Communication

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Diastereoselective and Enantioselective Conjunctive Cross-Coupling Enabled by Boron Ligand Design

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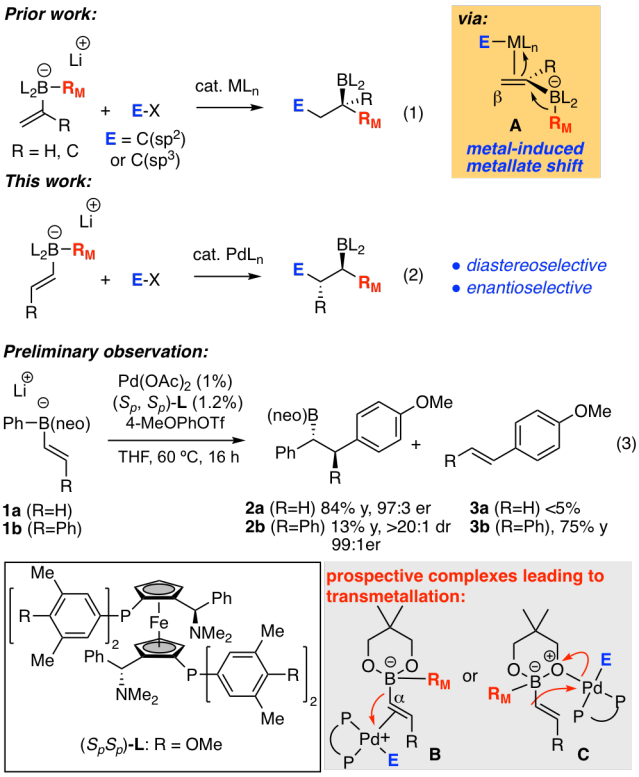
Supporting Information Placeholder

ABSTRACT: *Enantio- and diastereoselective conjunctive cross-coupling of β-substituted alkenylboron "ate" complexes is studied. While β substitution shifts the chemoselectivity of the catalytic reaction in favor of the Suzuki-Miyaura product, use of a boronic ester ligand derived from acenaphthoquinone allows the process to favor the conjunctive product, even with substituted substrates.*

Configurationally-defined benzhydryl stereocenters are important structural motifs that appear in a broad array of natural products and therapeutic agents.[1] Accordingly, a variety of catalytic methods have been developed to target their construction.[2] While recent advances in benzylic cross-coupling have provided important tools to target these features, an added synthetic challenge arises when benzylic stereocenters are sited adjacent to additional stereogenic centers.

Scheme 1. Conjunctive Cross-Coupling of β-Substituted Alkenylboronates



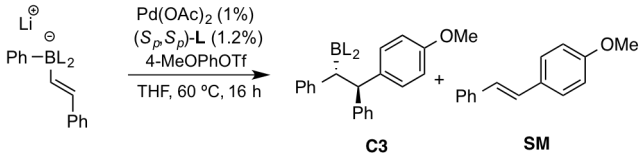
In these situations, multistep organic synthesis is often required for construction of the stereochemical dyad of interest.[3] Our group has been developing a catalytic conjunctive cross-coupling reaction that converts vinylboron "ate" complexes and electrophiles to enantiomerically-enriched secondary or tertiary alkylboronic esters bearing a single stereocenter (eq. 1, Scheme 1).[4] To address the problem of benzhydryl construction as outlined above, we questioned whether β-substituted alkenylboronic esters might engage in conjunctive cross-coupling and deliver compounds that bear vicinal stereogenic centers (eq. 2). In this report, we describe the development of this process and provide insight about how the structure of boron ligands can tip the reaction outcome in favor of the conjunctive coupling product or the classic Suzuki-Miyaura product.

Preliminary efforts to employ β-substituted alkenyl boronates in conjunctive cross-coupling reactions revealed a process that is dominated by direct Suzuki-Miyaura cross-coupling. For instance, in contrast to the conjunctive cross-coupling with the unsubstituted vinylB(neo)-derived "ate" complex **1a** which occurs in 84% yield and 97:3 er (Scheme 1, eq. 3), when styrenylB(neo) was converted to the derived "ate" complex **1b** and subjected to coupling with *p*-anisyltriflate, 1 mol% Pd(OAc)$_2$ and 1.2 mol% Mandyphos (**L**), only 13% of the conjunctive coupling product **2b** was obtained, with stilbene derivative **3b** being the predominant product. The disparate reaction outcomes with **1a** and **1b** as substrate may be understood by consideration of competing catalytic reaction pathways. Mechanistic studies intimate that the metal-induced metallate rearrangement which underlies the conjunctive coupling occurs by metal-alkene binding (**A**, equation 1, box),[4f] followed by simultaneous R_M migration and C-Pd bond formation at C_β. In contrast, recent studies of transmetallation from organoboronic acid derivatives to bis(phosphine)Pd complexes suggests that the direct Suzuki-Miyaura reaction could arise by either (a) an open transition state originating from a palladium alkene complex where C-Pd bond formation occurs at C_α with concomitant rupture of the C-B bond (**B**, shaded box, Scheme 1)[5], or (b) association of Pd with a boronic ester oxygen (**C**), which is then followed by transmetallation reaction through a closed four-centered transition state involving a five-coordinate Pd complex.[6] For the reaction of substrate **1b**, the added substitution at the β carbon of the alkene (R=H→Ph) would serve to inhibit conjunctive coupling as it requires Pd-C bond formation at a more hindered site. However, transmetallation

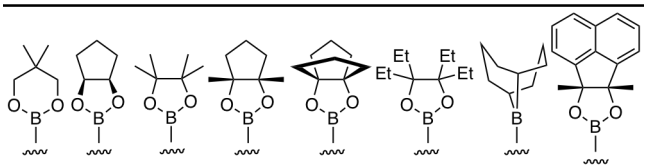
through either **B** or **C**, ultimately leading to C-Pd bond formation at C_α, would be relatively unaltered by the addition of β-substituents on the alkenyl group. Thus, the net effect of alkene β-substitution is to disfavor the metallate shift relative to the direct transmetalation reaction and thereby alter the course of the reaction. Following this analysis, it was considered that alternate ligand sets on the boron atom that selectively interfere with either Pd(II)-oxygen binding or that hinder access to C_α might reestablish the metallate shift as a major reaction pathway.

To investigate the effect of boron ligands on the chemoselectivity of the coupling reaction in equation 2, we converted a series of styrenyl boronic esters to the derived "ate" complexes and subjected them to coupling with $Pd(OAc)_2$ and MandyPhos ligand (S_p,S_p-**L**). As depicted in Table 1, with relatively unencumbered ligands on boron such as **L1** (neopentyl glycol) or **L2** (*cis*-1,2-cyclopentane diol) the Sukuzi-Miyaura product remains the predominant reaction product. However, when the boron center is more encumbered such as with **L3** (pinacol) and **L4**, the proportion of conjunctive cross-coupling (**C3**) product was increased, consistent with the notion that hindered access to either the oxygen atom or C_α may retard the rate of the direct transmetalation reaction relative to metallate shift. It can also be noted that chemoselectivity with boron centers bearing even more highly encumbered ligands (**L5**, **L6**) begins to suffer, an outcome we consider might be due to hindered olefin binding. Lastly, support for the notion that the oxygen atom may be involved

Table 1. Effect of Boron Ligand on Chemoselectivity in Conjunctive Coupling Reactions.[a]



entry	BL_2	**C3**:**SM**	**C3** yield	dr	er
1	**L1** (neo)	1:5.8	13 (10)	>20:1	99:1
2	**L2**	1:>20	<5	nd	nd
3	**L3** (pin)	1:2	35(30)	>20:1	98:2
4	**L4**	1.7:1	56(46)	>20:1	99:1
5	**L5**	1:2	30	>20:1	nd
6	**L6**	1:3	20	>20:1	nd
7	**L7** (9-BBN)	>20:1	92(75)	>20:1	67:33
8	**L8** (mac)	2.5:1	75(70)	>20:1	99:1
9[b]	**L8** (mac)	4.2:1	83(76)	>20:1	99:1



(a) Yields are by ^{1}H NMR versus an internal standard, yield in parentheses is after isolation. For entry 7, yield is of the derived alcohol; for the others, yield is of the boronic ester. Enantiomer ratio of derived alcohol was determined by SFC analysis on a chiral stationary phase and in comparison to authentic enantiomer mixture. Diastereomer ratio determined by analysis of the ^{1}H NMR spectrum. (b) Reaction at 40 °C and with 1 equiv CsF.

in the direct transmetalation process is provided by the reaction with hydrocarbon-based ligand **L7** (9-BBN) wherein the metallate shift-based path operates to the near exclusion of the Suzuki-Miyaura reaction.

Considering the observations in entries 1-6 of Table 1, we sought ligands that are both readily accessible and also effectively shield the oxygen atom and/or C_α without blocking access to the alkene C_β. As shown in entry 8, ligand **L8** (termed "mac"), readily prepared by methylation of acenaphthoquinone (*vide infra*), appears to satisfy these requirements, delivering the conjunctive product in good yield and enantioselectivity. Of note, the reaction chemoselectivity could be enhanced by conducting the reaction at 40 °C and in the presence of CsF; under these conditions the conjunctive coupling product is formed in 76% isolated yield, >20:1 dr, and with 99:1 enantioselectivity.

Diol **4** is readily available from acenaphthoquinone by a single-step diastereoselective (4.3:1 dr) carbonyl addition reaction employing trimethylaluminum in toluene,[7] followed by crystallization of the diol from ethyl acetate solvent. Conversion of boronic acids to derived B(mac) esters is readily accomplished by esterification in the presence of catalytic $FeCl_3$.[8] In contrast to common boronic ester ligands (i.e. pinacol, neopentylglycol), when the B(mac) derivatives are converted to the four coordinate "ate" complexes, the issue of stereoisomerism arises and it was considered that this feature might pose a complication for selective and efficient catalytic coupling reactions. To study the properties of B(mac) "ate" complexes, the addition of phenyllithium to *n*-butylB(mac) in THF-d_8 at room temperature was analyzed by ^{1}H NMR analysis. As shown in Scheme 2b, the kinetic addition product appeared to arise from addition of the nucleophile *cis* relative to the vicinal methyl groups forming ***trans*-6** in a 5:1 ratio.[9] Of note, stirring the reaction for 30 minutes at 60 °C resulted in a 2:1 diastereomer ratio, and after 12 hours an equilibrium 1:1 ratio of the isomers was observed. Importantly, when reaction partners are reversed such that of *n*-BuLi was added to PhB(mac), an inverted

Scheme 2. Methylated Acenaphthoquinone (mac) as a Ligand for Boronic Esters.

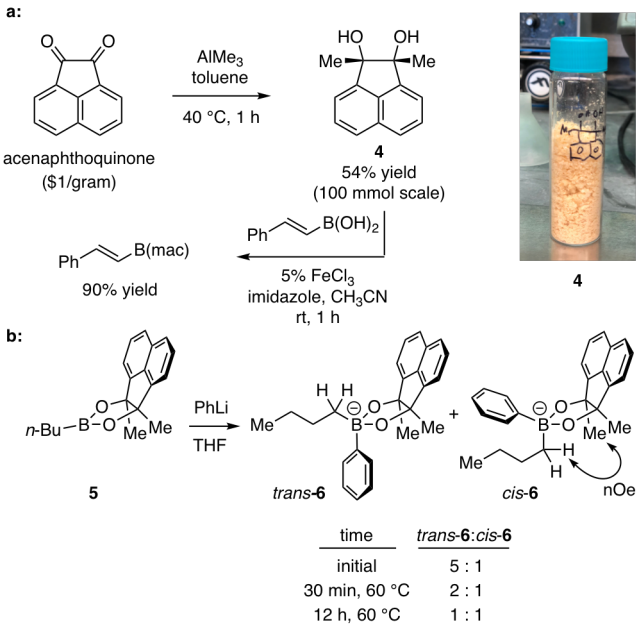
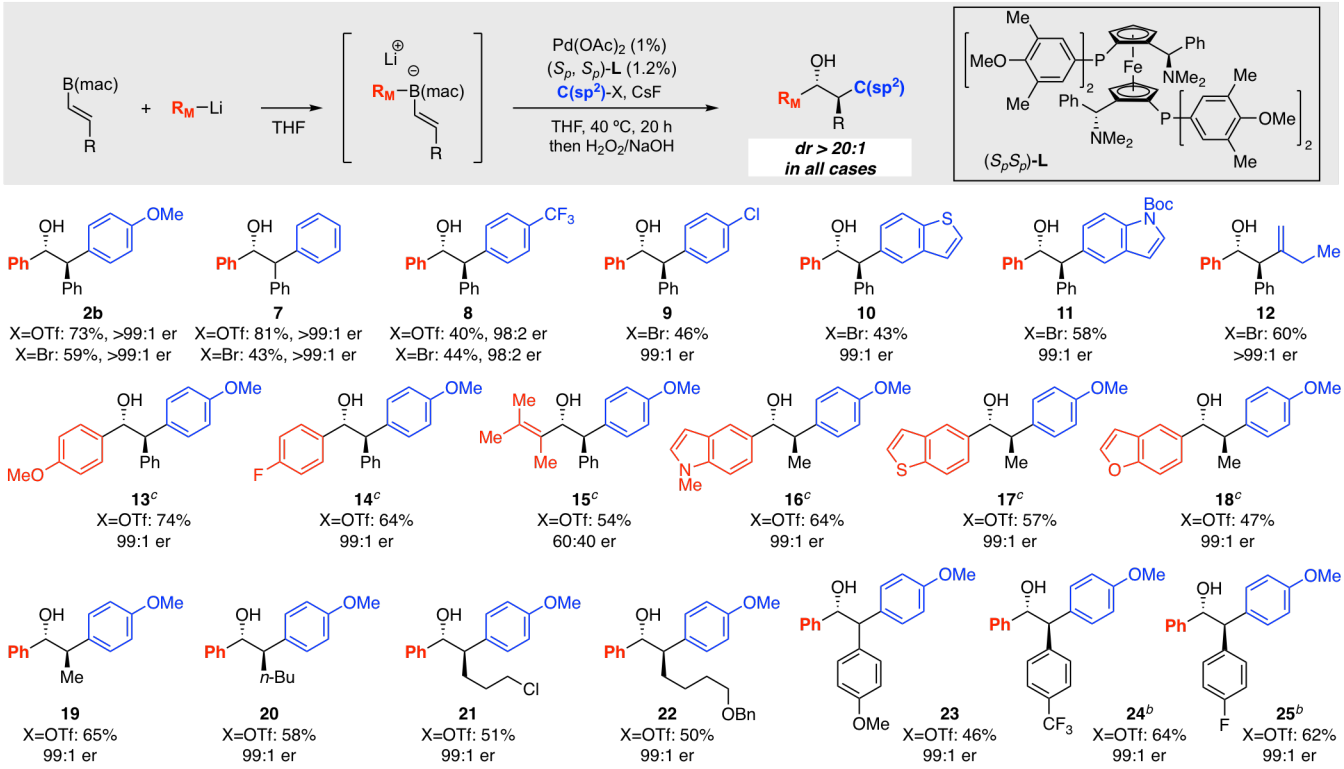


Table 2. Pd/MandyPhos-Catalyzed Conjunctive Coupling of β-Substituted B(mac)-Derived "Ate" Complexes.[a]



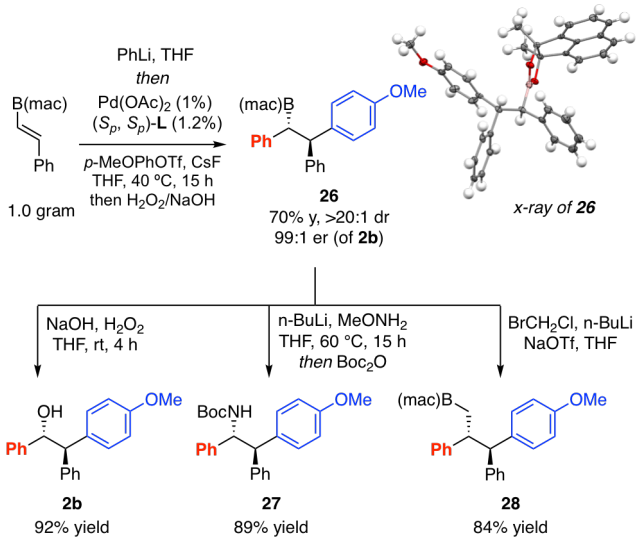
(a) Yields are isolated yields of purified material and represent and average yield of two different experiments. Enantiomer ratios was determined by SFC analysis on a chiral stationary phase and are in comparison to authentic racemic materials. Diastereoselectivity determined by analysis of the ^{1}H NMR spectrum. For reactions of organobromide electrophiles, an equivalent of KOTf was added. (b) Reaction at 60 °C. (c) Reaction conducted with 2% Pd and 2.2% **L1**.

initial kinetic ratio (ca. 1:12.5) results, but the same thermodynamic ratio is achieved upon heating (see Supporting Information for details). These experiments suggest that diastereomeric "ate" complexes should be interconverting during the course of reaction and that the configuration of these species will likely be inconsequential to conjunctive couplings.

With ready access to B(mac)-derived substrates and an understanding of their properties, these compounds were examined in conjunctive coupling reactions. As depicted in Table 2, the reaction can operate with both electron-rich and electron-poor electrophiles and, after oxidative work-up, provides the derived secondary alcohols with high diastereoselectivity (>20:1 dr) and enantioselectivity (generally above 98:2 er.). While substrates with heteroatom-containing functional groups do not pose an inherent problem, diminished yield was observed with electron-deficient electrophiles, an outcome that arises from competitive Suzuki-Miyaura coupling reactions (in general for Table 2, the remaining mass balance is comprised of Suzuki-Miyaura products). Fortunately, even with these substrates the stereoinduction remains high. It should also be noted that a substrate with a hindered migrating alkenyl group, reacted with anomalously low enantioselectivity, an observation that has been made in other systems.[4a,c] Examination of both aryl triflate and aryl bromide electrophiles showed that both electrophiles could be employed to furnish to conjunctive product; however, bromide electrophiles required the addition of KOTf to ameliorate the inhibitory activity of bromide salts[4b] and provided diminished product yields relative to their triflate counterparts. The reaction was also found to operate with several different migrating groups, with electron-rich migrating groups giving higher yields than those that are electron-poor. Surprisingly, under the current conditions, "ate" complexes containing alkyl migrating groups did not engage in the conjunctive coupling pathway and provided direct Suzuki-Miyaura coupling products instead. With respect to the substituent at the β-carbon of the alkenyl boronate, substrates containing electron-rich and electron-deficient arenes, as well as those containing alkyl groups were found to participate in the reaction. While an electron-rich β-substituent appeared to increase the conversion of the reaction, it also resulted in more competition from the Suzuki-Miyuara pathway (**23**; 1:1 conjunctive:Suzuki). Substrates with electron-deficient β-substituents furnished less Suzuki-Miyaura reaction, but required higher temperatures for the conjunctive process to proceed (**24**, 4:1 conjunctive:Suzuki). Lastly, while substrates with β-alkyl substitution (**16**-**22**) gave only modest yields, they reacted with outstanding selectivity and furnished products that would be otherwise difficult to access with single-step catalytic processes.

Although B(mac)-derived products are stable to column chromatography, they are poorly soluble in many organic solvents such that for the purposes of Table 2, it was most convenient to oxidize the coupling products and isolate the corresponding alcohols. To learn about other transformations of the B(mac) derivatives, a larger scale coupling reaction was undertaken and the reaction product examined. As shown in Scheme 3, a gram-scale coupling provided secondary boronic ester **26** with reaction efficiency and selectivity comparable to smaller scale reactions in Table 2. Con-

Scheme 3. Synthetic Transformations of AlkylB(mac) Derivatives.

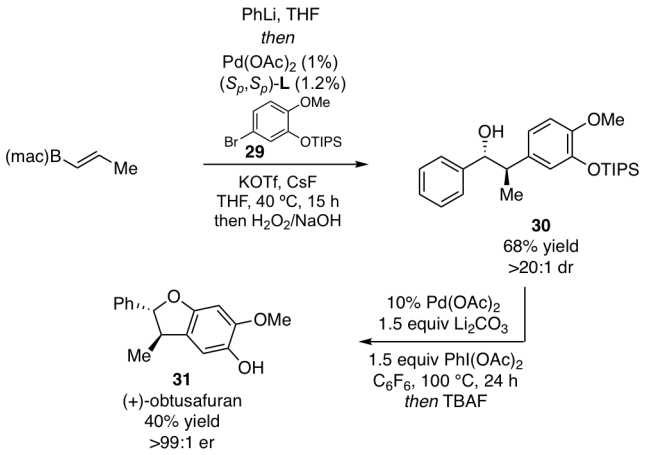


sistent with the observations in Table 2, purified intermediate **26** underwent oxidation efficiently, providing alcohol **2b** in outstanding yield and selectivity. Also noteworthy, is that direct amination[10]/Boc protection of **26** furnished carbamate **27** in excellent yield and as a single diastereomer. Lastly, it was found that B(mac)-derivate **26** underwent efficient modified Matteson homologation[11] to furnish primary B(mac) derivative **28** as a single diastereomer.

The diastereoselective conjunctive coupling establishes strategically-useful functional group arrays in ways that are not straightforward to access by contemporary asymmetric synthesis. This feature is illustrated by the application of the conjunctive coupling to the synthesis of obtusafuran[12] (Scheme 4). While this target was previously prepared by a convenient enantioselective ketone reduction and cyclization, construction of the requisite ketone starting material required five steps of chemical synthesis.[13] Employing *trans*-2-propenylB(mac) in a conjunctive coupling with PhLi and aryl bromide **29**, furnished **30** in excellent yield and stereoselection. Subsequent oxidative cyclization[14] and deprotection provided the target in just three synthesis steps (two reaction vessels) from simple starting materials.

In summary, we have established a catalytic, diastereo-, and enantioselective conjunctive coupling of β-substituted

Scheme 4. Construction of (+)-Obtusafuran by Conjunctive Cross-Coupling.



alkenylboronic esters. This process employs an encumbered diolato ligand to control the reaction of alkenylboron "ate" complexes, tipping the reaction in favor of a metallate shift-based pathway rather than direct transmetalation. Further studies on the mechanistic origin of chemoselectivity with B(mac) derived "ate" complexes will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information. Procedures, characterization and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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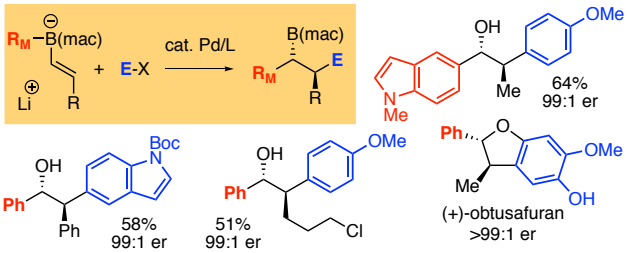
RM
B(mac)
Li
R
+ E-X
cat. Pd/L
B(mac)
E
RM
R
OH
OMe
N
Me
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Ph
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OMe
Me
OH
(+)-obtusafuran
>99:1 er
OH
Boc
N
Ph
Ph
58%
99:1 er
OH
OMe
Ph
Cl
51%
99:1 er