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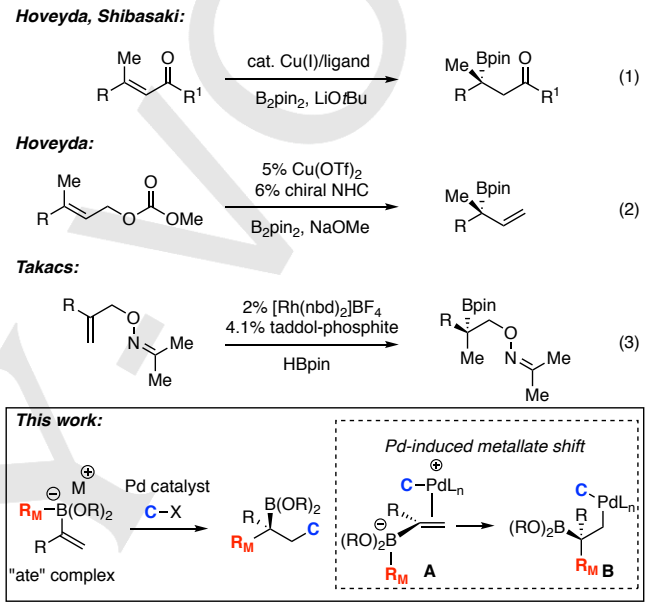
Enantioselective Construction of Tertiary Boronic Esters by Conjunctive Cross-Coupling

Jesse A. Myhill[‡], Liang Zhang[‡], Gabriel J. Lovinger, and James P. Morken*[a]

Abstract: Catalytic enantioselective conjunctive cross-coupling has been developed to construct tertiary alkylboronic esters. These reactions occur with good yield and enantioselectivity for a range of substrates. Mechanistic experiments reveal aspects of the catalytic cycle that allow hindered substrates to react without significant complicating side reactions.

Development of processes for the construction of fully substituted carbon stereocenters – be they tertiary alcohols, tertiary carbinamines, or all-carbon quaternary centers – stands as one of the more difficult challenges in the field of asymmetric catalysis.[1] Not only does the steric encumbrance that surrounds the carbon center hinder the reactions required for the assembly of such motifs, but the lack of a significant inherent structural bias between the prochiral faces of precursor substrates often renders stereoselective assembly of quaternary centers a challenging undertaking. To address this challenge, several groups have studied the catalytic enantioselective construction of tertiary boronic esters with the expectation that these compounds can be employed to address the assembly of a range of fully substituted carbon centers.[2] In this regard, notable advances in catalytic conjugate borylation[3] (eq. 1), allylic borylation[4] (eq. 2), and directed hydroboration[5] (eq. 3) have facilitated the construction of tertiary boronic esters from appropriately functionalized precursor substrates. In this report, we describe the utility of catalytic conjunctive cross-coupling[6,7,8] as a complimentary means to establish highly hindered tertiary boronic esters in an efficient and enantioselective fashion (Scheme 1).

The Pd-catalyzed conjunctive cross-coupling of vinylboron "ate" complexes and C(sp^2) electrophiles is proposed to occur through a 1,2-metallate shift involving a Pd(II)-alkene complex (**A** → **B**, Scheme 1). While this process efficiently constructs secondary alkyl boronic esters in an enantioselective fashion, its successful application to the construction of non-racemic tertiary boronic esters was uncertain due to three concerns: first, could a sterically encumbered Pd catalyst bearing a bidentate phosphine ligand effectively bind to a hindered α-substituted vinyl boronate (i.e. formation of **A**, Scheme 1)? Second, would the steric congestion associated with construction of a hindered C-C bond by a metallate-shift based pathway impose an added barrier to formation of **B** (Scheme 1) such that other reaction processes predominate? Third, would steric interactions introduced by the added alkene substituent diminish reaction enantioselectivity? Herein, we show that appropriate modification of reaction conditions enables the conjunctive coupling to produce highly hindered tertiary alkyl boronic esters and we provide insight into mechanistic features that allow these reactions to remain effective.



Scheme 1. Catalytic Conjunctive Cross-Coupling to Establish Tertiary Boronic Esters.

Our studies commenced by subjecting "ate" complex **1**, derived from isopropenylB(neo) and *n*-BuLi, to conjunctive coupling conditions developed for non-substituted vinylboron "ate" complexes.[6a] Thus, treatment with 1 mol% $Pd(OAc)_2$,1.2 mol% MandyPhos[9] ligand **L1**, and PhOTf at 60 °C for 14 h did indeed deliver the conjunctive coupling product **2**, but in only 24% isolated yield and with a significant amount (70%) of direct Suzuki-Miyaura cross-coupling product (Table 1, entry 1). Suspecting that the Suzuki-Miyaura reaction product might arise from direct transmetallation initiated by binding of Pd(II) to the boronic ester oxygen atom[10], we considered strategies that might preclude Pd-O association. While use of alternate ligands on Pd[11] had little effect on chemoselectivity (entry 2–4), employing a more hindered boronic ester (pinacolato) in place of the neopentylglycolate group had a pronounced effect and delivered the reaction product in outstanding yield and with useful levels of enantioselectivity (entry 5). In contrast, use of ethyleneglycolato or catecholato boron ligands did not furnish the conjunctive coupling product at all; however, according to ^{11}B NMR analysis, these ligand frameworks also did not furnish a stable "ate" complex. With the B(pin) derivative, while use of other MandyPhos ligands did not improve enantioselectivity, the stereoselectivity and chemoselectivity could be improved by conducting the reaction at room temperature wherein the reaction product **2** was isolated in 94% yield, and in 94:6 er (entry 10).

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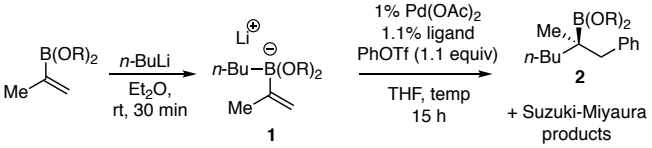
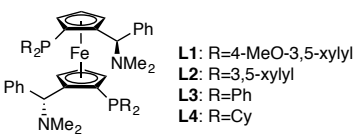
Table 1. Catalyst Studies in Conjunctive Coupling with Isopropenylboronates.



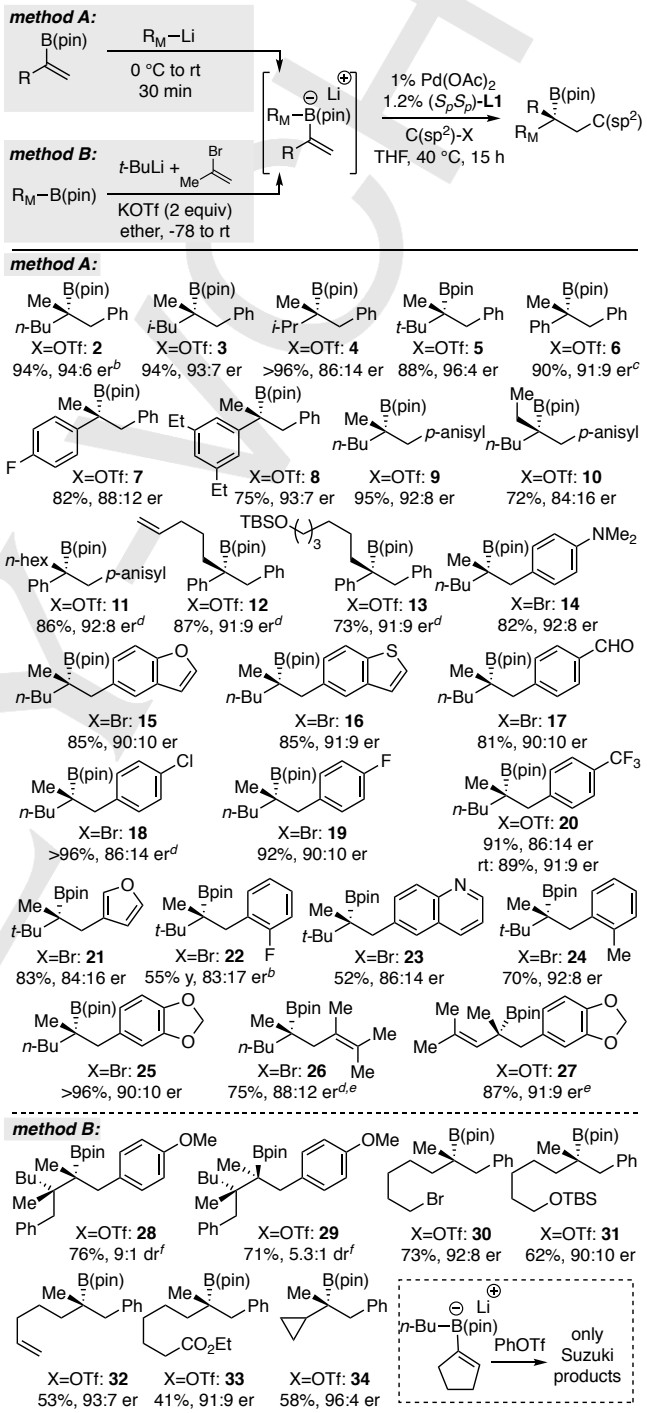
Entry	$B(OR)_2$	Ligand	temp	Yield[a]	**2**:SM pdt[b]	e.r.
1	B(neo)	**L1**	60 °C	22	1:2.9	90:10
2	B(neo)	**L2**	60 °C	23	1:2.3	91:9
3	B(neo)	**L3**	60 °C	22	1:3.6	nd
4	B(neo)	**L4**	60 °C	18	1:4.5	nd
5	B(pin)	**L1**	60 °C	90	1:0.11	90:10
6	B(pin)	**L2**	60 °C	83	1:0.25	88:12
7	B(pin)	**L3**	60 °C	94	1:0.13	86:14
8	B(pin)	**L4**	60 °C	88	1:0.20	60:40
9	B(pin)	**L1**	40 °C	91	1:0.11	92:8
10	B(pin)	**L1**	22 °C	94	1:0.06	94:6

[a] Yield is after isolation and purification by silica gel chromatography. [b] Ratio determined by NMR analysis of unpurified reaction mixture. Suzuki-Miyaura (SM) product refers to the combined amount of *n*-butylbenzene and α-methylstyrene.



To explore the scope of this reaction, "ate" complexes were prepared from organolithium reagents and substituted alkenyl boronates (Table 2, method A), or from isopropenyllithium and organoboronic esters (method B). The "ate" complexes were then subjected to catalytic conjunctive coupling in the presence of 1 mol% $Pd(OAc)_2$ and 1.1% (*S,S*)-Mandyphos (**L1**). To ensure complete reaction, each example was allowed to react for 15 h at 40 °C; the tertiary boronic ester products were generally isolated in good yield and selectivity. Using this procedure, a series of substrates was examined and it was found that a broad array of migrating groups and electrophiles could be engaged in the reaction. As the data in Table 2 suggests, in addition to an *n*-butyl migrating group, highly hindered substituents (i.e. R_M = *tert*-butyl; product **5**, **21**-**24**) are competent migrating groups as are aromatic groups (**6**-**8**, **11**-**13**). Of note, other α-substituted boronic esters can be employed (**10**-**13**) as can a variety of aryl, alkenyl, and heterocyclic electrophiles. Products **14**-**19** and **21**-**25** demonstrate that aryl bromides serve as competent electrophiles so long as potassium triflate is employed as a halide scavenger.[6b] It should be noted that enantioselectivity can be modestly improved, although reactivity is diminished for some substrates, by conducting the reaction at room temperature (substrate **20**). Lastly, when the "ate" complex was prepared using method B, comparable yields and selectivities were observed indicating that this strategy can allow direct use of readily available organoboronic ester substrates. Of note, products **28** and **29** establish that tertiary boronic esters obtained from conjunctive coupling can be subjected to a second conjunctive coupling reaction where the catalyst appears to be the dominant stereochemical control element. Lastly, it should be noted that a trisubstituted alkenylboron substrate did not deliver conjunctive coupling products with the current catalytic conditions.

Table 2. Tertiary Boronic Esters from Pd-Catalyzed Conjunctive Coupling[a]



[a] See text and Supporting Information for experimental details. Yields refer to isolated yield of purified material and are an average of two experiments. Reactions of organohalide electrophiles employed 1 equiv KOTf; when organolithium reagent was prepared by Li-halogen exchange, 2 equiv KOTf was employed. [b] This reaction was conducted at 22 °C. [c] This product was isolated as the derived alcohol after oxidation with $NaOH/H_2O_2$. [d] Reaction conducted at 60 °C. [e] Due to incomplete peak separation, er represents a lower limit. [f]Yield is overall, after two successive conjunctive couplings.

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Considering the broad range of organic transformations in which tertiary alkylboronic esters participate [12] suggests that simple routes to the construction of sterically congested chiral therapeutic agents might be enabled by conjunctive coupling reactions. To probe these prospects, we examined the assembly of mevalanolactone [13] (**38**) and the analgesic isoquinolone derivative **41** (Figure 1). Construction of **38** required reaction of an appropriately protected β-hydroxyethyl-substituted borate complex. For reasons that we have not determined, β-oxygenation was not tolerated in the migrating group, possibly due to β-elimination of the resulting ate complex.[14] However, an effective solution was found in the use of compound **35** where the silyl group serves as a masked hydroxyl group.[15] Conjunctive coupling followed by a modified Tamao-Fleming oxidation [16] furnished **37**, a known precursor[17] to **38**. Also as depicted in Figure 1, the analgesic agent **41** was easily assembled by conjunctive coupling followed by amination[18] and conversion of the intermediate amine group to an isocyanate (**40**); intramolecular substitution[19] furnished the isoquinolone **41**.

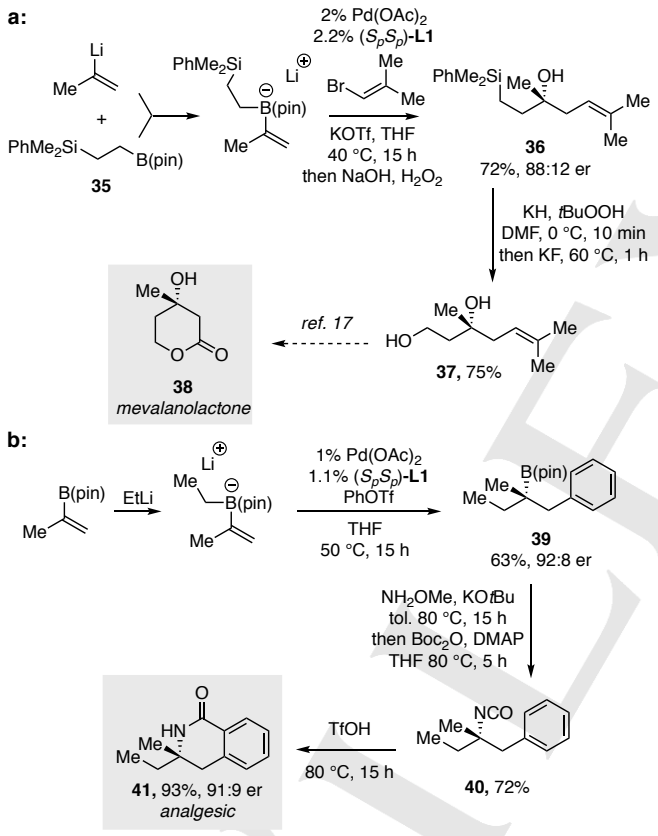

Figure 1. a: Construction of **38**. b: Construction of **41**.

In comparison to couplings with unsubstituted vinylboron "ate" complexes, it is notable that metallate shifts involving α-substituted substrates, especially those that fuse two fully-substituted carbon atoms (products **5**, **21**-**24**, **28**-**29**, Table 2), appear to occur with little additional impediment. This reactivity pattern is even more surprising in light of the marked sensitivity of other alkene palladation reactions to steric effects.[20] To learn about the mechanistic features that govern conjunctive coupling,

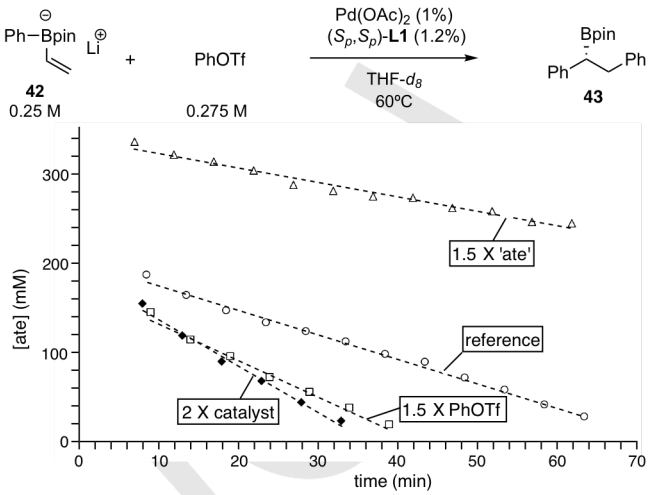

Figure 2. Kinetic profile of the conjunctive coupling, as determined by *in situ* ^{1}H NMR. Standard reaction (○) was conducted with 0.20 mmol of ate complex, 0.22 mmol PhOTf, and 1% catalyst loading in 0.8 mL THF-*d8* at 60 ºC and occurred with a rate of 2.73mM/min (R^2=0.99); rates for other conditions: Δ rate = 1.63 mM/min (R^2=0.97); ◆ rate = 5.15 mM/min (R^2=0.99); □ rate = 4.07 mM/min (R^2=0.99).

we assessed the kinetic profile of couplings with both substituted and unsubstituted alkenyl substrates. As shown in Figure 2, coupling of unsubstituted vinylboronic ester-derived "ate" complex **42** was followed by ^{1}H NMR and found to be a zero-order reaction. Analysis of the effect of individual reaction components showed the process to be first-order in catalyst (order = 1.1) and roughly first-order in electrophile (order = 1.4), but inverse order in "ate" complex (order = –0.9). A catalytic cycle that is consistent with these observations is shown in Figure 3a. The first-order dependence on [PhOTf] suggests turnover-limiting oxidative addition, while the inverse order dependence of reaction rate on [**42**] is accommodated by considering that **42** competes with PhOTf for binding to Pd(0) complex **A**, inhibiting the reaction by formation of a coordination complex **E**.[21]

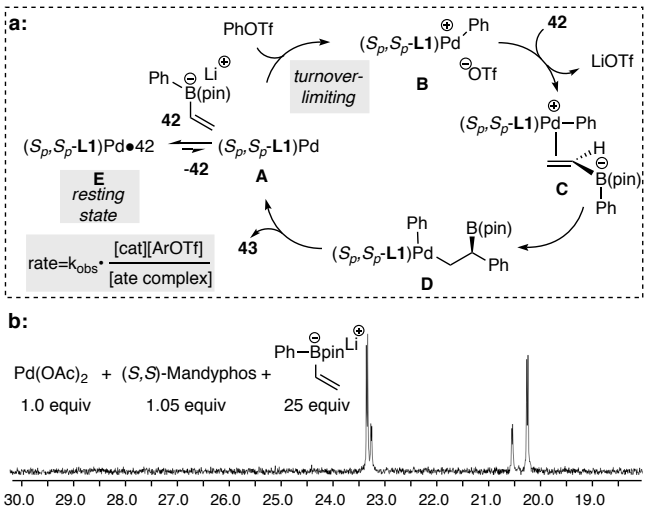

Figure 3. (a) Catalytic cycle consistent with the experimentally determined rate law. (b) ^{31}P NMR of a mixture of $Pd(OAc)_2$, MandyPhos ligand **L1**, and excess ate complex **42** in THF-d_8 under conditions of catalysis; the spectrum is unchanged upon addition of PhOTf.

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Support for the cycle described in Figure 3a was obtained by ^{31}P NMR analysis of a Pd/MandyPhos complex. The kinetic profile of the reaction suggests that complex **E** (Figure 3a) is the catalyst resting state and we found that a species consistent with this structure is generated upon treatment of $Pd(OAc)_2$ with MandyPhos ligand **L1** and an excess of "ate" complex **42**: at 23 °C and 50 °C, the ^{31}P NMR indicates the formation of two isomeric bisphosphine Pd complexes in which the phosphorous atoms within each isomer are non-equivalent.[22] This complex could also be prepared from $Pd_2(dba)_3$, **L1** and excess **42**. Consistent with the claim of **E** being a resting state, addition of PhOTf leads to the catalytic generation of conjunctive coupling product (^{1}H NMR analysis) but no change to the ^{31}P NMR spectrum.

Of relevance to the unanticipated high reactivity of hindered α-substituted alkenylboron-derived "ate" complexes in Table 2, when the kinetic profile of substrate **1** (Table 1, B(pin) derivative) was examined, it also exhibited zero-order kinetics with a rate (rate=2.01 mM/min, see Supplementary Material) near that of the unsubstituted case, indicating that the metallate shift remains a low-activation-barrier step in the catalytic cycle. To gain insight about the effects of substrate substitution on this elementary transformation, it was analyzed by DFT using dppf as a model for the more conformationally flexible MandyPhos ligand. As depicted in Figure 4, the barrier for the metallate shift from the unsubstituted vinyl complex is low, requiring only 5.03 kcal/mol for the ground state olefin complex to reach the transition state. Of note, when the vinyl group is replaced with an isopropenyl group[23] the olefin complex is destabilized by 3.23 kcal/mol; however, the barrier for the metallate shift is smaller (3.82 kcal/mol), such that the overall barrier for the metallate shift of the vinyl substrate is only 1 kcal/mol lower than that for isopropenyl "ate" complexes.[24] For both substrate classes, the metallate shift is highly exergonic suggesting that the unexpected tolerance of conjunctive coupling to highly hindered substrates can be traced to an early transition state for metallate shift where only nascent C-C torsional interactions are present.

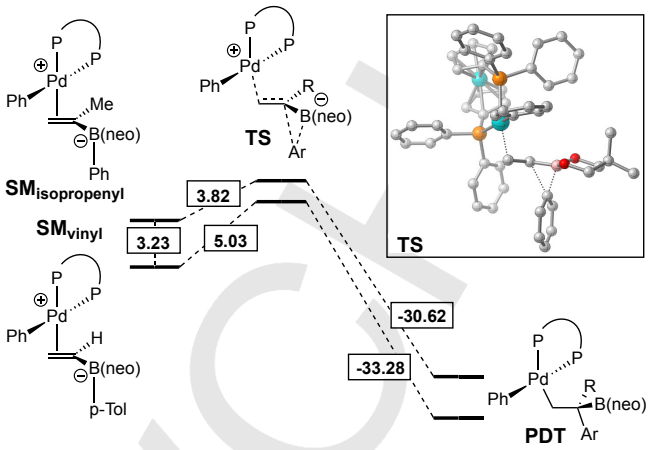

Figure 4. Energetics of Metallate Rearrangement. The ligand on Pd is dppf. Optimized geometries calculated using DFT (BP86/Def2-SVP; PCM solvent model with THF). ΔG Values are in kcal/mol; final energies calculated using DFT (M06/def2-TZVPP//def2-SVP; PCM solvent model with THF). Hydrogen atoms were removed from displayed structure for clarity.

In conclusion, we have established conditions under which the Pd-catalyzed conjunctive cross-coupling can operate on α-substituted boron "ate" complexes in an efficient and selective fashion and deliver versatile tertiary boronic ester products. Mechanistic experiments support a catalytic cycle where oxidative addition is turnover limiting, and the catalyst resting state appears to be an off-cycle Pd(0) coordinated to the "ate" complex, with the C-C bond-forming metallate shift occurring by a low barrier 1,2-migration.

Acknowledgements

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Keywords: Cross Coupling • Boron • Asymmetric Catalysis • Quaternary Center

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[21] Kinetic experiments were performed in triplicate and the complete details are in the Supplementary Material.

[22] Related bisphosphine Pd(0)-enone (dba) complexes exhibiting similar ^{31}P NMR splitting patterns have been characterized. See: a) W. A. Herrmann, W. R. Thiel, C. Broβmer, K. Öfele, T. Priermeier, W. Scherer, *J. Organomet. Chem.* **1993**, *461*, 51. b) J. P. Wolfe, S. Wagaw, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 7215. c) C. Amatore, G. Broeker, A. Jutand, F. Khalil, *J. Am. Chem. Soc.* **1997,** *119,* 5176. d) S. M. Reid, J. T. Mague, M. J. Fink, *J. Organomet. Chem.* **2000**, 616, *10*. While Pd(0)-enone complexes exhibit clear η^2-binding of Pd to the alkene, analysis of the complex between (MandyPhos)Pd(0) and ate complex **42** by ^{1}H NMR does not clearly indicate the nature of the bonding; association of Pd either with the prochiral alkene or the enantiotopic pinacol oxygens would give rise to diastereoisomerism.

[23] To minimize error, regioisomeric substrates were employed for calculations with a *p*-tolyl migrating to a vinyl, and phenyl migrating to the isopropenyl group.

[24] Consistent with the calculated overall barrier difference, in a direct competition experiments (1:1 mixture) the vinyl "ate" complex exhibits ca. 4 times higher reactivity than the isopropenyl derivative.

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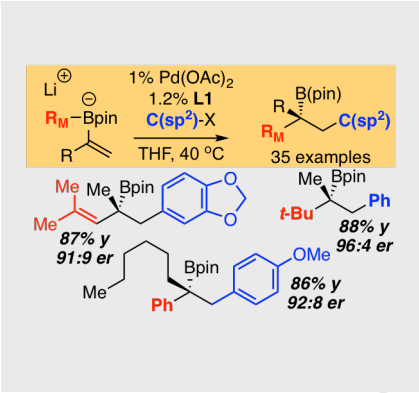
Entry for the Table of Contents

Layout 1:

COMMUNICATION

Catalytic conjunctive cross-coupling has been developed to construct enantiomerically-enriched tertiary alkylboronic esters. These reactions occur with good yield and enantioselectivity for a range of substrates. Mechanistic experiments reveal aspects of the catalytic cycle that allow hindered substrates to react without significant complicating side reactions.



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