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Communication

Enantioselective Allylation of Alkenyl Boronates Promotes a 1,2-Metalate Rearrangement with 1,3-Diastereocontrol

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ABSTRACT: Alkenyl boronates add to Ir(π-allyl) intermediates with high enantioselectivity. A 1,2-metalate shift forms a second C−C bond and sets a 1,3-stereochemical relationship. The three-component coupling provides tertiary boronic esters that can undergo multiple additional functionalizations. An extension to trisubstituted olefins sets three contiguous stereocenters.

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Multicomponent couplings generate complex molecular architectures from simple substrates.[1−3] Enantioselective variants are particularly valuable, especially when multiple stereocenters are set in a single operation.[4,5] Within the field of multicomponent couplings, organoboronic esters have played a prominent role.[6−12] They are widely available and generally

Scheme 1. C−C Bond Formation from Boronate Intermediates

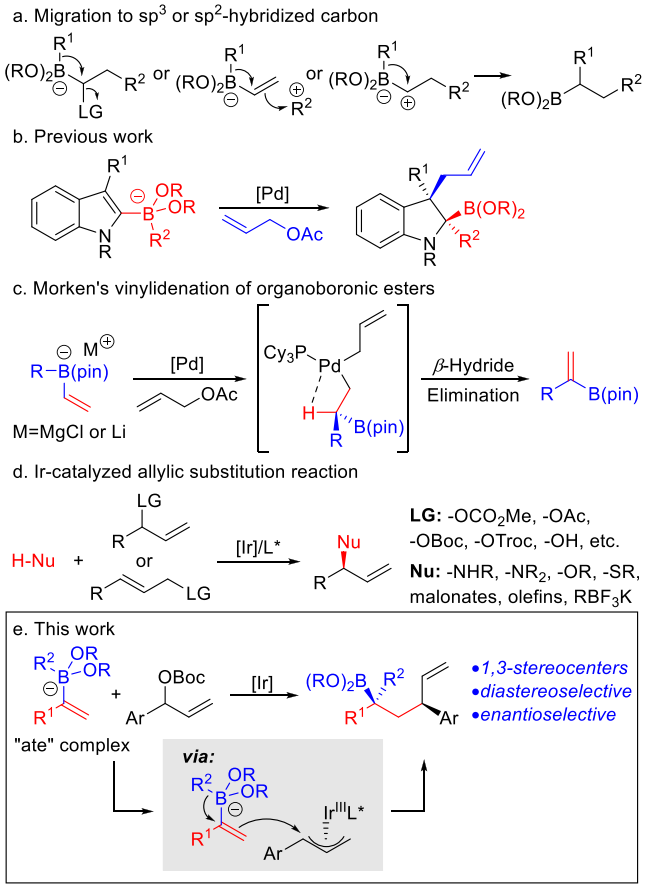
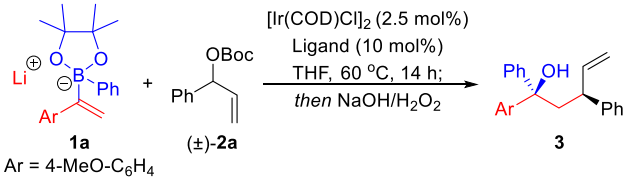
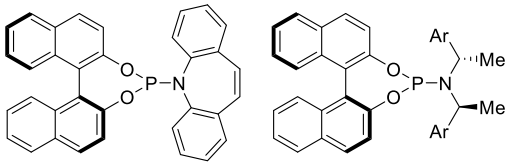


Table 1. Optimization of Ligand and Reaction Conditions[a]



entry	ligand	(±)-**2a** (equiv)	yield (%)	dr	er
1	(*S*)-**L1**	1.1	68	4:1	82:18
2	(*S*)-**L1**	2.1	81	4:1	96:4
3[b]	(*S*)-**L1**	2.1	92	5:1	99:1
4[c]	(*S*)-**L1**	2.1	0	-	-
5[d]	(*S*)-**L1**	1.1	0	-	-
6	(*S*,*S*,*S*$_a$)-**L2**	1.1	54	1:1	61:39
7	(*S*,*S*,*S*$_a$)-**L3**	1.1	42	1:1	58:42



(*S*)-**L1**

(*S*,*S*,*S*$_a$)-**L2**: Ar = Ph
(*S*,*S*,*S*$_a$)-**L3**: Ar = 2-MeO-C$_6$H$_4$

[a]**1a** was preformed using PhLi (1.0 equiv), Et_2O, 0 °C−r.t., 30 min. $[Ir(COD)Cl]_2$ (2.5 mol %) + 10 mol % of the ligand in THF. Isolated yields after oxidation via treatment of boronic ester with NaOH and H_2O_2. The er of the major diastereomer as determined by HPLC analysis. The dr was determined by ^{1}H NMR. [b]1.0 equiv of LiCl was added. [c]The reaction was performed in the absence of a catalyst. [d]Linear cinnamyl *tert*-butyl carbonate was used as the electrophile.

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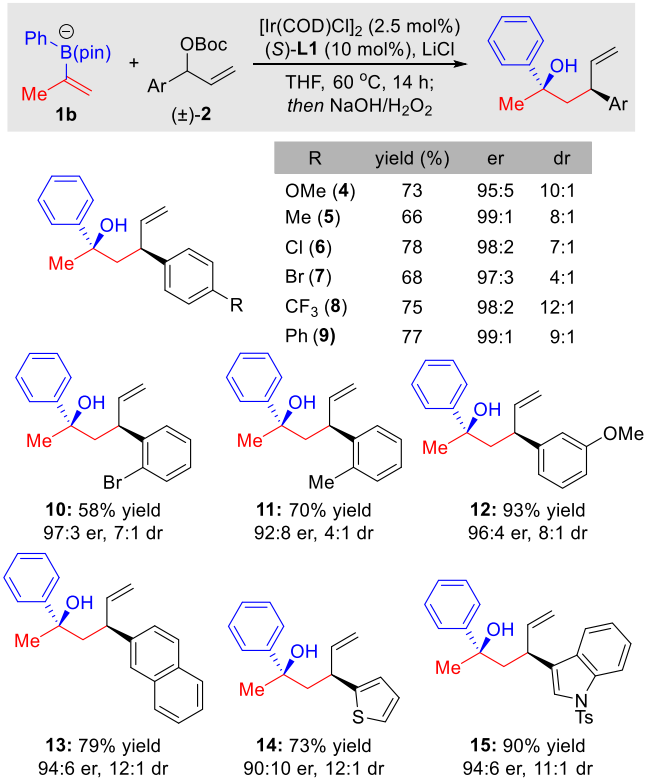
Scheme 2. Scope of Allylic Carbonates[a]



[a]All reactions were conducted in THF (0.3 M) using 2-isopropenylboronic acid, pinacol ester (0.3 mmol), PhLi (0.3 mmol), $[Ir(COD)Cl]_2$ (2.5 mol %), (*S*)-**L1** (10 mol %), allylic carbonates (0.63 mmol), and LiCl (0.3 mmol). Yields of the isolated and purified material after oxidation by treatment of boronic ester with NaOH and H_2O_2. The er of the major diastereomer as determined by HPLC analysis. The dr was determined by ^{1}H NMR.

display good air and moisture stability.[13,14] Furthermore, incorporation of organoboronic esters provides a functional handle for further diversification.[15]

Some of the most valuable transformations of organoboronic esters involve 1,2-metalate shifts from anionic "ate" complexes. 1,2-Migration from boron to an adjacent electrophilic sp^3 hybridized center generally results in expulsion of a leaving group, most notably in the Matteson homologation (Scheme 1a).[16] Alternatively, alkenyl boronates utilize an external electrophilic activator to promote the 1,2-metalate shift (Scheme 1a). For example, halogenation of olefins can induce a metalate rearrangement in the Zweifel olefination[17−20] or Aggarwal arylation.[21−23] Similarly, a dearomatizing 1,2-migration onto heterocyclic rings can be induced via the *N*-acylation of pyridines.[24,25] Finally, radical addition to alkenyl boronates can initiate a 1,2-metalate rearrangement.[26−28]

π-Acidic late transition-metal complexes, such as Pd^{II} and Ni^{II}, can induce a 1,2-migration of an alkyl or aryl fragment of an alkenyl boronate. The conjunctive cross-coupling of vinyl boronate complexes with aryl triflates features inner-sphere activation of vinyl boronates with a $Pd(aryl)^+$ intermediate.[29−34] In related studies, our group developed an enantioselective coupling of indole boronates with allylic acetates to set multiple contiguous stereocenters (Scheme 1b).[35−41] This process may occur via a stepwise process involving an enantioselective allylation followed by a diastereoselective 1,2-metalate rearrangement.

We sought to broaden the scope of this asymmetric allylation to include less reactive alkenyl boronic esters in a multicomponent coupling. However, the Morken group found that a vinyl boronate complex generated 1,1-disubstituted alkenyl boronic esters rather than allylated products in the presence of allyl acetate and a palladium catalyst (Scheme 1c).[42] This vinylidenation was proposed to occur via an inner-sphere mechanism wherein addition of the ate complex to a $Pd^{II}(\pi$-allyl) intermediate was followed by a β-hydride elimination. We speculated that the use of a 1,1-disubstituted alkenyl boronate complex would prevent this pathway and provide access to allylation products. However, several attempts with a variety of ligands and allylic alcohol derivatives in the presence of a palladium catalyst provided poor reactivity and little observable product (see the Supporting Information for details).

We questioned if an alternative metal could promote an outer-sphere mechanism and provide the desired allylation coupling product. In this context, iridium-catalyzed allylic substitution reactions accommodate a wide variety of nucleophiles and electrophiles to provide branched allylic alkylation products with high regioselectivity (Scheme 1d).[43−47] Herein we describe a multicomponent coupling involving alkenyl boronates and $Ir(\pi$-allyl) intermediates that provides tertiary boronic esters and forms nonadjacent stereocenters in an enantio- and diastereoselective manner (Scheme 1e).

We first exposed alkenyl ate complex **1a** (Table 1) to various allylic alcohol derivatives in the presence of several iridium complexes (see the Supporting Information for details). Key findings of the optimization process are highlighted in Table 1.

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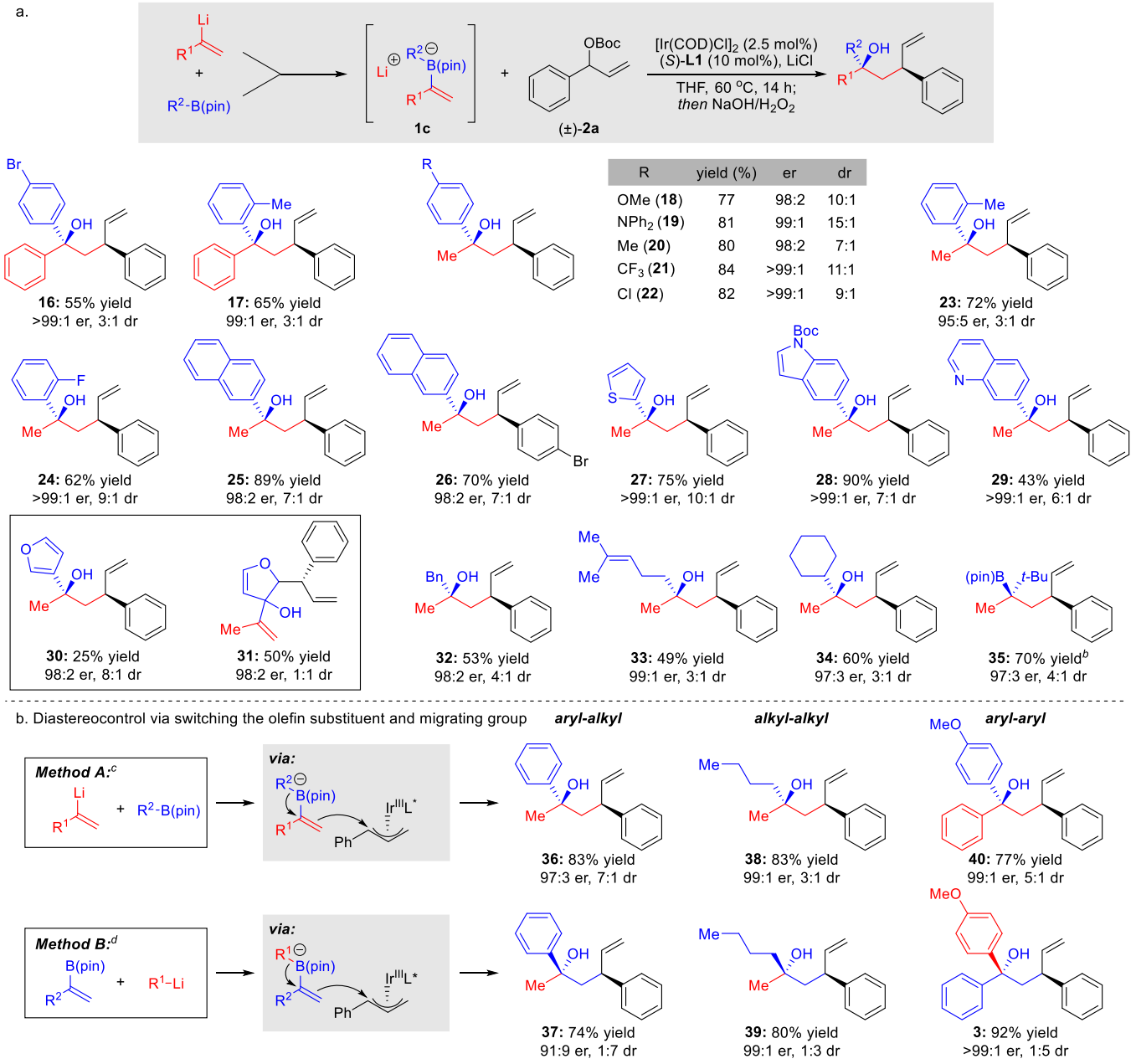
Scheme 3. Scope of Alkenyl Boronates[a]



[a]All reactions were conducted in THF (0.3 M) using boronic ester (0.3 mmol), 2-bromopropene (0.3 mmol), *t*-BuLi (0.6 mmol), $[Ir(COD)Cl]_2$ (2.5 mol %), (*S*)-**L1** (10 mol %), (±)-**2a** (0.63 mmol), and LiCl (0.3 mmol). Yields of the isolated and purified material after oxidation by treatment of boronic ester with NaOH and H_2O_2. The er of the major diastereomer as determined by HPLC analysis. The dr was determined by ^1H NMR. [b]Tertiary boronic esters required extended oxidation times with poor conversion to the corresponding alcohol. [c]Reactions were conducted using either isopropenyllithium (0.3 mmol) or α-lithiostyrene (0.3 mmol) and the corresponding boronic ester (0.3 mmol). [d]Reactions were conducted using oganolithium (0.3 mmol) and the corresponding 1,1-disubstituted alkenylboronic ester (0.3 mmol).

Typically, the organoboronic ester product was oxidized to the alcohol derivative, although isolation of the organoboron product is possible (see Scheme 4). The best results were obtained with Carreira's phosphoramidite ligand, (*S*)-**L1**.[48−51] Our initial attempt with 1.1 equiv of (±)-**2a** in the presence of $[Ir(COD)Cl]_2$ and (*S*)-**L1** provided alcohol **3** in 68% yield and 4:1 dr, with the major diastereomer displaying 82:18 er (entry 1). We speculated that (±)-**2a** might be undergoing a kinetic resolution under the reaction conditions.[52−56] Accordingly, upon increasing the carbonate loading to 2.1 equiv, we obtained product **3** in improved yields and enantioselectivity (entry 2). Addition of LiCl[57] further improved the yield and dr, with the major diastereomer now displaying excellent er (entry 3). Absence of the catalyst (entry 4) and use of the linear cinnamyl *tert*-butyl carbonate provided no observed product (entry 5). Catalysts featuring Feringa's phosphoramidite ligands (S,S,S_a)-**L2** and (S,S,S_a)-**L3** provided only modest yields, no diastereoselectivity, and poor er (entries 6, 7).

We next explored the scope of secondary allylic carbonates that were compatible with these reaction conditions (Scheme 2). Under optimized conditions, consistently high yields,

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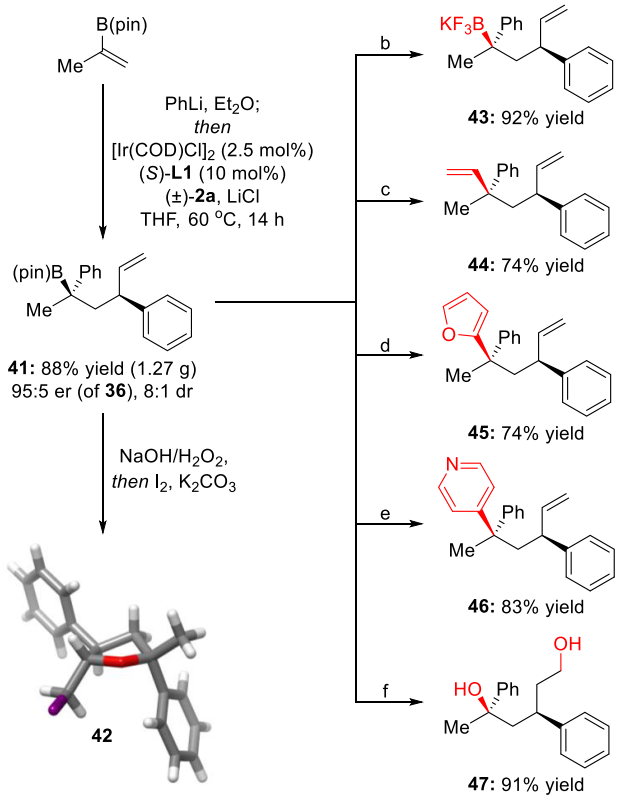
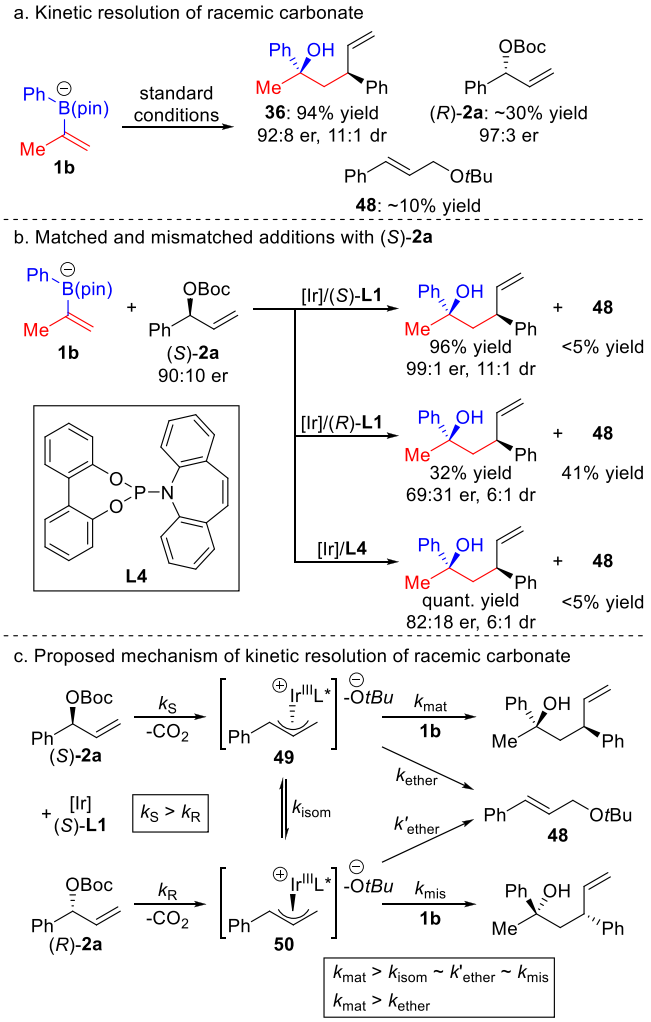
Scheme 4. Synthetic Transformations of Tertiary Boronic Ester[a]



[a]The reaction was conducted in THF (0.3 M) using 2-isopropenylboronic acid, pinacol ester (4.0 mmol), PhLi (4.0 mmol), $[Ir(COD)Cl]_2$ (2.5 mol %), (*S*)-L1 (10 mol %), (±)-**2a** (8.2 mmol), and LiCl (4.0 mmol). The er of the major diastereomer as determined by HPLC analysis of the gram-scale reaction of **41** after oxidation. The dr was determined by ^{1}H NMR. All yields refer to isolated yields of the purified material. [b]KHF_2. [c]Vinyl lithium, then I_2, and then NaOMe. [d]ArLi and then NBS. [e]ArLi, then 2,2,2-trichloroethyl chloroformate, and then $NaOH/H_2O_2$. [f]BH3·DMS and then $NaOH/H_2O_2$.

Scheme 5. Mechanistic Studies[a]



[a]All reactions were conducted on a 0.3 mmol scale using PhLi (0.3 mmol), 2-isopropenylboronic acid, pinacol ester (0.3 mmol), $[Ir(COD)Cl]_2$ (2.5 mol %), ligand (10 mol %), secondary phenyl carbonate (0.63 mmol), and LiCl (0.3 mmol). Isolated yields after oxidation by treatment with NaOH and H_2O_2. The er of the major diastereomer as determined by HPLC. The dr was determined by ^{1}H NMR.

enantioselectivities, and diastereoselectivities were observed with electron-donating (**4**, **5**) and electron-withdrawing groups (**6**–**9**). Likewise, ortho-substituted aryl secondary allylic carbonates **10** and **11** were compatible. The 3-methoxyphenyl carbonate (**12**) displayed excellent yield and selectivity, while the bulkier 2-naphthyl-derived carbonate (**13**) reacted with improved dr and similar er. Carbonates featuring heterocycles such as 2-thiophene or 3-indole (**14**, **15**) provided similarly high selectivity. Aliphatic secondary carbonates failed to provide the desired product under the current reaction conditions.

Alkenyl ate species can be accessed either through addition of lithium reagents to alkenyl boronic esters or through addition of alkenyl lithium reagents to RB(pin) substates. We adopted the latter approach to further explore the scope of the coupling by virtue of the wide commercial availability of boronic esters (Scheme 3a). We first synthesized bis-aryl, tertiary alcohols from the addition of aryl boronic esters to preformed α-lithiostyrene. Both electron-withdrawing (**16**) and electron-donating (**17**) aryl boronic esters were tolerated with moderate to high yields, excellent enantioselectivities, and modest diastereoselectivities. The stability of an aryl bromide under the reaction conditions involving organolithium species is noteworthy. Addition of boronic esters to preformed isopropenyllithium allowed us to explore a wide range of aryl and alkyl boronic esters. With regards to para-substituted boronic esters, high yields and selectivities were observed with both electron-donating (**18**, **19**, **20**) and electron-withdrawing groups (**21**, **22**). Methyl and fluoro groups were accommodated in the ortho position (**23**, **24**), with somewhat higher enantio- and diastereoselectivity being observed with the fluorinated substrate. Bulkier 2-naphthylboronic esters (**25**, **26**) also provided the desired product in excellent yield and stereoselectivity. Heterocyclic boronic esters (**27**, **28**, **29**) provided the desired products in high yields, with excellent er and dr. Interestingly, 3-furylboronic ester provided low yields of the desired product **30** due to a dearomatizing 1,2-migration, which provided dihydrofuran **31** in 50% yield as a 1:1 mixture of unassigned diastereomers.[21] The anticipated alkenyl addition product **30** and the dihydrofuran **31** were both recovered with 98:2 er. Finally, we explored the scope of

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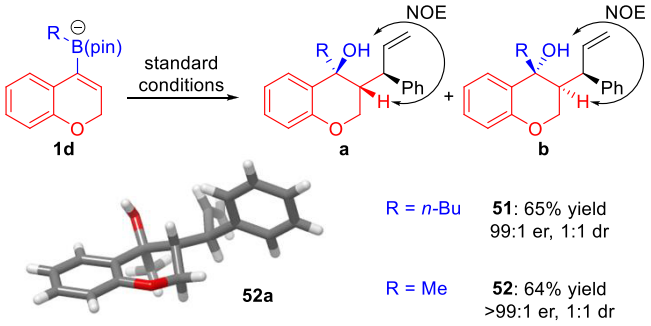
Scheme 6. Setting Three Contiguous Stereocenters[a]



[a]The reaction was conducted on a 0.3 mmol scale using 2-bromo-2*H*-chromene (0.3 mmol), *s*-BuLi (0.3 mmol), boronic ester (0.3 mmol), $[Ir(COD)Cl]_2$ (2.5 mol %), (*S*)-**L1** (10 mol %), (±)-**2a** (0.63 mmol), and LiCl (0.3 mmol). Yields of the isolated and purified material after oxidation by treatment of boronic ester with NaOH and H_2O_2. The er of the major diastereomer as determined by HPLC analysis. The dr determined by ^{1}H NMR.

alkyl-derived ate complexes. Primary (**32**, **33**), secondary (**34**), and tertiary (**35**) boronic esters all coupled cleanly and selectively. Coupling products derived from tertiary boronic esters often provided poor conversion to the alcohol (**35**) during oxidation.

Diastereomeric products could be accessed by switching the migrating group and the olefin substituent (Scheme 3b). For example, addition of isopropenyllithium to phenyl boronic ester provided **36** from R^2 = Ph as the migrating organic fragment. Alternatively, addition of methyllithium to 2-boryl styrene provided the diastereomeric product **37** as a consequence of R^1 = Me now participating in the migration step. We have demonstrated this flexibility with aryl−alkyl (**36**, **37**), alkyl−alkyl (**38**, **39**), and aryl−aryl (**40**, **3**) derived tertiary alcohols with similar yields and enantioselectivities of the major diastereomer in each case.

To explore the synthetic utility of asymmetric allylation, the coupling reaction was executed on a gram-scale to provide tertiary boronic ester **41** in 88% yield and 8:1 dr and 95:5 er (Scheme 4). Next, synthetic transformations were performed on boronic ester **41** to demonstrate the compatibility of these compounds for derivatizations. Oxidation of **41** followed by iodoetherification of the tertiary alcohol provided crystalline iodide **42**, which established absolute and relative stereochemistry. Other useful synthetic intermediates were prepared, such as the trifluoroborate salt (**43**)[58] and diene (**44**).[59] The boronic ester was arylated to provide both the furan (**45**)[21] and pyridine (**46**)[25] using transition-metal-free cross-coupling chemistry. Finally, hydroboration/oxidation provided diol **47**. In all cases, good to excellent yields were obtained with retention of stereochemistry.

Mechanistic Considerations. The Carreira group has investigated the mechanisms of allylic substitution reactions catalyzed by Ir[(*S*)-**L1**] complexes.[60] However, the addition of alkenyl boronates to Ir(π-allyl) intermediates and the associated metalate shift gave rise to some interesting mechanistic questions. To determine if the racemic carbonate was undergoing a kinetic resolution, we conducted the allylation using ate complex **1b** and isolated both the product **36** and the unreacted starting material (Scheme 5). Recovered carbonate (*R*)-**2a** was isolated in 97:3 enantioselectivity, indicating that an efficient kinetic resolution had occurred (Scheme 5a).[61] We also isolated cinnamyl *tert*-butyl ether **48**, which could arise from the decomposition of the Ir^{III}(π-allyl) intermediate derived from the less reactive enantiomer of the carbonate.[53,54] To further illustrate this mechanistic hypothesis, the reaction was probed with enantioenriched carbonate (*S*)-**2a** using either (*S*)-**L1** or (*R*)-**L1** (Scheme 5b). Ligand (*S*)-**L1** provided the desired product in 96% yield with excellent stereoselectivity and no observable byproduct. Alternatively, ligand (*R*)-**L1** provided the three-component coupling product in only 32% yield with greatly diminished enantioselectivity. The linear cinnamyl ether **48** was obtained in comparable yields. Lastly, enantioenriched carbonate (*S*)-**2a** was coupled with boronate **1b** in the presence of achiral ligand **L4** to obtain the product in quantitative yield with a slight drop in the er compared to (*S*)-**2a** (Scheme 5b). From these results, a proposed mechanism of the pathway is shown in Scheme 5c. First, the racemic allylic carbonate undergoes a kinetic resolution by the Ir(phosphoramidite) complex to provide diastereomeric Ir^{III}(π-allyl) intermediates **49** and **50**, wherein $k_S > k_R$. Loss of carbon dioxide renders the oxidative addition step irreversible. The Ir^{III}(π-allyl) intermediates can then either react with alkenyl boronate to form the desired product or react with *tert*-butoxide to form ether **48**.

Quantitative assessment of the various reaction pathways accessible to the Ir^{III}(π-allyl) intermediates will require additional investigation, but qualitative conclusions can be drawn with existing data. The rate of product formation from the fast-reacting enantiomer (k_{mat}) is much faster than the rate of ether formation (k_{ether}). This conclusion arises from the observation that little ether was observed when optically active substrate (*S*)-**2a** reacted in the presence of the matched ligand. Alternatively, the rate of product formation from the slower-reacting enantiomer (k_{mis}) is similar to the rate of etherification (k'_{ether}) because the mismatched reaction formed ether **48** and the coupled product in similar yields. Moreover, π−σ−π isomerization of the Ir^{III}(π-allyl) complex is slower than the matched reaction ($k_{mat} > k_{isom}$) based on the modest drop in optical activity observed using the enantioenriched substrate and the achiral ligand **L4** (Scheme 5b). However, the mismatched reaction of (*S*)-**2a** in the presence of (*R*)-**L1** proceeded with substantial epimerization to give the same major enantiomer of product as from (*R*)-**2a**, indicating that $k_{isom} \sim k_{mis}$. Taken together, the results indicate the chiral ligand (*S*)-**L1** affects the enantioselectivity of the reaction through effects on both the oxidative addition step and the addition of the alkenyl boronate nucleophile.

To gain insight into the diastereoselectivity of the reaction, we investigated trisubstituted boronate **1d** to form three contiguous stereocenters (Scheme 6).[35,62,63] Under optimized conditions, product **51** (R = *n*-Bu) was isolated in 65% yield as a 1:1 mixture of diastereomers, both of which display 99:1 er. Likewise, **52** (R = Me) was obtained in similar yield and stereoselectivity. In both diastereomers of both products, irradiation of the benzopyran methine showed an NOE signal corresponding to the OH hydrogen, while we observed no correlation between the butyl or methyl group with the adjacent sp^3-hybridized methine. The NMR data is bolstered by an X-ray crystal of **52a**. This evidence suggests the surprising conclusion that both diastereomers result from a cis addition of the migrating R group and the allyl fragment across the olefin, with the diastereomers arising from opposite facial selectivity. Understanding the mode of addition for disubstituted alkenyl boronate complexes is an ongoing effort.

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Conclusions. In summary, we have showcased a three-component coupling of organolithium reagents, organoboronic esters, and secondary allylic aryl carbonates. Significant findings include (1) expansion of the scope of suitable nucleophiles to engage Ir(π-allyl) intermediates to include alkenyl boronates; (2) the establishment of two new C−C bonds and two nonadjacent stereocenters in a single operation; and (3) the ability to set three contiguous stereocenters using trisubstituted ate complexes. Ongoing work seeks to better understand the addition of alkenyl ate complexes into Ir(π-allyl) intermediates and the generality of this reaction in the formation of multiple stereocenters.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c01242.

Experimental procedures, characterization data, spectra, and crystal data for **42** and **52a** (PDF)

Accession Codes

CCDC 2060331 and 2068375 contain 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 no competing financial interest.

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