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Communication

Desymmetrization of Vicinal Bis(boronic) Esters by Enantioselective Suzuki–Miyaura Cross-Coupling Reaction

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ABSTRACT: The development of an enantioselective catalytic Suzuki–Miyaura reaction that applies to *meso* 1,2-diborylcycloalkanes is described. This reaction provides a modular route to enantiomerically enriched substituted carbocycles and heterocycles that retain a synthetically versatile boronic ester. With appropriately constructed substrates, compounds bearing additional stereogenic centers and fully substituted carbon atoms can be generated in a straightforward fashion. Preliminary mechanistic experiments suggest that substrate activation arises from the cooperative effect of vicinal boronic esters during the transmetalation step.

The Suzuki–Miyaura reaction stands as one of the most useful C–C bond-forming transformations for the construction of natural products and pharmaceutically active agents.[1] In addition to accomplishing a challenging chemical transformation, valuable features are that the reaction is generally tolerant of air and moisture, and it can be effected with small amounts of transition metal-based catalysts. Since many chemical targets of interest are chiral compounds, intense research has been directed toward the development of enantioselective Suzuki–Miyaura coupling reactions.[2] The preponderance of these studies has focused on reactions that result in biaryl C–C bond construction,[3] undoubtedly reflecting the fact that the Suzuki–Miyaura reaction is most reliable with C(sp^2) electrophiles and C(sp^2) organoboron reagents. Enantioselective Suzuki–Miyaura reactions that result in bond formation at C(sp^3) centers are much less developed and are generally focused on cross-couplings of geminal bis(boronates),[4] substituted allylboronates,[5] or stereoablative coupling employing either racemic electrophiles,[6] racemic organoboron reagents,[7] or both.[8,9] Herein, we describe an enantioselective Suzuki–Miyaura reaction that applies to *meso* 1,2-bis(boronates) and provides a tool for construction of polysubstituted carbocycles and heterocycles in an enantioselective fashion. Considering that vicinal disubstituted cyclic motifs are found in a number of bioactive agents (Figure 1a), this process may find use in asymmetric synthesis.

In contrast to primary organoboron reagents, secondary coupling partners are significantly less reactive in non-radical-based Suzuki cross-coupling, such that couplings of these more hindered substrates often suffer from chain-walking due to *β*-hydride elimination processes.[10,11] Indeed, other than recent systems developed by Burke[12] and by Biscoe and Sigman,[13] secondary boronate cross-couplings have relied upon inherently reactive substrates (cyclopropyl,[14] benzylic,[15] allylic,[16] or those with directing groups[17]) for effective reaction. Recent studies in our laboratory revealed that *aliphatic* 1,2-bis(boronic esters) (**1**, Figure 1b) are remarkably reactive substrates in Suzuki–Miyaura reactions with the presence of an adjacent

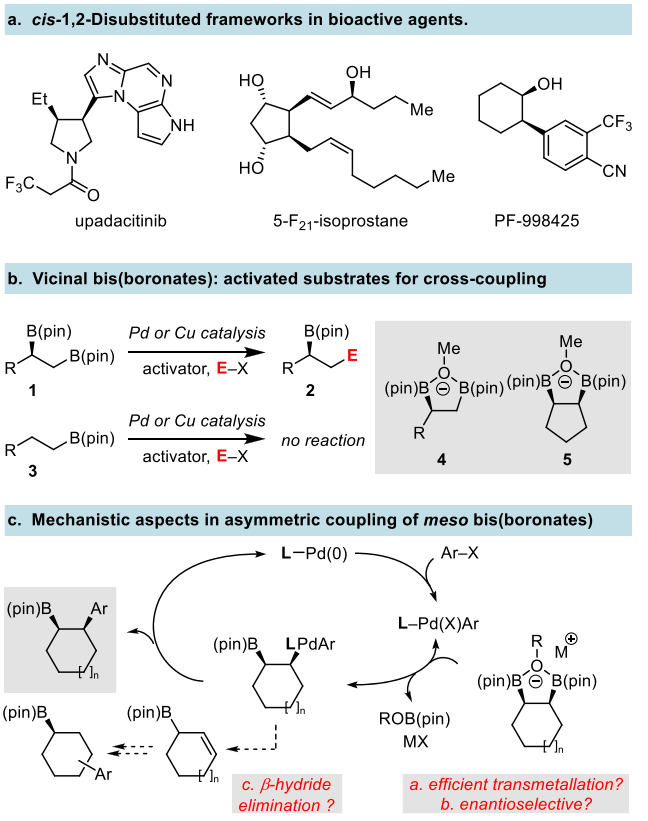

Figure 1. (a) Bioactive agents that might arise by enantioselective cross-coupling of *meso* vicinal diboronates. (b) Vicinal diboronates exhibit enhanced reactivity in cross-coupling. (c) Potential challenges in cross-coupling of cyclic vicinal diboronates.

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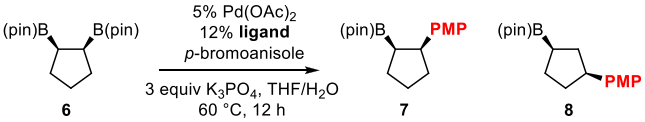
organoboronate providing >50-fold rate acceleration in Pd-catalyzed cross-coupling.[18] More recent experiments involving copper catalysis revealed similar substrate activation, with the origin of rate enhancement being traced to the intermediacy of a strained cyclic chelated ate complex (i.e., **4**, Figure 1b).[19] Indeed, species such as **4** and **5** were detected spectroscopically upon treatment of the vicinal bis(boronic ester) with methoxide. Considering the challenge that secondary boronic esters pose in cross-coupling under nonradical pathways, it was of interest to determine whether vicinal boronate activation might be sufficient to prompt reaction of these challenging substrates. As a component of reaction design, achiral *meso* bis(boronates) were considered as substrates with the expectation that appropriate chiral catalysts might enable enantioselective desymmetrization[20] during the course of cross-coupling. Approaching this problem brings three questions to the fore (Figure 1c): (a) Can efficient cross-couplings occur with secondary boronate coupling partners? (b) Can enantioselectivity be engendered in the transmetalation step? (c) Will β-hydrogen elimination occur to such an extent that complex product mixtures result? During the preparation of this manuscript, an aligned study in desymmetrization of 1,2-diboryl cyclopropanes was described by Tortosa;[18g] however, cyclopropyl boronates are inherently more reactive in cross-coupling reactions and their ring strain precludes competitive β-hydrogen elimination. In this report, we show that, with appropriate catalysts, substrate activation is indeed sufficient to render even nonstrained substrates reactive, and thereby provides a strategically useful route to enantiomerically enriched substituted four- through eight-membered carbocycles and heterocycles.

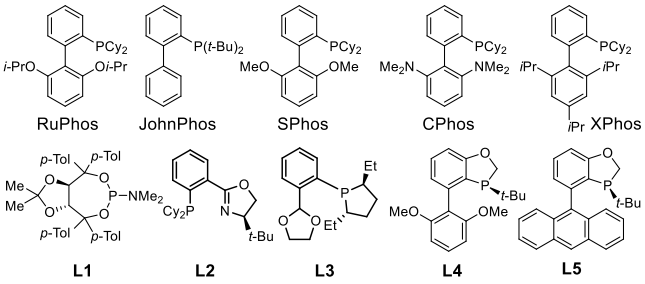
To initiate studies, we examined ligand effects in the cross-coupling of *cis*-1,2-diborylcyclopentane (**6**, Table 1), a substrate that is easily obtained by diboration of cyclopentene.[21] Reactions were conducted with 5 mol % $Pd(OAc)_2$, 12 mol % of a given ligand, and K_3PO_4 (3 equiv) in THF/H_2O (1:1) as the reaction solvent. When either triphenylphosphine (entry 1) or *n*-BuP(adamantyl)$_2$ (entry 2) were employed as ligands, the reaction appeared to proceed by a pathway involving β-hydrogen elimination-based chain-walking and furnished product **8** in modest yield. Of note, the product derived from double coupling was not detected, thereby supporting the notion that vicinal boronate activation plays a critical role in accelerating the reaction. When *ortho*-biarylphosphines[22] were employed, the product of direct cross-coupling (**7**) was produced and, depending on ligand structure (entries 3, 5, 6), could comprise the majority of the reaction mixture. Of note, the reaction with XPhos (entry 7) was high yielding and delivered compounds in a combined yield of 82%. Having established the capacity for efficient cross-coupling, several classes of chiral ligands were examined (see Supporting Information for additional data). While reactions with binap and phosphoramidites were not efficient and only provided chain-walking isomer **8** in low enantioselectivity, reactions employing chiral oxaphosphole-derived biaryl ligands[23] delivered the reaction products in high yield and enantioselectivity (entries 12, 13). Moreover, with **L5** (AntPhos) a significant portion of the reaction mixture consisted of the direct cross-coupling product **7**, and this ligand was selected for analysis with other substrates.

While enantioselective cross-coupling of 1,2-diborylcyclopentane occurs with good overall yield, it delivers only a modest amount of direct cross-coupling product **7** (42% yield)

Table 1. Ligand Effects on the Catalytic Enantioselective Suzuki Reaction of *cis*-1,2-Diborylcyclopentane (6)[a]



entry	ligand	7 (%)	er 7	8 (%)	er 8
1	PPh_3	< 5	na	42	na
2	*n*-BuP(adamantyl)$_2$	1	na	45	na
3	RuPhos	29	na	4	na
4	JohnPhos	6	na	2	na
5	SPhos	37	na	8	na
6	CPhos	19	na	5	na
7	XPhos	33	na	49	na
8	(*S*)-Binap	< 5	na	19	51:49
9	**L1**	< 5	na	18	70:30
10	**L2**	< 5	na	< 5	na
11	**L3**	< 5	na	15	51:49
12	**L4**	6	94:6	65	85:15
13	**L5**	42	>99:1	42	91:9



[a]Reactions were carried out with 0.10 mmol of starting material; er values were determined by chiral chromatography (SFC) and have an error of ±1%. PMP = *p*-methoxyphenyl. For entries 1−7 the boronic ester was isolated; for entries 8−13 the derived alcohol was isolated. For entry 10, 6 mol % ligand was used.

due to competitive chain-walking. However, when the substrate bears additional substitution on the ring, chain-walking is minimized and excellent yield of cross-coupling product is obtained. For example, coupling product **9** (Figure 2), a compound with three stereogenic centers, was obtained in 89% isolated yield and excellent enantiopurity (96:4 er). Similarly, desymmetrization delivers **10**, a compound bearing a fully substituted carbon stereocenter, in excellent yield and similarly high selectivity. 3,4-Diborylpyrrolidines also undergo efficient and selective cross-coupling to provide substituted heterocycles **12**−**17** effectively. Aside from five-membered cyclic substrates, those containing four- and six-membered rings are also effective coupling partners. Even though, chain-walking in cross-coupling of four-membered ring substrates has been observed,[24] reactions of diborylcyclobutanes with Pd/**L5** provide single regioisomer products. Of note, the efficiency and selectivity for the reactions were found to be dependent on the nature of the electrophile: a number of bromoarenes react with good stereocontrol; however, reactions with pyridine-based electrophiles occur with diminished enantioselectivity (**19**, **27**). Compound **24** resulted in a crystalline product whose absolute configuration could be established by X-ray analysis (CCDC 2239914). Lastly, the reaction could be extended to couplings of seven- and eight-membered diboryl

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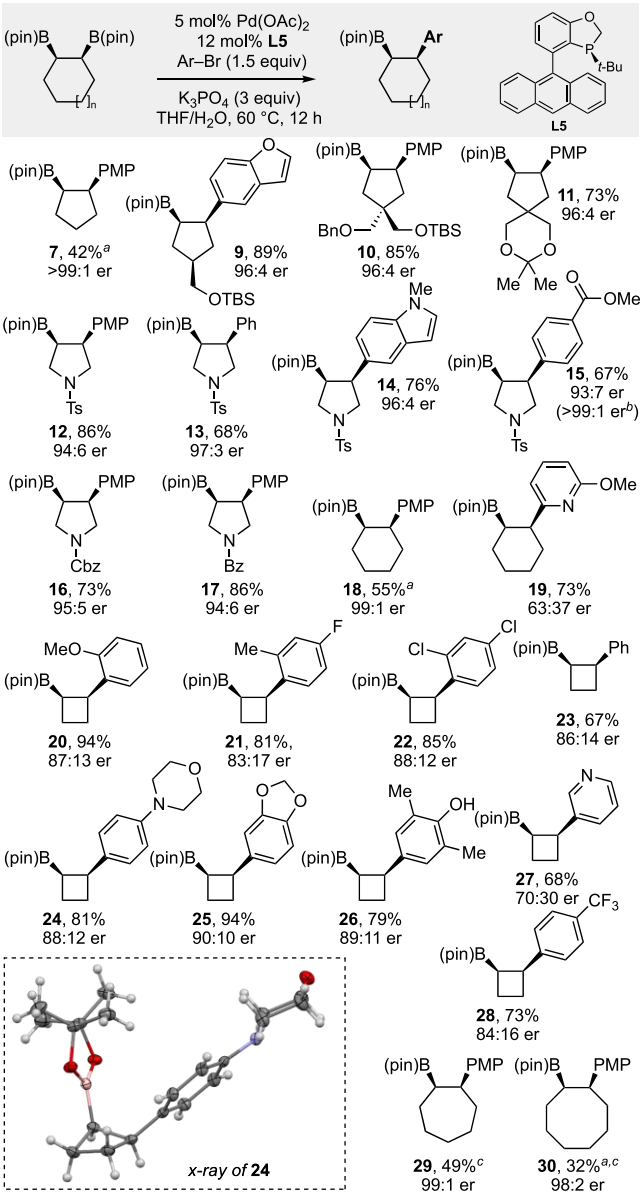

Figure 2. Substrate scope in enantioselective Suzuki–Miyaura reaction of *meso* bis(boronates). Reactions for **18**, **19**, **29**, and **30** were conducted in dioxane/water; reactions for **29** and **30** were conducted at 100 °C. [a]Isolated as the derived alcohol. [b]Enantiomeric purity obtained after recrystallization. [c]Yield determined by ^{1}H NMR analysis versus an internal standard; product could not be completely separated from the regioisomers derived from chain-walking.

substrates, delivering **29** and **30**; however, experiments with acyclic substrates have yet to deliver cross-coupling product (data not shown).

To examine practical features of the enantioselective cross-coupling, compound **32** was prepared from **31** on a larger scale (20 mmol scale) by directed diboration[25] followed by silylation of the alcohol (Figure 3a). It was found that the subsequent cross-coupling to provide **33** could be conducted with only 1.2 mol % $Pd(OAc)_2$ and 3 mol % ligand **L5** and still proceeded efficiently and with good enantioselectivity (80% yield, 96:4 er). To determine if the steric environment of the remaining boronic ester prohibits subsequent functionalization, a series of transformations were conducted (Figure 3b). Matteson homologation[26] of **33** to give **34** was found to proceed in

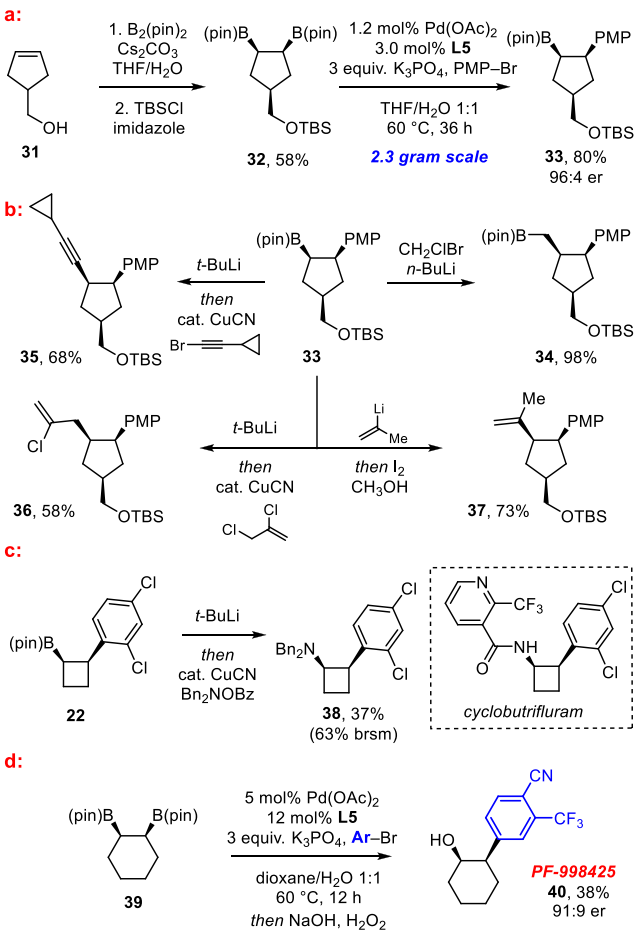

Figure 3. Preparative aspects of the enantioselective cross-coupling of *meso* 1,2-diboryl alkanes. See Supporting Information for complete experimental details.

outstanding yield (98%). Additionally, Cu-catalyzed coupling of the *t*-BuLi-activated boronic ester[27] to give either alkyne **35** or alkene **36** proceeded stereospecifically and in useful yield. Efficient Zweifel–Evans[28] olefination provided the isopropenyl-substituted carbocycle **37** in good yield and as a single diastereomer. As an alternate transformation, amination of cyclobutane **22** (Figure 3c) was examined. While direct amination with lithiated methoxyamine[29] was not effective, Cu-catalyzed amination of the activated ate complex[27] proceeded in modest yield and represents an inroad to the construction of cyclobutrifluram. Lastly, preparation of PF-998425[30] was examined (Figure 3d) by coupling with an electron-deficient aromatic electrophile; while the overall yield for the reaction was modest, the enantioselectivity was very good and enabled the synthesis of the *cis*-disubstituted cyclohexane in a short reaction sequence. Comparison of the optical rotation of **40** versus that reported for PF-998425[30] allowed assignment of the absolute configuration.

Experiments conducted with different organoboron substrates in the presence of $Pd(OAc)_2$/**L5** provided insight about mechanistic features that govern this reaction. The absence of reaction with either cyclopentyl-B(pin) or racemic *trans*-1,2-diborylcyclopentane (**42**) (eq 1, Figure 4) suggests a critical proximity effect for the synergistic activation of vicinal diboryl substrates. The observation that unreactive cyclopentyl-B(pin) does not poison the reaction of *cis*-diborylcyclopentane **6** (eq

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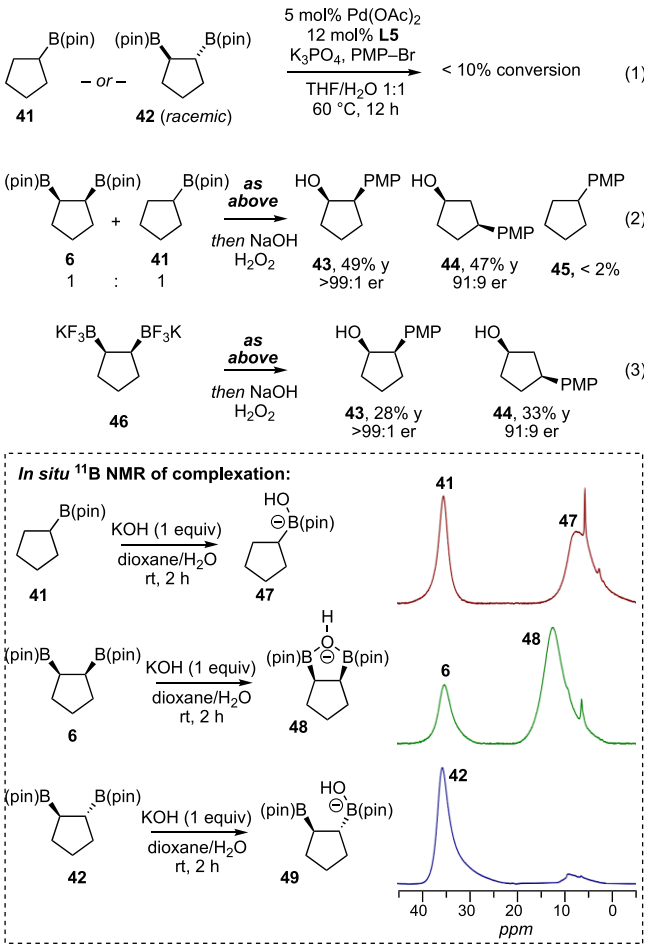

Figure 4. Cross-coupling and complexation reactions with different organoboron substrates. Yields determined by ^{1}H NMR versus an internal standard.

2) suggests the vicinal diboryl substrate (**6**) undergoes faster transmetalation than the monoboryl derivative. In addition, the observation that 1,2-bis(trifluoroborate) **46** (eq 3) and bis(pinacolatoborate) **6** (see Table 1, entry 13) undergo coupling with similar efficiency, regioselectivity, and enantioselectivity suggests that the reactive species with each substrate is the same. A plausible candidate for the reactive intermediate is the bis(boronic acid).[31] Lastly, we examined the complexation of KOH (1 equiv) with either cyclopentylB(pin) (**41**), *cis*-diborylcyclopentane **6**, or the *trans* derivative **42** (box, Figure 4). Analysis of the ^{11}B NMR spectrum clearly shows a pronounced ability of the 1,2-*cis* derivative to not only bind hydroxide but also bind in a way that furnishes a downfield-shifted borate (relative to **47**) indicative[19] of a cyclic complex such as **48**.

In conclusion, we have described an enantioselective Suzuki–Miyaura cross-coupling between vicinal 1,2-diborylcycloalkanes and aromatic electrophiles. The reaction operates on simple unstrained hydrocarbons and provides a useful route to nonracemic substituted carbocycle and heterocycle building blocks.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c01571.

Procedures, characterization, and spectral data (PDF)

Accession Codes

CCDC 2239914 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare the following competing financial interest(s): C.A. and R.A.S. are employees and stockholders of Pfizer Inc.

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