling reaction. Thus, due to the incorporation of the diboronyl moiety, a weaker coordinating group such as a carboxyester can be employed instead of strongly coordinating amides, as demonstrated previously by Molander and co-workers.[10] A slight excess of the 3,3-diboronyl compound (0.2–0.5 equiv excess) was necessary to compensate for the occurrence of adventitious protodeboronation, allowing the reactions to take place in good yields.[14]

$$\mathrm{R{-}BF_3K} \xrightarrow[\text{deprotection}]{\text{slow in situ}} \mathrm{R{-}B(OH)_2} \xrightarrow[\text{Pd(0)}]{\text{R'X}} \mathrm{R{-}R'} \qquad (9)$$

Lewis Basicity of the Carbonyl Group. Although a successful cross-coupling reaction was developed using diboronyl **3d** as described above, the synthesis of a trifluoroborate salt is, in general, less step-economical in comparison with the synthesis of most organoboronates. Therefore, an important objective is to achieve direct cross-coupling of pinacol boronates stereoselectively in order to enhance the overall efficiency of the sequence. However, due in part to their bulkiness, pinacol boronates, in general, have a Lewis acidity lower than that of boronic acids and, therefore, are less favorable substrates in cross-coupling chemistry. In order to address this problem, a systematic examination of various carbonyl groups that possess different nucleophilicity is necessary in order to optimize the interaction between the carbonyl oxygen and the boron atom. As described previously (Table 1), when the carbonyl group is a weakly coordinating ester, no conversion was obtained, indicating that a more basic carbonyl oxygen is necessary (entry 1, Table 2). Substituting

Table 2. Suzuki–Miyaura Cross-Coupling Reactions of 3,3-Diboronyl 3b and 5 with Carbonyl Groups Having Different Lewis Basicity



entry	substrate	RZ	yield (%)[a]	ee (%)[b]
1	**3b**	MeO	no conversion	ND
2	**5a**	BnHN	trace	ND
3	**5b**	*N*-morpholinyl	75	90
4	**5c**	*N*-pyrrolidinyl	86	90
5	**5d**	MeO(Me)N	82	99
6	**5e**[c]	MeO(Me)N	96	N/A

[a]Isolated yields of products after flash column chromatography. [b]Measured by enantioselective HPLC. [c]Bpin instead of Bdan. The reaction was performed at 60 °C. ND = not determined.

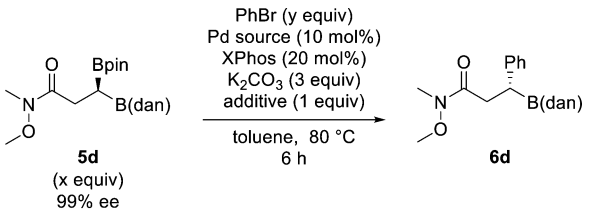
the carboxyester group with an *N*-benzyl amide did not solve the problem, affording decomposed products (entry 2, Table 2). In order to further enhance the nucleophilicity of the carbonyl group, tertiary amides such as morpholine and pyrrolidine amides (**5b** and **5c**) were prepared and tested. To our satisfaction, both of these compounds could be cross-coupled to give the desired model product in good yields and, more importantly, in high enantiomeric excess (entries 3 and 4, Table 2). The preservation of enantiomeric integrity, however, was not complete, as indicated by a slight erosion of the enantiomeric excess after the reaction. Based on the trend observed up to this point, it was hypothesized that the slight erosion of ee was possibly due to incomplete coordination between the carbonyl oxygen and the boron atom. One way to

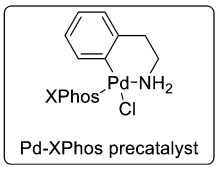
DOI: 10.1021/acs.joc.5b00991
J. Org. Chem. 2015, 80, 7134–7143

increase this interaction is to increase the Lewis basicity of the amide carbonyl by exploiting the α-effect in the amide N-substituent.[17] As a result, the Weinreb amide **5d** was synthesized and tested for the subsequent cross-coupling reaction. Satisfactorily, potentially due to the increased nucleophilicity of the Weinreb amide, the cross-coupling product can be produced directly from the pinacol boronate with a good yield and an excellent ee, with inversion of stereochemistry (see Supporting Information for stereochemical evidence of an inverting cross-coupling) (entry 5, Table 2). This series of results demonstrates the importance of counterbalancing the nucleophilicity of the carbonyl group when the boron atom is not very Lewis acidic. To highlight that the second boron atom is indeed influential on the efficacy of the cross-coupling reactions, the Bdan subunit of 3,3-diboronyl compound **5d** was replaced with a pinacol boronate. Theoretically, through substitution of the weakly Lewis acidic Bdan unit to a more Lewis acidic Bpin unit, the Lewis acidity of the first boronate should be enhanced, thus allowing cross-coupling to be performed under milder conditions. Indeed, achiral 3,3-diboronyl compound **5e** was found to be highly reactive in cross-coupling reactions, allowing a lower temperature (60 °C) to be employed to afford the racemic cross-coupled product **6e** with an excellent yield (entry 6, Table 2). This result again emphasizes the importance of the second boron atom during mono-cross-coupling reactions of 3,3-diboronyl substrates.

Optimization of Reaction Conditions. After successfully identifying that a Weinreb amide is an effective coordinating group to achieve direct cross-coupling of pinacol boronate **5d**, we conducted an optimization of cross-coupling conditions. Other palladium sources and ligands were found to be inferior to $Pd(dba)_2$ and XPhos, giving the desired products with lower conversion and yields (entries 2–4, Table 3). As observed by Suginome and co-workers, the Brønsted acidic additive phenol was found to be necessary to achieve a complete retention of stereochemical integrity (compare entries 1 and 5, Table 3).[6b] One beneficial difference between the new 3,3-diboronyl substrate **5d** in comparison with the previously reported trifluoroborate salt **3d** is that the 3,3-diboronyl **5d** is more stable under the reaction conditions. Thus, the most valuable substrate, diboronyl **5d**, can be used as the limiting reagent without any observation of undesired protodeboronation side product (entry 6, Table 3). However, likely due to the robust nature of the pinacol boronate, a higher catalyst loading was found to be required for a higher yield. Other reaction parameters such as the base and additives were also examined (Table 4). When water was used as an additive, good yields of cross-coupling products could also be obtained especially when a higher catalyst loading was employed (entries 1–5, Table 4). It is noteworthy that the enantiomeric excess is similar to the reactions without any additive (entry 5, Table 3, and entry 5, Table 4). Other bases, such as KF and Cs_2CO_3, and NaO*t*Bu led to lower yield or increased rate of substrate decomposition (entries 3 and 4, Table 4). Ultimately, the optimized conditions employed phenol as the additive, with 20 mol % of the catalyst to afford the cross-coupling products in an excellent yield with complete retention of enantiomeric integrity (entry 7, Table 4). Of note, lower temperature (50 °C) led to incomplete conversion to the desired product (entry 8, Table 4).

Table 3. Optimization of Pd Source and Stoichiometry of Starting Materials in the Cross-Couplings of 3,3-Diboronyl Substrate 5d with Bromobenzene

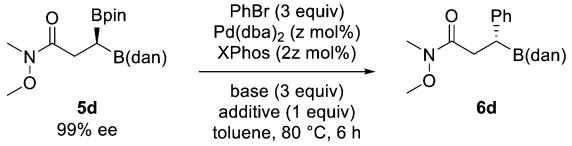




entry	diboronyl/halide (x equiv/y equiv)	Pd source	additive	yield (%)[a]	ee (%)[b]
1	1.5/1	$Pd(dba)_2$	PhOH	82	99
2	1.5/1	$Pd(PtBu_3)_2$	PhOH	trace	ND
3	1.5/1	Pd-XPhos precatalyst	PhOH	35	ND
4	1.5/1	$Pd(OAc)_2$	PhOH	22	ND
5	1.5/1	$Pd(dba)_2$		52	91
6	1/3	$Pd(dba)_2$	H_2O	70	ND

[a]Isolated yields of products after flash column chromatography. [b]Measured by enantioselective HPLC. ND = not determined.

Table 4. Optimization of Catalyst Loading, Base, and Additive for the Cross-Coupling between Optically Enriched 3,3-Diboronyl Substrate 5d and Bromobenzene



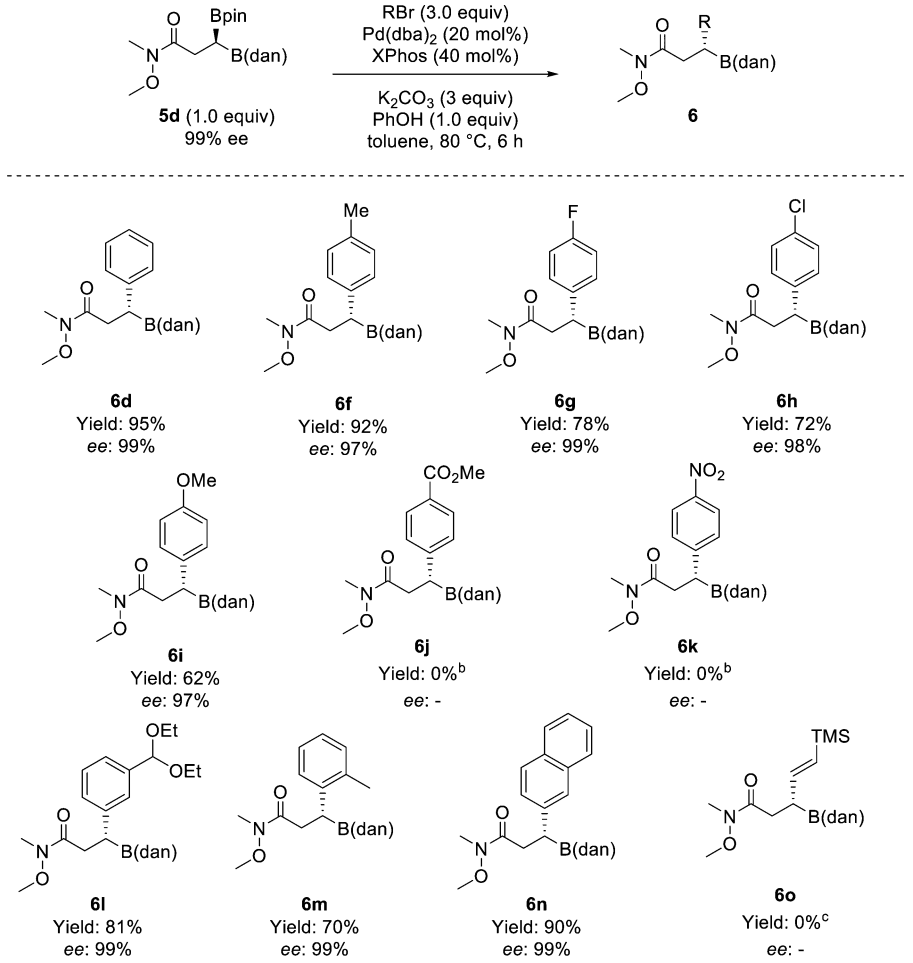
entry	Pd (z mol %)	additive	base	yield (%)[a]	ee (%)[b]
1	20	H_2O	K_2CO_3	80	ND
2	20	H_2O	Cs_2CO_3	78	ND
3	20	H_2O	KF	38	ND
4	20	H_2O	NaO*t*Bu	trace	ND
5	30	H_2O	K_2CO_3	94	91
6	10	PhOH	K_2CO_3	75	ND
7	20	PhOH	K_2CO_3	95	99
8[c]	20	PhOH	K_2CO_3	trace	ND

[a]Isolated yields of products after flash column chromatography. [b]Measured by enantioselective HPLC. [c]The reaction was performed at 50 °C. ND = not determined.

Scope of Aryl Bromides for the Cross-Coupling of Chiral 3,3-Diboronyl Substrate 5d. With the optimized conditions in hand (entry 7, Table 4), the scope of electrophilic substrates was next examined (Scheme 1). We found that aryl bromides with various functional groups such as methyl, fluoro, chloro, and methoxy substituents are all tolerated, affording products **6f–i** in good yields and excellent enantiomeric purity with inversion of stereochemistry. Unfortunately, when electron-deficient arenes like methyl 4-bromobenzoate and 1-bromo-4-nitrobenzene were employed as the cross-coupling partner, the corresponding protodeboronation product was isolated, similar to the result obtained when diboronyl substrate **3d** was used as the cross-coupling partner. Different regiochemical patterns such as meta- or ortho-substituents are

DOI: 10.1021/acs.joc.5b00991
J. Org. Chem. 2015, 80, 7134–7143

Scheme 1. Scope of Aryl Bromides in the Cross-Coupling with Optically Enriched 3,3-Diboronyl Substrate 5d[a]



[a]The ee values were measured by enantioselective HPLC. [b]Complex mixture. [c]No conversion.

also tolerated, although longer reaction times are generally necessary in order to obtain the desired products in complete conversions (Scheme 1, products **6l,m**). Moreover, a polyaryl halide such as 2-bromonaphthalene was also found to be a suitable cross-coupling partner, allowing the coupling product **6n** to be isolated in high yield and ee. Unfortunately, a model alkenyl halide failed to couple with 3,3-diboronyl substrate **5d**. Overall, although the new diboronyl substrate **5d** is less reactive than trifluoroborate **3d**, it possesses higher stability under reaction conditions that allow the cross-coupling sequence to be performed in a more step-economical fashion.

Iterative Cross-Coupling of Chiral 3,3-Diboronyl Compounds to Access Optically Enriched Diarylmethanes. Diarylmethanes have emerged as important motifs in many classes of pharmaceutically relevant compounds (Figure 4).[18] As such, we saw diboronyl compound **5d** as a precursor to this class of compounds and thus sought to explore a possible iterative cross-coupling of both boronyl units (Scheme 2). The coupling of the pinacol boronate moiety was first performed using the optimized conditions for this substrate. Of note, the cross-coupling was successfully performed on a gram scale with no erosion of yield or ee. Since Bdan groups are known to be stable under most cross-coupling conditions, the Bdan substituent was converted to the corresponding pinacol boronate **7** under acidic conditions. A direct coupling of the Bpin group was first attempted using the optimized conditions

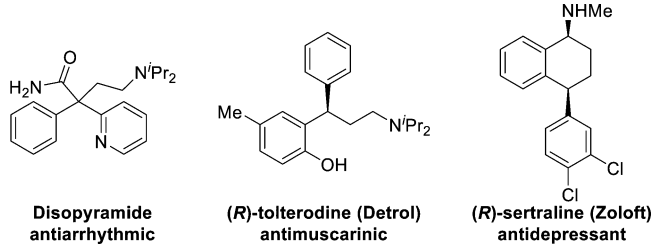
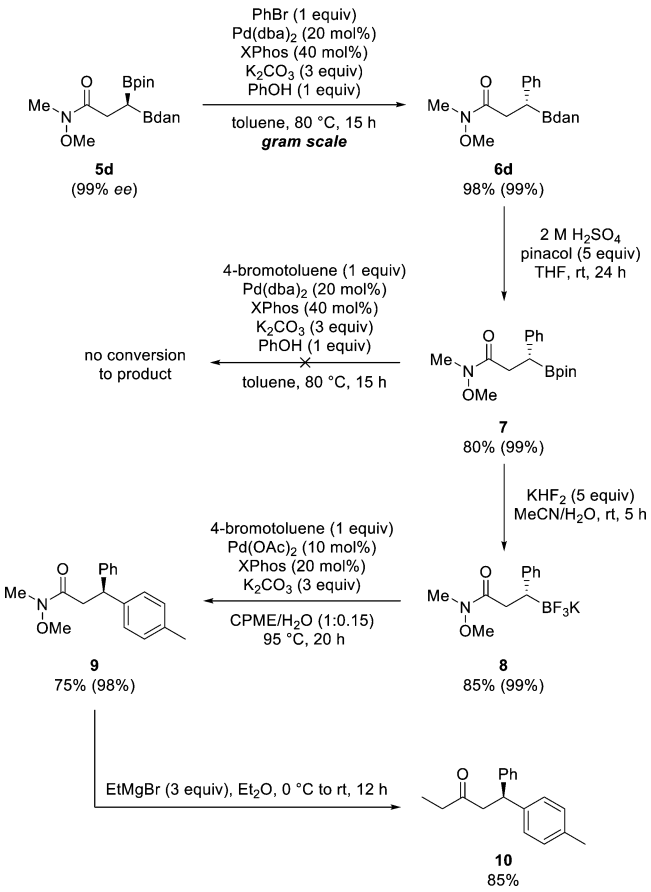


Figure 4. Diarylmethane-containing pharmaceutical compounds.

for **5d**. Unfortunately, no conversion to the desired product was observable under these conditions. This result emphasizes the importance of the Lewis aciditiy of the second boronyl group in the success of these cross-coupling reactions. The pinacol boronate was thus converted to the corresponding trifluoroborate **8** in order to facilitate the second cross-coupling, which gratifyingly proceeded smoothly to afford the diarylmethane product **9** in 75% yield and 98% ee.[19] Based on previous reports of similar cross-coupling processes,[10,14] the transmetalation presumably proceeded with inversion of stereochemistry due to the presence of the Weinreb amide coordinating group. This assumption was confirmed by a derivatization of **7** into a known intermediate and comparison of the signs of optical rotation values (see Supporting Information). The sequence of two cross-couplings from **5d** to **9**, thus occurs with a double

DOI: 10.1021/acs.joc.5b00991
J. Org. Chem. 2015, 80, 7134−7143

Scheme 2. Iterative Cross-Coupling of Diboronyl Alkanes To Produce a Diarylmethane Product



inversion of stereochemistry. Following the second cross-coupling, the Weinreb amide was then successfully reduced via addition of a Grignard reagent to afford the corresponding ketone **10** in 85% yield.

CONCLUSION

In summary, by enhancing the Lewis acidity of the 3,3-diboronyl substrate by transforming the pinacol boronate to a trifluoroborate salt, cross-coupling reactions of optically enriched 3,3-diboronyl **3d** can be performed chemo- and stereoselectively with various organic electrophiles under palladium catalysis. Both the coordination of the carbonyl oxygen to the boron atom and the stabilization provided by the second boronyl unit in the α-B−Pd(II) intermediate are thought to assist the transmetalation process, thus facilitating this notoriously difficult mechanistic step in cross-coupling reactions of alkyl boronates. On the other hand, by enhancing the Lewis basicity of the carbonyl group from an ester to a Weinreb amide, direct coupling of the boron pinacolate becomes possible, allowing cross-coupling reactions to be performed with these relatively less acidic but more commonly used boronate derivatives. The stereoselective cross-coupling manifold reported herein occurs with preservation of stereochemical integrity, and it represents a rare example of the successful use of nonbenzylic secondary alkyl boronates. The resulting enantioenriched benzylic boronates can undergo different reactions including a second iterative cross-coupling, providing access to pharmaceutically relevant diarylmethanes. In addition, the presence of the Weinreb amide moiety on the substrate allows postcoupling modifications to be easily made. These applications highlight the versatility of chiral secondary alkyl boronates and demonstrate the numerous synthetic possibilities associated with enantioenriched *gem*-diboronyl compounds.

EXPERIMENTAL SECTION

Unless otherwise stated, all reactions were performed under a nitrogen atmosphere using flame-dried glassware. Acetonitrile was distilled from CaH_2. THF, toluene, dichloromethane, and methanol were treated by a solvent system prior to use. Thin layer chromatography (TLC) was performed on silica gel 60 F254 plates and was visualized with UV light and $KMnO_4$ stain. NMR spectra were recorded on 400 or 500 MHz instruments. The residual solvent protons (^{1}H) or the solvent carbons (^{13}C) were used as internal references. Boron NMR spectra are referenced to external $BF_3{\cdot}OEt_2$. ^{1}H NMR data are presented as follows: chemical shift in parts per million (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; qt, quartet of triplets, dtd, doublet of triplet of doublets; dse, double of septets; m, multiplet. The error of coupling constants from ^{1}H NMR analysis is ±0.3 Hz. High-resolution mass spectra were recorded on a TOF analyzer. The resolution of the IR instrument is 4 wavenumber. Methyl (*E*)-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)acrylate was synthesized according to the literature procedure.[20] The enantiomeric excesses for chiral compounds were determined using a HPLC Agilent instrument with Chiralcel-OD, Chiralpak-AS, or Chiralpak-IC columns with UV detection.

Preparation of 1,1-Diboronyl Compound 3b. *(S)-Methyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (**3b**).* CuCl (1.0 mg, 10 μmol), (*R*)-(*R*)-Walphos(CF_3) (10 mg, 15 μmol), and NaO*t*Bu (1.9 mg, 20 μmol) were dissolved in THF (0.4 mL) and stirred at room temperature for 30 min before the addition of pinacolato diboron (140 mg, 0.55 mmol) in THF (0.3 mL). The reaction was further stirred for 10 min, and methyl (*E*)-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)acrylate (126 mg, 0.500 mmol) was then added along with THF (0.3 mL) and dropwise addition of MeOH (41 μL, 1.00 mmol). After 12 h of stirring, the reaction mixture was evaporated in vacuo and directly purified by flash silica column chromatography (EtOAc/hexanes = 1:4) to give **3b** (167 mg, 88%) as a colorless solid. The product could be recrystallized from hot MeOH to give X-ray quality crystals (72%). The characterization data matched that of a previous report.[14]

General Procedure for the Synthesis of Trifluoroborate Salts. Pinacol boronate (7.00 mmol) was dissolved in MeCN (80 mL) before the addition of saturated aqueous KHF_2 (4.50 M, 6.30 mL, 28.0 mmol) took place. The resulting solution was stirred at room temperature for 5 h, concentrated, and evaporated in vacuo. After being dried in high vacuum overnight, the crude mixture was dissolved in hot MeCN (50 mL × 3), filtered, and concentrated in vacuo. To the resulting oil was added Et_2O (50 mL), followed by sonication for 30 min to afford a suspension of colorless powders in the solution. The pure product was then filtered and dried in vacuo to provide the desired product as a solid.

*Potassium Trifluoro(3-methoxy-1-(1H-naphtho[1,8-de][1,3,2]-diazaborinin-2(3H)-yl)-3-oxopropyl)borate (**3d**).* The title compound was obtained as a white powder (2.30 g, 91%). The characterization data matched that of a previous report.[14]

*Potassium Trifluoro(3-(methoxy(methyl)amino)-3-oxo-1-phenylpropyl)borate (**8**).* The title compound was obtained as a waxy gray solid (1.78 g, 85%): ^{1}H NMR (400 MHz, acetone-d_6) δ 7.16 (d, J = 7.3 Hz, 2H), 7.02 (dd, J = 7.5, 7.5 Hz, 2H), 6.86 (ddd, J = 7.3, 7.3, 1.3 Hz, 1H), 3.58 (s, 3H), 2.98 (s, 3H), 2.74 (dd, J = 15.2, 6.0 Hz, 1H), 2.63 (dd, J = 15.2, 6.0 Hz, 1H), 2.28−2.21 (m, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 150.8, 129.3, 127.8, 123.6, 66.1, 61.3, 35.7 (the boron-bound carbon was not detected due to quadrupolar relaxation of boron); ^{11}B NMR (128 MHz, acetone-d_6) δ 4.5; ^{19}F

DOI: 10.1021/acs.joc.5b00991
J. Org. Chem. 2015, 80, 7134−7143

NMR (376 MHz, acetone-d_6) δ −145.2; IR (microscope, cm^{-1}) ν 3392, 3057, 3023, 2938, 1711, 1642, 1450, 1071, 998; HRMS (EI) m/z [M − K] calcd for $C_{11}H_{14}BF_3NO_2$ 260.1077; found 260.1075; $[\alpha]_D^{20}$ −2 (c = 0.23, acetone).

General Procedure for the Stereoselective Cross-Coupling of 1,1-Diboronyl 3d. *(R)-Methyl-3-(1H-naphtho[1,8-de][1,3,2]-diazaborinin-2(3H)-yl)-3-phenylpropanoate (**4d**).* $Pd(OAc)_2$ (10 μmol), XPhos (20 μmol), K_2CO_3 (0.30 mmol), aromatic or alkenyl bromide (0.10 mmol), and 1,1-diboronyl **3d** (0.12 or 0.15 mmol) were stirred in toluene (1.0 mL) and H_2O (0.10 mL) at 80 °C for 6 h. The reaction mixture was then allowed to cool to ambient temperature and evaporated in vacuo. The crude reaction mixture was purified with flash silica column chromatography (hexanes/EtOAc = 85:15) to afford the title product (29 mg, 0.09 mmol, 89% yield) as a yellow oil. The characterization data for this compound matched that of a previous report.[14]

Preparation of Other Diboronyl Compounds. *Methyl 3,3-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (**3a**).* CuCl (30 mg, 0.30 mmol), DPEPhos (162 mg, 0.30 mmol), and NaOtBu (86 mg, 0.90 mmol) were dissolved in THF (8.0 mL) and stirred at room temperature for 30 min before the addition of pinacolato diboron (7.6 g, 30 mmol) in THF (6.0 mL). The reaction was further stirred for 10 min and methyl propiolate (841 mg, 890 μL, 10 mmol) was then added along with THF (6 mL) and dropwise addition of MeOH (1.3 g, 1.7 mL, 40 mmol). After 12 h of stirring, the reaction mixture was evaporated in vacuo and directly purified by flash silica column chromatography (EtOAc/hexanes = 1:19) to give the title compound (1.9 g, 56%) as colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.64 (s, 3H), 2.56 (d, J = 8.3 Hz, 2H), 1.24 (s, 12 H), 1.22 (s, 12H), 1.07 (t, J = 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 82.8, 51.0, 29.9, 24.3, 24.0 (the boron-bound carbon was not detected due to quadrupolar relaxation of boron); ^{11}B NMR (160 MHz, $CDCl_3$) δ 33.6; IR (microscope, cm^{-1}) ν 2979, 2951, 1739; HRMS (EI) m/z [M − CH_3]$^+$ calcd for $C_{15}H_{27}B_2O_6$ 325.1994; found 325.1977.

General Procedure for the Synthesis of β-Diboronyl Amides. To a stirred solution of **3b** (1.0 mmol) in toluene (2.0 mL) were added amine (3.0 mmol), 1,2,4-triazole (69 mg, 1.0 mmol), and DBU (152 mg, 150 μL, 1.0 mmol), sequentially. The reaction was stirred for 2 h at 95 °C before being concentrated in vacuo. The crude product was then purified by flash silica column chromatography (hexanes/EtOAc = 1:1) to give amides in pure form.

*N-Benzyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanamide (**5b**).* The title compound was prepared using the general procedure for the amide formation. Flash silica column chromatography (hexanes/EtOAc = 30:70) yielded **5b** (200 mg, 0.50 mmol, 46% yield) as a brown solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14−7.09 (m, 2H), 7.01 (d, J = 7.9 Hz, 2H), 6.32 (d, J = 7.2 Hz, 2H), 6.08 (br s, 2H), 3.76−3.58 (m, 6H), 3.54−3.40 (m, 2H), 2.66−2.58 (m, 2H), 2.51 (dd, J = 14.8, 5.9 Hz, 1H), 1.30, (s, 6H), 1.27 (s, 6H), 1.04 (t, J = 7.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 141.3, 136.3, 127.6, 119.6, 117.3, 105.5, 83.1, 66.9, 66.6, 45.9, 42.6, 30.8, 25.0, 24.7 (the boron-bound carbon was not detected due to quadrupolar relaxation of boron); ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.6; IR (microscope, cm^{-1}) ν 3362, 3052, 2976, 2898, 1625, 1600, 1521; HRMS (EI) m/z calcd for $C_{23}H_{31}B_2N_3O_4$435.2501; found 435.2515; $[\alpha]_D^{20}$ −13 (c = 0.70, $CHCl_3$); mp 183−185 °C.

*(R)-3-(1H-Naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)-1-(pyrrolidin-1-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-one (**5c**).* The title compound was prepared using the general procedure for amide formation. Flash silica column chromatography (hexanes/EtOAc = 30:70) yielded **5c** (192 mg, 0.46 mmol, 46% yield) as an off-white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13−7.08 (m, 2H), 7.00 (d, J = 8.2 Hz, 2H), 6.31 (d, J = 8.0 Hz, 2H), 6.12 (br s, 2H), 3.60−3.40 (m, 4H), 2.61−2.56 (m, 2H), 2.02−1.85 (m, 4H), 2.51 (dd, J = 14.8, 5.9 Hz, 1H), 1.29, (s, 6H), 1.28 (s, 6H), 1.02 (t, J = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 141.5, 136.3, 127.5, 119.6, 117.2, 105.4, 82.7, 46.6, 46.2, 32.6, 26.0, 25.0, 24.8, 24.4 (the boron-bound carbon was not detected due to quadrupolar relaxation of boron); ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.7; IR (microscope, cm^{-1}) ν 3403, 3324, 3051, 2974, 2928, 1628, 1600, 1514; HRMS (EI) m/z calcd for $C_{23}H_{31}B_2N_3O_3$ 419.2552; found 419.2552; $[\alpha]_D^{20}$ −15 (c = 0.10, $CHCl_3$); mp 182−183 °C.

General Procedure for the Synthesis of Weinreb Amides. Compounds **5d** and **5e** were synthesized according to a modified protocol reported by Evans et al.[21] To a mixture of *N*-methoxy-*N*-methylamine hydrochloride (3.1 g, 32 mmol) in THF (32 mL) at 0 °C was added trimethylaluminum (15.6 mL, 2 M in toluene, 32 mmol). The solution was stirred at room temperature for 30 min and cooled to 0 °C before the addition diboronyl alkane (6.3 mmol) in THF (10 mL). The reaction mixture was then stirred at 0 °C for 2 h and at room temperature overnight. After the solution was quenched by the addition of 1 M HCl, it was extracted by dichloromethane (3 × 100 mL), dried with anhydrous $MgSO_4$, and filtered. This crude solution was then concentrated and purified with flash silica column chromatography (hexanes/EtOAc = 1:1) to afford the pure product as a white solid.

*(R)-N-Methoxy-N-methyl-3-(1H-naphtho[1,8-de][1,3,2]-diazaborinin-2(3H)-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanamide (**5d**).* The title compound was synthesized according to the general procedure to give a white solid (1.7 g, 4.1 mmol, 65%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14−7.10 (m, 2H), 7.02 (d, J = 8.1 Hz, 2H), 6.33 (d, J = 7.2 Hz, 2H), 6.02 (br s, 2H), 3.76 (s, 3H), 3.23 (s, 3H), 2.75 (d, J = 7.7 Hz, 2H), 1.30, (s, 6H), 1.28 (s, 6H), 1.12 (t, J = 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 141.3, 136.3, 127.5, 119.6, 117.3, 105.5, 83.3, 61.3, 32.6, 29.0, 25.0, 24.6 (the boron-bound carbon was not detected due to quadrupolar relaxation of boron); ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.0; IR (microscope, cm^{-1}) ν 3367, 3053, 2975, 1652, 1601, 1513; HRMS (EI) m/z calcd for $C_{21}H_{29}B_2N_3O_4$ 409.2344; found 409.2353; $[\alpha]_D^{20}$ −44 (c = 0.09, $CHCl_3$); mp 165−167 °C.

*N-Methoxy-N-methyl-3,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanamide (**5e**).* The title compound was synthesized according to the general procedure to give the product as a white solid (368 mg, 1.0 mmol, 52%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (s, 3H), 3.18 (s, 3H), 2.72 (d, J = 7.7 Hz, 2H), 1.27 (s, 12H), 1.25 (s, 12H), 1.05 (t, J = 8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 83.0, 61.1, 32.6, 28.8, 24.8, 24.6 (the boron-bound carbon was not detected due to quadrupolar relaxation of boron); ^{11}B NMR (160 MHz, $CDCl_3$) δ 33.6; IR (microscope, cm^{-1}) ν 2977, 2935, 1666 HRMS (EI) m/z [M − CH_3]$^+$ calcd for $C_{16}H_{30}B_2NO_6$ 354.2259; found 354.2274; mp 67−69 °C.

General Procedure for the Cross-Coupling of 1,1-Diboronyl Compounds 5b, 5c, and 5e. $Pd(dba)_2$ (10 μmol), XPhos (20 μmol), K_2CO_3 (0.30 mmol), bromobenzene (0.10 mmol), phenol (0.25 mmol), and 1,1-diboronyl alkane (0.15 mmol) were stirred in toluene (1.0 mL) at 80 °C for 15 h. The reaction mixture was then cooled, filtered through Celite, and evaporated in vacuo. The crude product was then purified with flash silica column chromatography to afford the title product.

*(R)-1-Morpholino-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)-3-phenylpropan-1-one (**6b**).* The title compound was prepared using the general procedure for the stereoselective cross-coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 30:70) yielded **6b** (29 mg, 0.08 mmol, 75% yield) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.36 (m, 2H), 7.30−7.20 (m, 3H), 7.10−7.07 (m, 2H), 7.01 (d, J = 8.1, 2H), 6.27 (d, J = 7.3 Hz, 2H), 6.03 (br s, 2H), 3.75−3.50 (m, 6H), 3.45−3.40 (m, 2H), 3.02 (dd, J = 9.8, 4.3 Hz, 1H), 2.94 (dd, J = 15.2, 9.9 Hz, 1H), 2.80 (dd, J = 15.1, 4.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 143.6, 141.1, 136.3, 129.0, 128.2, 127.5, 126.1, 119.7, 117.5, 105.9, 66.8, 66.4, 46.2, 42.2, 36.1, 24.9 (the boron-bound carbon was not detected due to quadrupolar relaxation of boron); ^{11}B NMR (160 MHz, $CDCl_3$) δ 32.3; IR (microscope, cm^{-1}) ν 3419, 3341, 3356, 3006, 2969, 2922, 2857, 1628, 1599, 1513; HRMS (EI) m/z calcd for $C_{23}H_{24}BN_3O_2$ 385.1962; found 385.1975; $[\alpha]_D^{20}$ +1.6 (c = 0.22, $CHCl_3$) for 90% ee; HPLC (Chiralcel OD) 50:50 *i*-PrOH/hexanes, 0.5 mL/min, λ = 230 nm, T_{major} = 42.5 min, T_{minor} = 49.5 min, ee = 90%.

DOI: 10.1021/acs.joc.5b00991
J. Org. Chem. 2015, 80, 7134−7143

*(R)-3-(1H-Naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)-3-phenyl-1-(pyrrolidin-1-yl)propan-1-one (**6c**).* The title compound was prepared using the general procedure for the stereoselective cross-coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 30:70) yielded **6c** (32 mg, 0.09 mmol, 86% yield) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.35 (m, 2H), 7.31−7.22 (m, 3H), 7.08 (dd, J = 8.2, 7.5 Hz, 2H), 6.99 (dd, J = 8.3, 0.8 Hz, 2H), 6.27 (dd, J = 7.3 Hz, 0.9 Hz, 2H), 6.15 (br s, 2H), 3.57−3.50 (m, 2H), 3.40−3.35 (m, 2H), 3.09 (dd, J = 10.6, 3.8 Hz, 1H), 2.92 (dd, J = 15.6, 10.6 Hz, 1H), 2.74 (dd, J = 15.6, 3.9 Hz, 1H), 1.96−1.84 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 144.0, 141.3, 136.3, 128.9, 128.1, 127.5, 125.8, 119.7, 117.3, 105.8, 46.8, 46.0, 38.0, 26.1, 24.9, 24.4 (the boron-bound carbon was not detected due to quadrupolar relaxation of boron); ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.7; IR (microscope, cm^{-1}) ν 3418, 3316, 3053, 2972, 2874, 1627, 1597, 1513, 1504; HRMS (EI) m/z calcd for $C_{23}H_{24}BN_3O$ 369.2012; found 369.2014; $[\alpha]_D^{20}$ +16 (c = 0.78, $CHCl_3$) for 89% ee; HPLC (Chiralcel OD) 20:80 i-PrOH/hexanes, 0.5 mL/min, λ = 210 nm, T_{major} = 26.9 min, T_{minor} = 31.9 min, ee = 89%.

*N-Methoxy-N-methyl-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanamide (**6e**).* The title compound was prepared using the general procedure for the stereoselective cross-coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 60:40) yielded **6e** (31 mg, 0.1 mmol, 96% yield) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.26 (m, 4H), 7.20−7.14 (m, 1H), 3.66 (s, 3H), 3.19 (s, 3H), 3.05−2.93 (m, 1H), 2.90−2.85 (m, 1H), 2.74 (dd, J = 11.0, 5.7 Hz, 1H), 1.25 (s, 6H), 1.20 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 142.1, 128.5, 128.4, 125.5, 83.3, 61.2, 35.9, 32.3, 24.6, 24.5 (the boron-bound carbon was not detected due to quadrupolar relaxation of boron); ^{11}B NMR (160 MHz, $CDCl_3$) δ 32.3; IR (microscope, cm^{-1}) ν 3059, 3026, 2976, 2934, 1660, 1602; HRMS (EI) m/z calcd for $C_{17}H_{26}BNO_4$ 319.1955; found 319.1959.

General Procedure for the Stereoselective Cross-Coupling Reactions of 1,1-Diboronyl 5d. $Pd(dba)_2$ (20 μmol), XPhos (40 μmol), K_2CO_3 (0.30 mmol), aryl bromide (0.30 mmol), phenol (0.10 mmol), and 1,1-diboronyl **5d** (0.10 mmol) were stirred in toluene (1.0 mL) at 80 °C for 15 h. The reaction mixture was then cooled, filtered through Celite, and evaporated in vacuo. The crude product was then purified with flash silica column chromatography to afford the title product.

*(R)-N-Methoxy-N-methyl-3-(1H-naphtho[1,8-de][1,3,2]-diazaborinin-2(3H)-yl)-3-phenylpropanamide (**6d**).* The title compound was prepared using the general procedure for the stereoselective cross-coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 60:40) yielded **6d** (34 mg, 0.1 mmol, 95% yield) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.35 (m, 2H), 7.29−7.24 (m, 3H), 7.11−7.08 (m, 2H), 7.00 (dd, J = 8.3, 0.7 Hz, 2H), 6.26 (dd, J = 7.3 Hz, 0.9 Hz, 2H), 5.92 (br s, 2H), 3.69 (s, 3H), 3.25 (s, 3H), 3.10−2.90 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 143.7, 141.1, 136.3, 128.9, 128.0, 127.5, 125.9, 119.7, 117.5, 105.9, 61.4, 34.7, 32.4 (the boron-bound carbon was not detected due to quadrupolar relaxation of boron); ^{11}B NMR (160 MHz, $CDCl_3$) δ 32.0; IR (microscope, cm^{-1}) ν 3417, 3348, 3054, 3023, 2962, 2935, 1642, 1630, 1600, 1512; HRMS (EI) m/z calcd for $C_{21}H_{22}BN_3O_2$ 359.1805; found 359.1812; $[\alpha]_D^{20}$ +6.5 (c = 0.90, $CHCl_3$) for 99% ee; HPLC (Chiralcel OD) 20:80 i-PrOH/hexanes, 0.5 mL/min, λ = 210 nm, T_{major} = 18.5 min, T_{minor} = 21.5 min, ee = 99%.

*(R)-N-Methoxy-N-methyl-3-(1H-naphtho[1,8-de][1,3,2]-diazaborinin-2(3H)-yl)-3-p-tolylpropanamide (**6f**).* The title compound was prepared using the general procedure for the stereoselective cross-coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 60:40) yielded **6f** (34 mg, 0.09 mmol, 92% yield) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 7.10−7.05 (m, 2H), 7.00 (d, J = 7.8 Hz, 2H), 6.26 (d, J = 7.3 Hz, 2H), 5.92 (br s, 2H), 3.69 (s, 3H), 3.24 (s, 3H), 3.05−2.98 (m, 2H), 2.95−2.87 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 141.2, 140.6, 136.3, 135.3, 129.5, 127.9, 127.5, 119.7, 117.3, 105.8, 61.4, 34.9, 32.4, 21.0 (the boron-bound carbon was not detected due to quadrupolar relaxation of boron); ^{11}B NMR (160 MHz, $CDCl_3$) δ 32.1; IR (microscope, cm^{-1}) ν 3416, 3344, 3052, 3008, 2934, 1642, 1630, 1600, 1511; HRMS (EI) m/z calcd for $C_{22}H_{24}BN_3O_2$ 373.1962; found 373.1964; $[\alpha]_D^{20}$ 0.0 (c = 0.54, $CHCl_3$) for 97% ee; HPLC (Chiralcel OD) 20:80 i-PrOH/hexanes, 0.5 mL/min, λ = 210 nm, T_{major} = 16.9 min, T_{minor} = 19.0 min, ee = 97%.

*(R)-3-(4-Fluorophenyl)-N-methoxy-N-methyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)propanamide (**6g**).* The title compound was prepared using the general procedure for the stereoselective cross-coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 60:40) yielded **6g** (29 mg, 0.08 mmol, 78% yield) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24−7.19 (m, 2H), 7.11−7.04 (m, 4H), 7.01 (dd, J = 8.3, 0.8 Hz, 2H), 6.27 (dd, J = 7.3, 0.7 Hz, 2H), 5.87 (br s, 2H), 3.70 (s, 3H), 3.24 (s, 3H), 3.10−2.80 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 161.1 (d, J = 244 Hz), 141.0, 139.3, 136.3, 129.4 (d, J = 7.7 Hz), 127.5, 119.6, 117.6, 115.7 (d, J = 21.1 Hz), 105.9, 61.4, 34.9, 32.4 (the boron-bound carbon was not detected due to quadrupolar relaxation of boron); ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.6; ^{19}F NMR (469 MHz, $CDCl_3$) δ −117.4; IR (microscope, cm^{-1}) ν 3422, 3348, 3054, 3007, 2967, 2937, 1642, 1601, 1506; HRMS (EI) m/z calcd for $C_{21}H_{21}BN_3O_2F$ 377.1711; found 377.1717; $[\alpha]_D^{20}$ +0.70 (c = 0.92, $CHCl_3$) for 99% ee; HPLC (Chiralcel OD) 20:80 i-PrOH/hexanes, 0.5 mL/min, λ = 210 nm, T_{major} = 21.0 min, T_{minor} = 25.2 min, ee = 99%.

*(R)-3-(4-Chlorophenyl)-N-methoxy-N-methyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)propanamide (**6h**).* The title compound was prepared using the general procedure for the stereoselective cross-coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 60:40) yielded **6h** (28 mg, 0.07 mmol, 72% yield) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 7.12−7.08 (m, 2H), 7.02 (d, J = 7.8 Hz, 2H), 6.28 (dd, J = 7.3, 0.7 Hz, 2H), 5.86 (br s, 2H), 3.70 (s, 3H), 3.24 (s, 3H), 3.10−2.84 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 142.2, 140.9, 136.3, 131.6, 129.4, 129.0, 127.5, 119.7, 117.7, 106.0, 61.4, 34.6 (the boron-bound carbon was not detected due to quadrupolar relaxation of boron); ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.9; IR (microscope, cm^{-1}) ν 3420, 3350, 3053, 3008, 2964, 2936, 1645, 1601, 1513; HRMS (EI) m/z calcd for $C_{21}H_{21}BN_3O_2Cl$ 393.1415; found 393.1413; $[\alpha]_D^{20}$ +4.7 (c = 0.11, $CHCl_3$) for 98% ee; HPLC (Chiralcel OD) 20:80 i-PrOH/hexanes, 0.5 mL/min, λ = 230 nm, T_{major} = 22.0 min, T_{minor} = 28.6 min, ee = 98%.

*(R)-N-Methoxy-3-(4-methoxyphenyl)-N-methyl-3-(1H-naphtho-[1,8-de][1,3,2]diazaborinin-2(3H)-yl)propanamide (**6i**).* The title compound was prepared using the general procedure for the stereoselective cross-coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 60:40) yielded **6i** (24 mg, 0.06 mmol, 62% yield) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, J = 8.7 Hz, 2H), 7.08 (dd, J = 8.3, 7.4 Hz, 2H), 7.01 (dd, J = 8.3, 0.8 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 6.27 (dd, J = 7.3, 0.9 Hz, 2H), 5.92 (br s, 2H), 3.85 (s, 3H), 3.69 (s, 3H), 3.24 (s, 3H), 3.05−2.85 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 157.7, 141.1, 136.3, 135.6, 129.0, 127.5, 119.7, 117.4, 114.3, 105.7, 61.4, 55.3, 35.0, 24.9 (the boron-bound carbon was not detected due to quadrupolar relaxation of boron); ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.7; IR (Microscope, cm^{-1}) 3416, 3349, 3053, 3004, 2960, 2935, 1640, 1628, 1600, 1509; HRMS (EI) m/z calcd for $C_{22}H_{24}BN_3O_3$ 389.1911; found 389.1917; $[\alpha]_D^{20}$ −5.6 (c = 0.99, $CHCl_3$) for 99% ee; HPLC (Chiralcel OD) 20:80 i-PrOH/hexanes, 0.5 mL/min, λ = 210 nm, T_{major} = 24.2 min, T_{minor} = 28.1 min, ee = 99%.

*(R)-3-(3-(Diethoxymethyl)phenyl)-N-methoxy-N-methyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)propanamide (**6l**).* The title compound was prepared using the general procedure for the stereoselective cross-coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 60:40) yielded **6l** (37 mg, 0.08 mmol, 81% yield) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.34 (m, 3H), 7.24−7.18 (m, 1H), 7.10−7.05 (m, 2H), 7.00 (d, J = 8.1 Hz, 2H), 6.25 (d, J = 7.3 Hz, 2H), 5.92 (br s, 2H), 5.54 (s, 1H), 3.80−3.55 (m, 7H), 3.24 (s, 3H), 3.05−2.85 (m, 3H), 1.27 (t, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 141.1, 139.7, 136.3, 128.8, 128.1, 127.5, 126.2, 124.3, 119.7, 117.4, 105.8, 101.8, 61.3, 58.5, 34.7, 32.4, 18.5, 15.3 (the boron-bound carbon was not detected due to

DOI: 10.1021/acs.joc.5b00991
J. Org. Chem. 2015, 80, 7134−7143

quadrupolar relaxation of boron); ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.2; IR (microscope, cm^{-1}) ν 3417, 3352, 3053, 3006, 2973, 2933, 1649, 1590, 1528; HRMS (EI) m/z calcd for $C_{26}H_{32}BN_3O_4$ 461.2486; found 461.2492; $[\alpha]_D^{20}$ −10 (c = 0.22, $CHCl_3$) for 99% ee; HPLC (Chiralcel OD) 20:80 *i*-PrOH/hexanes, 0.5 mL/min, λ = 210 nm, T_{major} = 15.0 min, T_{minor} = 16.9 min, ee = 99%.

*(R)-N-Methoxy-N-methyl-3-(1H-naphtho[1,8-de][1,3,2]-diazaborinin-2(3H)-yl)-3-o-tolylpropanamide (**6m**).* The title compound was prepared using the general procedure for the stereoselective cross-coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 50:50) yielded **6m** (26 mg, 0.07 mmol, 70% yield) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28−7.15 (m, 4H), 7.11−7.06 (m, 2H), 7.00 (d, J = 8.2 Hz, 2H), 6.25 (d, J = 7.3 Hz, 2H), 5.90 (br s, 2H), 3.72 (s, 3H), 3.30−3.20 (m, 4H), 3.15−3.05 (m, 1H), 3.00−2.90 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 142.1, 141.2, 136.3, 136.1, 130.7, 127.5, 126.8, 126.5, 125.7, 119.7, 117.4, 105.8, 61.4, 34.2, 32.4, 20.7 (the boron-bound carbon was not detected due to quadrupolar relaxation of boron); ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.8; IR (microscope, cm^{-1}) ν 3419, 3346, 3053, 3009, 2958, 2932, 2856, 1650, 1629, 1600, 1512, 1504; HRMS (EI) m/z calcd for $C_{22}H_{24}BN_3O_2$ 373.1962; found 373.1957; $[\alpha]_D^{20}$ +9.4 (c = 0.11, $CHCl_3$) for 99% ee; HPLC (Chiralcel OD) 2.5:97.5 *i*-PrOH/hexanes, 0.5 mL/min, λ = 210 nm, T_{major} = 60.1 min, T_{minor} = 54.7 min, ee = 99%.

*(R)-N-Methoxy-N-methyl-3-(naphthalen-2-yl)-3-(1H-naphtho-[1,8-de][1,3,2]diazaborinin-2(3H)-yl)propanamide (**6n**).* The title compound was prepared using the general procedure for the stereoselective cross-coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 60:40) yielded **6n** (37 mg, 0.09 mmol, 90% yield) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91−7.84 (m, 3H), 7.70 (s, 1H), 7.56−7.45 (m, 2H), 7.40 (dd, J = 8.4, 1.4 Hz, 1H), 7.11−7.06 (m, 2H), 7.01 (d, J = 7.8 Hz, 2H), 6.25 (d, J = 7.2 Hz, 2H), 5.96 (br s, 2H), 3.72 (s, 3H), 3.30−3.00 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 141.4, 141.1, 136.3, 133.9, 132.0, 128.6, 128.1, 127.7, 127.5, 127.2, 126.3, 125.7, 125.4, 119.7, 117.5, 105.9, 61.4, 34.7, 30.9 (the boron-bound carbon was not detected due to quadrupolar relaxation of boron); ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.6; IR (microscope, cm^{-1}) ν 3417, 3346, 3052, 3010, 2967, 2935, 1642, 1630, 1600, 1506; HRMS (EI) m/z calcd for $C_{25}H_{24}BN_3O_2$ 409.1962; found 409.1969; $[\alpha]_D^{20}$ +23 (c = 0.16, $CHCl_3$) for 99% ee; HPLC (Chiralcel OD) 5:95 *i*-PrOH/hexanes, 0.5 mL/min, λ = 210 nm, T_{major} = 76.2 min, T_{minor} = 80.8 min, ee = 99%.

Iterative Cross-Coupling Sequence. *Synthesis of Pinacol Boronate **7**. (R)-N-Methoxy-N-methyl-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanamide (**7**).* To a stirred solution of **6d** (359 mg, 1.00 mmol) in THF (10 mL) were added 2 M H_2SO_4 (1.5 mL, 3.0 mmol) and pinacol (591 mg, 5.00 mmol) sequentially. The reaction was stirred for 24 h at room temperature before being quenched by the addition of water (10 mL). The mixture was then extracted by diethyl ether (10 mL × 3), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was then purified by flash silica column chromatography (hexanes/EtOAc = 9:1) to give pure **7** (255 mg, 80%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.26 (m, 4H), 7.20−7.14 (m, 1H), 3.66 (s, 3H), 3.19 (s, 3H), 3.05−2.93 (m, 1H), 2.90−2.85 (m, 1H), 2.74 (dd, J = 11.0, 5.7 Hz, 1H), 1.25 (s, 6H), 1.20 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 142.1, 128.5, 128.4, 125.5, 83.3, 61.2, 35.9, 32.3, 24.6, 24.5 (the boron-bound carbon was not detected due to quadrupolar relaxation of boron); ^{11}B NMR (160 MHz, $CDCl_3$) δ 32.3; IR (microscope, cm^{-1}) ν 3059, 3026, 2976, 2934, 1660, 1602; HRMS (EI) m/z calcd for $C_{17}H_{26}BNO_4$ 319.1955; found 319.1959; $[\alpha]_D^{20}$ −20 (c = 0.60, $CHCl_3$).

*Synthesis of Diarylmethane **9**. (S)-N-Methoxy-N-methyl-3-phenyl-3-(p-tolyl)propanamide (**9**).* $Pd(OAc)_2$ (5.6 mg, 25 μmol), XPhos (24 mg, 50 μmol), K_2CO_3 (104 mg, 0.750 mmol), 4-bromotoluene (43 mg, 0.25 mmol), and trifluoroborate salt **8** (75 mg, 0.25 mmol) were added into a sealed tube (10 mL Biotage microwave vial). The tube was then sealed and purged with N_2 (three times) before the addition of CPME (1.0 mL) and H_2O (0.15 mL). The reaction mixture was stirred at 95 °C for 20 h in an oil bath, after which the reaction mixture was cooled and evaporated in vacuo. The crude reaction mixture was purified with flash silica column chromatography (hexane/EtOAc = 80:20) to afford the purified product **9** (53 mg, 75%) as a colorless waxy solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.26 (m, 4H), 7.19−7.15 (m, 3H), 7.09 (d, J = 7.9 Hz, 2H), 4.66 (dd, J = 7.7, 7.7 Hz, 1H), 3.57 (s, 3H), 3.17 (d, J = 7.7 Hz, 2H), 3.12 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 144.5, 141.2, 135.8, 129.2, 128.5, 127.8, 127.7, 126.3, 61.3, 53.4, 46.0, 38.0, 32.2, 21.0; IR (microscope, cm^{-1}) ν 3026, 3002, 2936, 1663, 1513, 1417, 1384, 1178, 995; HRMS (EI) m/z $[M + H]^+$ calcd for $C_{18}H_{22}NO_2$ 284.1645, found 284.1645; $[\alpha]_D^{20}$ +14 (c = 0.15, $CHCl_3$) for 98% ee; HPLC (Chiralpak IC) 5:95 *i*-PrOH/hexanes, 0.5 mL/min, λ = 230 nm, T_{major} = 37.0 min, T_{minor} = 39.3 min, ee = 98%.

*Transformation of Weinreb Amide **9** into Ketone **10**. (S)-1-Phenyl-1-(p-tolyl)pentan-3-one (**10**).* Weinreb amide **9** (19 mg, 0.07 mmol) was dissolved in Et_2O (1.3 mL) and cooled to 0 °C. Ethyl magnesium bromide (0.20 mmol, 3 M solution in Et_2O, 67 μL) was added via syringe. The resulting solution was allowed to warm to room temperature and was stirred overnight. The reaction was cooled to 0 °C and quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O (5 mL × 3), and the combined ethereal layers were washed with brine, dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give pure **10** in 85% yield as a white waxy solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.27 (m, 2H), 7.24−7.23 (m, 2H), 7.20−7.17 (m, 1H), 7.14−7.09 (m, 4H), 4.61 (dd, J = 7.6, 7.6 Hz, 1H), 3.16 (d, J = 7.6 Hz, 2H), 2.36 (q, J = 7.3 Hz, 2H), 2.32 (s, 3H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.6, 144.2, 141.0, 135.9, 129.2, 128.5, 127.7, 127.6, 126.3, 48.6, 45.7, 36.8, 21.0, 7.6; IR (microscope, cm^{-1}) ν 3026, 2976, 2922, 1715, 1494, 1111, 821, 699; HRMS (EI) m/z calcd for $C_{18}H_{20}O$ 252.1514; found 252.1515 $[\alpha]_D^{20}$ +3.2 (c = 0.32, $CHCl_3$) for 98% ee.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra, and HPLC chromatograms. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00991.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dennis.hall@ualberta.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was generously funded by the Natural Science and Engineering Research Council of Canada, and the University of Alberta. J.C.H.L. was supported by a Queen Elizabeth II Graduate Scholarship. H.-Y.S. was supported by an NSERC Canada Graduate Scholarship-D and an Alberta Innovates Health Solutions Studentship.

■ REFERENCES

(1) (a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004. (b) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417−1492.

(2) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (c) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544−4568. (d) Fu, G. C.; Littke, A. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211. (e) Miyaura, N. *J. Organomet. Chem.* **2002**, *653*, 54−57. (f) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419−2440. (g) Franzén, R.; Xu, Y. *Can. J. Chem.* **2005**, *83*, 266−272. (h) Suzuki, A. *Chem. Commun.* **2005**, 4759−4763. (i) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2008**, *64*, 3047−3101. (j) Doucet, H. *Eur. J. Org. Chem.* **2008**, 2013−2030. (k) Molander, G. A.; Canturk, B. *Angew.*

DOI: 10.1021/acs.joc.5b00991
J. Org. Chem. 2015, 80, 7134−7143

Chem., Int. Ed. **2009**, *48*, 9240−9261. (l) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 672−675. (m) *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*, 2nd ed.; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2011; Vol. *1*. (n) Bonin, H.; Fouquet, E.; Felpin, F.-X. *Adv. Synth. Catal.* **2011**, *353*, 3063−3084. (o) Lennox, A. J. J.; Lloyd-Jones, G. C. *Isr. J. Chem.* **2010**, *50*, 664−674. (p) Sun, H.-Y.; Hall, D. G. At the Forefront of the Suzuki−Miyaura Reaction: Advances in Stereoselective Cross-Couplings. In *Topics in Organometallic Chemistry: Synthesis and Application of Organoboron Compounds*; Fernandez, E., Whiting, A., Eds.; Springer: Heidelberg, Germany, 2014.

(3) (a) Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389−391. (b) Taylor, B. L. H.; Harris, M. R.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 7790−7793. (c) Greene, M. A.; Yonova, I. M.; Williams, F. J.; Jarvo, E. R. *Org. Lett.* **2012**, *14*, 4293−4296. (d) Harris, M. R.; Hanna, L. E.; Greene, M. A.; Moore, C. E.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 3303−3306.

(4) (a) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694−6695. (b) Lundin, P. M.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11027−11029. (c) Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11908−11909. (d) Lu, Z.; Wilsily, A.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 8154−8157. (e) Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 15362−15364. (f) Wilsily, A.; Tramutola, F.; Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 5794−5797.

(5) (a) Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024−5025. (b) Matthew, S. C.; Glasspoole, B. W.; Eisenberger, P.; Crudden, C. M. *J. Am. Chem. Soc.* **2014**, *136*, 5828−5831.

(6) (a) Daini, M.; Suginome, M. *J. Am. Chem. Soc.* **2011**, *133*, 4758−4761. (b) Awano, T.; Ohmura, T.; Suginome, M. *J. Am. Chem. Soc.* **2011**, *133*, 20738−20741.

(7) Molander, G. A.; Wisniewski, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 16856−16868.

(8) (a) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461−470. (b) Ridgway, B. H.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 458−460.

(9) Ohmura, T.; Awano, T.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 13191−13193.

(10) Sandrock, D. L.; Jean-Gérard, L.; Chen, C.-y.; Dreher, S. D.; Molander, G. A. *J. Am. Chem. Soc.* **2010**, *132*, 17108−17110.

(11) Li, L.; Zhao, S.; Joshi-Pangu, A.; Diane, M.; Biscoe, M. R. *J. Am. Chem. Soc.* **2014**, *136*, 14027−14030.

(12) (a) Endo, K.; Ohkubo, T.; Hirokami, M.; Shibata, T. *J. Am. Chem. Soc.* **2010**, *132*, 11033−11035. (b) Endo, K.; Ohkubo, T.; Shibata, T. *Org. Lett.* **2011**, *13*, 3368−3371. (c) Endo, K.; Ohkubo, T.; Ishioka, T.; Shibata, T. *J. Org. Chem.* **2012**, *77*, 4826−4831. (d) Endo, K.; Ishioka, T.; Ohkubo, T.; Shibata, T. *J. Org. Chem.* **2012**, *77*, 7223−7231.

(13) For asymmetric cross-couplings of these 1,1-diboronylalkane substrates, see: (a) Sun, C.; Potter, B.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 6534−6537. (b) Sun, H.-Y.; Kubota, K.; Hall, D. G. *Chem.—Eur. J.* **2015**, DOI: 10.1002/chem.201406680.

(14) Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011**, *3*, 894−899.

(15) Noguchi, H.; Hojo, K.; Suginome, M. *J. Am. Chem. Soc.* **2007**, *129*, 758−759.

(16) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961−6963.

(17) Nigst, T. A.; Antipova, A.; Mayr, H. *J. Org. Chem.* **2012**, *77*, 8142−8155.

(18) Ameen, D.; Snape, T. J. *Med. Chem. Commun.* **2013**, *4*, 893−907.

(19) To our knowledge, there is no direct conversion of a Bdan group into the corresponding trifluoroborate salt. Please also refer to the following reference: Churches, Q. I.; Hooper, J. F.; Hutton, C. A. *J. Org. Chem.* **2015**, *80*, 5428−5435.

(20) Lee, J. C. H.; Hall, D. G. *J. Am. Chem. Soc.* **2010**, *132*, 5544−5545.

(21) Evans, D. A.; Cee, V. J.; Siska, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 9433−9441.

DOI: 10.1021/acs.joc.5b00991
J. Org. Chem. 2015, 80, 7134−7143