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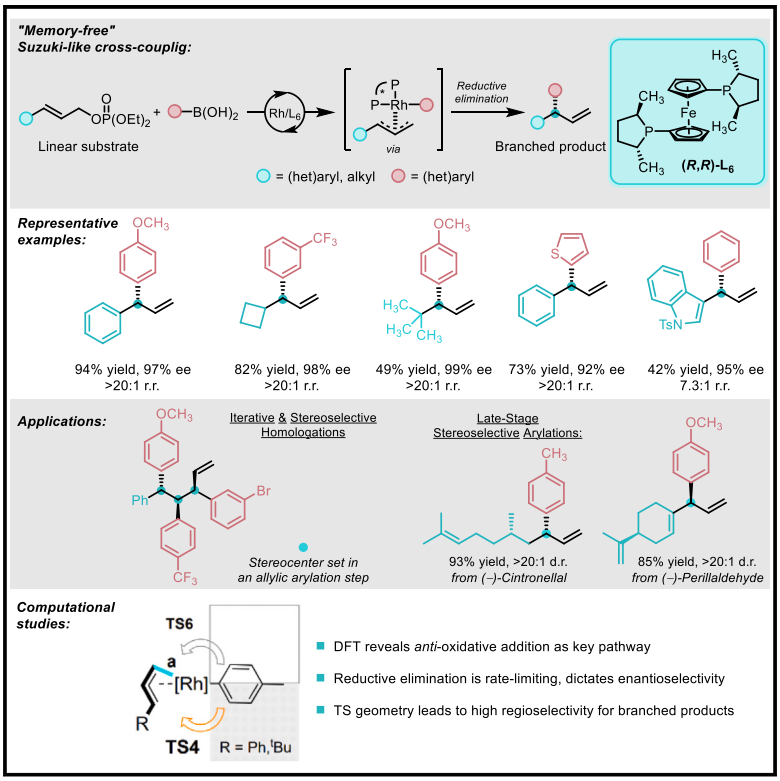
Ligand-enabled override of the memory effect in Rh-catalyzed asymmetric Suzuki reactions

Graphical abstract



Highlights

- Developed an asymmetric Suzuki-type cross-coupling to give branched allylic products
- Broadly applicable to sterically demanding substrates and existing stereogenic centers
- Enables iterative synthesis of contiguous centers with full ligand control
- Mechanistic studies identify reductive elimination as the enantio-determining step

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In brief

Chiral allylic building blocks are pivotal in fields spanning pharmaceuticals to polymers. Here, a Suzuki-type cross-coupling overcomes the long-standing problem in Rh-catalyzed systems known as the "memory effect", to yield branched allylic products from either branched or linear substrates. The method broadens the synthetic toolbox for C–C bond formation, as it tolerates a remarkably wide range of nucleophiles and electrophiles, and it enables the iterative expansion of stereochemical complexity by allowing the synthesis of 1,2-polyaryl chains with total ligand-controlled stereoselectivity.

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Ligand-enabled override of the memory effect in Rh-catalyzed asymmetric Suzuki reactions

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THE BIGGER PICTURE Carbon–carbon bonds are fundamental to the structure of countless molecules central to life, including pharmaceuticals, natural products, and materials. However, constructing these bonds with precise stereochemical control remains a significant challenge, especially when working with prochiral allylic substrates and (hetero)aryl nucleophiles. This work addresses a major limitation in rhodium-catalyzed reactions—the so-called "memory effect"—to enable a broadly applicable regioselective and stereoselective method for allylic arylation with (hetero)aryl nucleophiles.

SUMMARY

Chiral non-racemic allylic species are key building blocks for many carbon-containing molecules, including pharmaceuticals and polymers. Metal-catalyzed asymmetric additions of nucleophiles to allylic species undergo different pathways depending on the metal and nucleophile combination, hindering the development of useful addition reactions with aromatic nucleophiles. We report an asymmetric cross-coupling method between aryl boronic acids and linear allylic phosphates to give branched allylic products. This Suzuki-type reaction overcomes the "memory effect" in Rh catalysis, enabling an overall SN2′ transformation by rate-determining reductive elimination and forming a new stereogenic center adjacent to a terminal vinyl moiety. The method tolerates preexisting stereogenic centers, allowing for synthetic strategies where drugs and natural products are elaborated via diastereoselective allylic arylations. The method is used, as the catalyst-controlled stereochemistry-setting step, in an iterative strategy to give arrays of aryl-substituted contiguous stereogenic centers. This approach will complement existing catalyst-controlled stereoselective methods for forming C–C bonds.

INTRODUCTION

Branched allylic compounds are important building blocks in the synthesis of natural products, pharmaceuticals, and agrochemicals due to the allylic moiety's versatility in further transformations.[1] Direct cross-coupling between allylic (pseudo)halides and nucleophiles represents a straightforward approach via regioselective and enantioselective formation of C–C or C–X bonds.[2] Significant progress has been achieved in developing Pd-,[2,3] Ni-,[4] Rh-,[5] and Cu-[6]catalyzed enantioselective substitution reactions of allylic species with various nucleophiles. Iridium complexes, in particular, are highly effective catalysts because they typically yield branched products when allylic electrophiles with one terminal substituent are used, while other transition-metal catalysts tend to give achiral linear products. Over the past two decades, Ir-catalyzed asymmetric allylic substitutions have accommodated a wide variety of (stabilized) nucleophiles and proven to be a powerful tool to construct complex molecules.[7–12] However, Ir catalysis often exhibits limited compatibility with organometallic reagents,[8] especially with (hetero)aryl organometallic reagents, making selective asymmetric allylic arylation challenging (Figure 1A).[13] Although some reports highlight using aryl nucleophiles with catalysts based on other transition metals,[14–20] these methods typically need an aryl-substituted allylic electrophile to afford good reactivity and/or enantioselectivity. It is important to develop versatile stereoselective allylic

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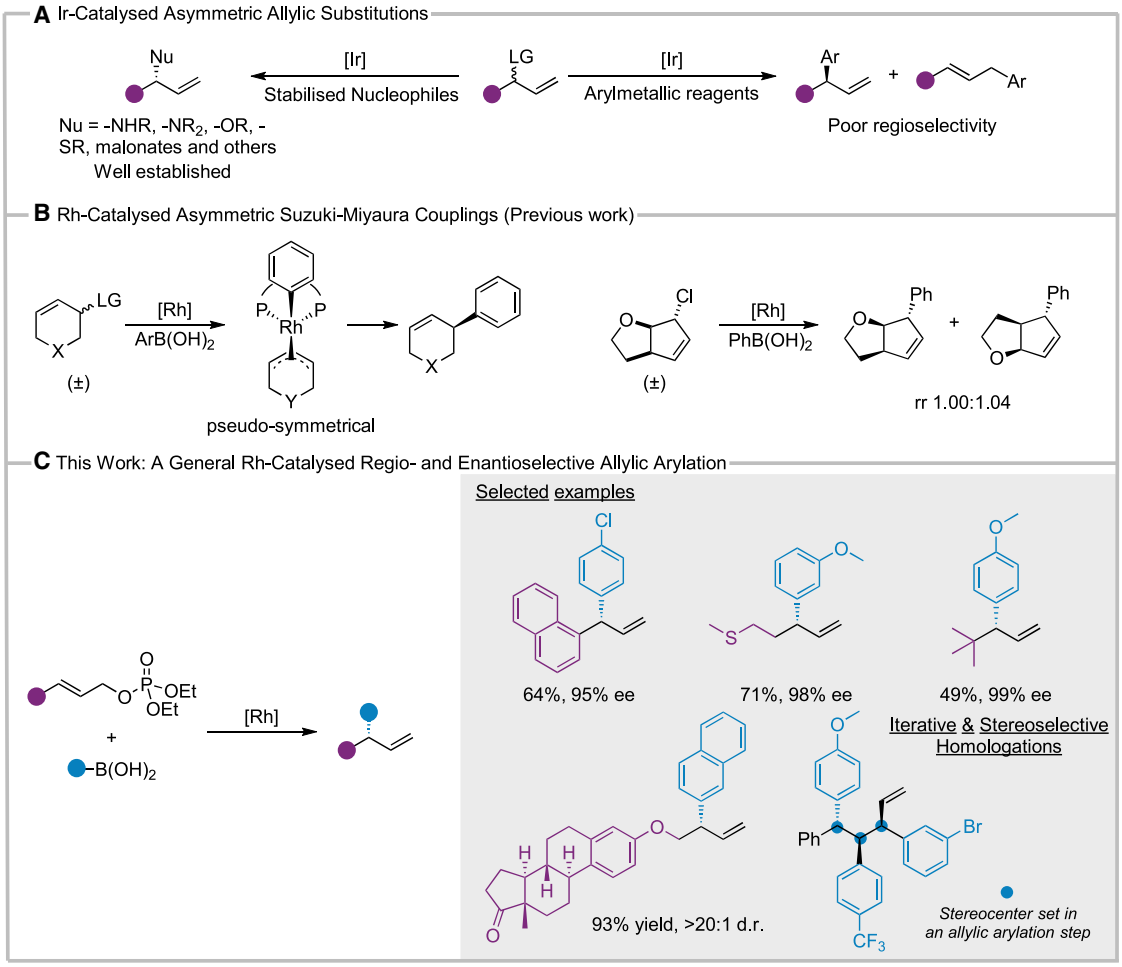

Figure 1. Motivation

(A) Ir-catalyzed asymmetric allylic substitutions.

(B) Rh-catalyzed asymmetric Suzuki-Miyaura couplings (previous work).

(C) This work: a general Rh-catalyzed regioselective and enantioselective allylic arylation.

arylation methods because the field lacks useful methods for using (hetero)aryl nucleophiles to access important branched allylic products, and known methods are not robust enough to be used in complex molecule synthesis beyond the preparation of relatively simple building blocks.

Rh-catalyzed allylic substitutions are believed to exhibit a "memory effect" causing the nucleophile to predominately attack at the position of the leaving group.[21–29] Therefore, Rh-catalyzed branched selective allylic arylations are dominated by using branched allylic (pseudo)halide substrates,[24,30–33] including an example from the You group where racemic branched allylic carbonates were arylated using boronic acids.[29] Very few examples of Rh-catalyzed asymmetric allylic substitution of prochiral allylic electrophiles with achiral nucleophile are known,[34,35]—none of which use non-stabilized (pKa > 25) nucleophiles. Rh-catalyzed arylations of racemic cyclic allylic halides with (hetero)arylboronic acid derivatives have been reported,[5,36–39] but to allow enantioconvergent transformations to take place, a pseudo-symmetrical η^3 Rh-π-allyl intermediate is required (Figure 1B, left),[37,38] severely limiting the scope of these Suzuki-Miyaura-type couplings. Generally, no regioselectivity is observed when electrophiles that lack symmetry about the allylic leaving group are employed (Figure 1B, right),[39] but chelation has recently been reported to enable regioselective and enantioselective arylations.[40,41]

RESULTS AND DISCUSSION

We envisioned that chiral Rh-based catalyst systems, which could mitigate the memory effect and selectively form aryl-substituted branched products regardless of the substrate isomer used, would be tremendously useful. We imagined such a system could operate by controlling σ-π-σ isomerization, and enantioinduction would occur via dynamic kinetic asymmetric processes.[5,42,43] Here, we report asymmetric allylic arylation reaction using acyclic substrates and a commercially available ligand (**L6**, Table 1), where either branched (Table 1, entry 8) or linear (entry 13) starting materials can be used. We prefer

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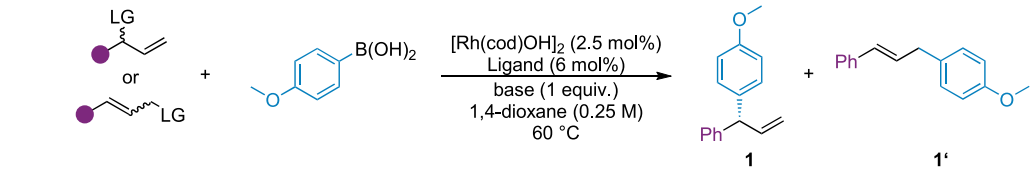
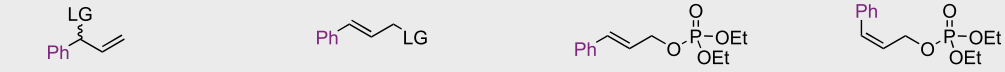
Table 1. Reaction optimization



Electrophiles:



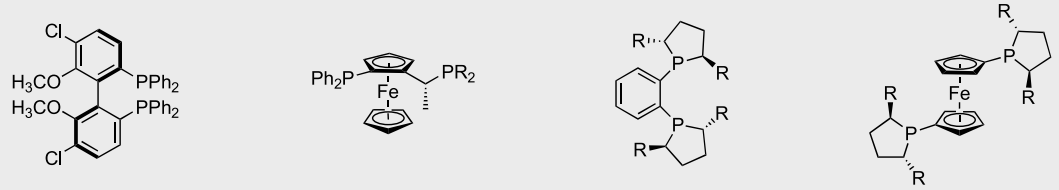
E1 LG = OAc
E2 LG = $OCOOCH_3$
E3 LG = OBoc

E4 LG = OAc
E5 LG = $OCOOCH_3$

E6

E7

Ligands:



L1

L2 R = Cy
L3 R = ^{t}Bu

L4 R = Me
L5 R = Et

L6 R = Me

Entry	Electrophile	Ligand	Base	Yield (%)[a]	ee (%)[b]	rr (1/1′)[c]
1	**E1**	**L1**	$NaOCH_3$	26[c]	94	1:1
2	**E1**	**L2**	$NaOCH_3$	75[c]	88	4:1
3	**E1**	**L3**	$NaOCH_3$	47	>99	1.9:1
4	**E1**	**L4**	$NaOCH_3$	81[c]	76	8.1:1
5	**E1**	**L5**	$NaOCH_3$	99[c]	36	8.1:1
6	**E1**	**L6**	$NaOCH_3$	54	98	>20:1
7	**E2**	**L6**	$NaOCH_3$	42	97	7.3:1
8	**E3**	**L6**	$NaOCH_3$	71	97	7.3:1
9	**E4**	**L6**	$NaOCH_3$	N. R.	–	–
10	**E5**	**L6**	$NaOCH_3$	29	94	>20:1
11	**E6**	**L6**	$NaOCH_3$	89	96	>20:1
12	**E7**	**L6**	$NaOCH_3$	49	82	10:1
13	**E6**	**L6**	K_3PO_4	94	97	>20:1

Reaction conditions: electrophile (0.4 mmol, 1 equiv), *para*-methoxyphenylboronic acid (1.2 mmol, 3 equiv), $[Rh(cod)OH]_2$ (0.01 mmol, 2.5 mol %), ligand (0.024 mmol, 6 mol %), base (0.4 mmol, 1 equiv), 1,4-dioxane (1.6 mL, c = 0.25 M), 60°C, 16 h. Absolute configuration of 1 was determined by comparing signs of optical rotation to the previously reported value of compound (+)-(*R*)-1-methoxy-4-(1-phenylallyl)benzene.[15] N. R., no reaction.
[a]Isolated yields of **1** and **1′**.
[b]The ee values were determined by upercritical fluid chromatography (SFC) analysis on a chiral non-racemic stationary phase.
[c]Determined by ^{1}H NMR analysis of the reaction mixture.

using—and therefore further developed—linear starting materials because (1) we observed better regioselectivities with linear substrates in initial screening (Table 1, ~7:1 vs. >20:1); (2) we were concerned that branched allylic alcohol-derived starting materials might not be synthetically (or thermodynamically) accessible in the case of sterically demanding substrates, ultimately limiting the scope of the reaction; and (3) it overcomes the canonical memory effect.

We initially selected branched acetate **E1** as a model electrophile in combination with a variety of C_2-symmetrical bisphosphine ligands used in other Rh-catalyzed reactions[36,39,40] (Table 1, entry 1; see supplemental information for additional data). While **L1** gave good enantioselectivity (94%), the linear and branched regioisomers were obtained in a 1:1 ratio. Josiphos **L2** showed improved regioselectivity (4:1) but <90% ee (Table 1, entry 2), while **L3** showed perfect

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enantiocontrol (>99% ee) but poor regioselectivity (1.9:1) (Table 1, entry 3).

DuPhos ligands **L4** and **L5** produced an 8.1:1 mixture of regioisomers with poor ee (entries 4 and 5), but ferrocene-derived DuPhos **L6** delivered both excellent regioselectivity (>20:1) and enantioselectivity (98% ee), although only in 54% isolated yield (Table 1, entry 6), in which starting **E1** could be recovered in ~15% ee. With the aim of increasing the yield, we tested different allylic electrophiles (Table 1, entries 7–12). Branched carbonates **E2** and **E3** gave reduced (<8:1) regioselectivity (entries 7 and 8). Linear acetate **E4** did not appear to undergo any reaction under the examined conditions, leading to the recovery of **E4** (Table 1, entry 9), whereas carbonate **E5** provided **1** in low yield (29%) but with good regioselectivity and enantioselectivity (Table 1, entry 10), and (*E*)-phosphate **E6** was found to give **1** in 89% yield with >20:1 rr and 96% ee (Table 1, entry 11). Interestingly, using the double-bond isomer of **E6**—(*Z*)-phosphate **E7**—gave drastically reduced yield (49%) and selectivity (82% ee, 10:1 rr) (Table 1, entry 12). The different outcome observed with **E7** may be due to variations in the structures of intermediates formed. We were able to improve the yield with **E6** by using K_3PO_4 without compromising regioselectivity or enantioselectivity (94%, >20:1 rr, and 97% ee; Table 1, entry 13).

We investigated the scope of boronic acids that could be used with linear phosphate **E6** (Figure 2A). The reaction accommodates a range of electron-rich and electron-poor substituents at the *para*-position (**1**–**7**). We note that, surprisingly, an ester-containing boronic acid gave lower regioselectivity than normal (**6**, 4:1), while a *para*-ketone-containing boronic acid gave **7** with 97% yield, 97% ee, and >20:1 rr. Meta-substituted arylboronic acids were well tolerated in the reaction, including those featuring methylsulfide (**9**), vinyl (**13**), free hydroxyl (**14**), and ester (**15**) groups, delivering the desired products with high yields (>80%) and selectivities (>20:1 rr and >95% ee).

Ortho-substituted arylboronic acids are typically challenging in Rh-catalyzed asymmetric addition reactions, and here, *ortho*-methylphenylboronic acid afford branched **16** with 87% ee and >20:1 rr, albeit in 28% yield. Less hindered *ortho*-fluorophenylboronic acid afforded product **17** with excellent yield and selectivities (83% yield, >20:1 rr, and 99% ee). Furthermore, a range of heteroarylboronic acids, which are commonly found in pharmaceutical agents,[44] was found to be compatible with this method. Thiophene, dibenzofuran, dibenzothiophene, and indazole-derived boronic acids performed well (**21** and **24**–**27**). In the case of thiophene-derived boronic acids **21** and **22**, lower ee values (92%–94% ee) were observed, as well as lesser regioselectivity in the case of **22** (12:1) and only 31% yield when forming benzofuran **23**.

Next, we examined the scope of aryl-substituted allylic electrophiles (Figure 2B). In comparison to relevant methods,[14–20] the scope of the current reaction is excellent, with a wide variety of non-trivial substitution patterns, such as 3,4-dichloro-substituted **28** and **29**, and challenging *ortho*-substituted halides and sterically and electronically demanding groups tolerated. As an example of a highly challenging heteroaromatic substituent, we examined an indole-derived electrophile that gave **37** in 7.3:1 rr with 42% yield and 95% ee.

The method proved to tolerate a wide range of alkyl-substituted allylic phosphates, which is incompatible with relevant asymmetric allylic arylations,[15,18,20] without any modification of the reaction conditions. A methyl-substituted electrophile produced products **38** and **39** with >99% ee and excellent yields and regioselectivity. A variety of substituted alkyl chains featuring phenyls (**40** and **41**), ethers (**42** and **43**), and thioethers (**44** and **45**) were tolerated despite the potential of these functional groups to bind to transition metals and interfere with catalysis. A chloro-containing electrophile provided **46** and **47** (both >80% and >93% ee), but in one case, a small amount of linear byproduct was observed (**47**, 16:1 rr). Using an electrophile containing a *cis*-alkene, which could potentially react under these conditions, we obtained **48** in 95% yield and 98% ee and **49** in 96% yield and 98% ee, with no sign of olefin isomerization, carbometallation, or chain walking. Remarkably, even a highly hindered ^{t}Bu-substituted electrophile gave products **54** and **55** under standard conditions with >99% ee. Alkenyl boronic acids or esters were not compatible with the current methodology (see supplemental information).

To investigate the rationale behind high enantioselectivity and regioselectivity, we carried out computational studies of the catalytic cycle and competing transition structures (TSs). Experimentally, rapid transmetalation is observed between Rh(I) and arylboronic acids,[38] and so our calculations start from the Rh-aryl complex [**Rh**], along with dimethyl phosphonate for conformational simplicity. Density functional theory (DFT) calculations were performed at the M-11L/6-311+G(d,p),SDD//B3LYP-D3/6-31G(d),LANL2DZ(f)) level of theory with solvation model based on density (SMD) solvation (1,4-dioxane).

We computed the competing pathways that lead to the formation of **2**, the major branched product (***R*-prod**), and its enantiomer (***S*-prod**) (lowest energy pathways are shown Figure 3A). The Rh(I)-aryl intermediate bound to chiral bisphosphine **L6** ([**Rh**]) can undergo syn- or anti-oxidative addition (OA) to either *Re* or *Si* face of the allyl phosphonate, depending on which alkene enantioface the metal is coordinated. The anti-OA has a lower energy barrier (**TS1** and **TS2** with $\Delta G^{\ddagger}$ of 12.5 and 16.9 kcal/mol with respect to separated species) than the *syn*-OA pathway (see supplemental information). In these OA TSs (**TS1** and **TS2**), the forming C–Rh bond is *anti*- to the breaking C–O bond, resembling an S_N2' nucleophilic addition, giving cationic η^3-Rh complexes (**int1** and **int2**). Alternative, less stable conformers were computed (see supplemental information). Intermediates **int1** and **int2** can undergo reductive elimination (RE) via competing TSs at internal (**TS3** and **TS4**) or external positions (**TS5** and **TS6**) (Figure 3B). We found RE to be the rate- and enantio-determining step, which occurs irreversibly. RE barriers to form linear products are significantly higher, by 5.8–6.5 kcal/mol, compared with the most stable branched pathway via **TS3** (predicted regioisomeric ratio exceeding 99.9% for ***R*-prod**).Competing diastereomeric TSs yielding the major and minor enantiomer of the branched product (***R*-prod** and ***S*-prod**) differ by 3.1 kcal/mol, with a predicted selectivity of 98.2% ee at 60°C. These computational data are quantitatively consistent with experimental observations. Based on the computed potential energy surface (PES), we predict that OA will occur reversibly, such that the interconversion between

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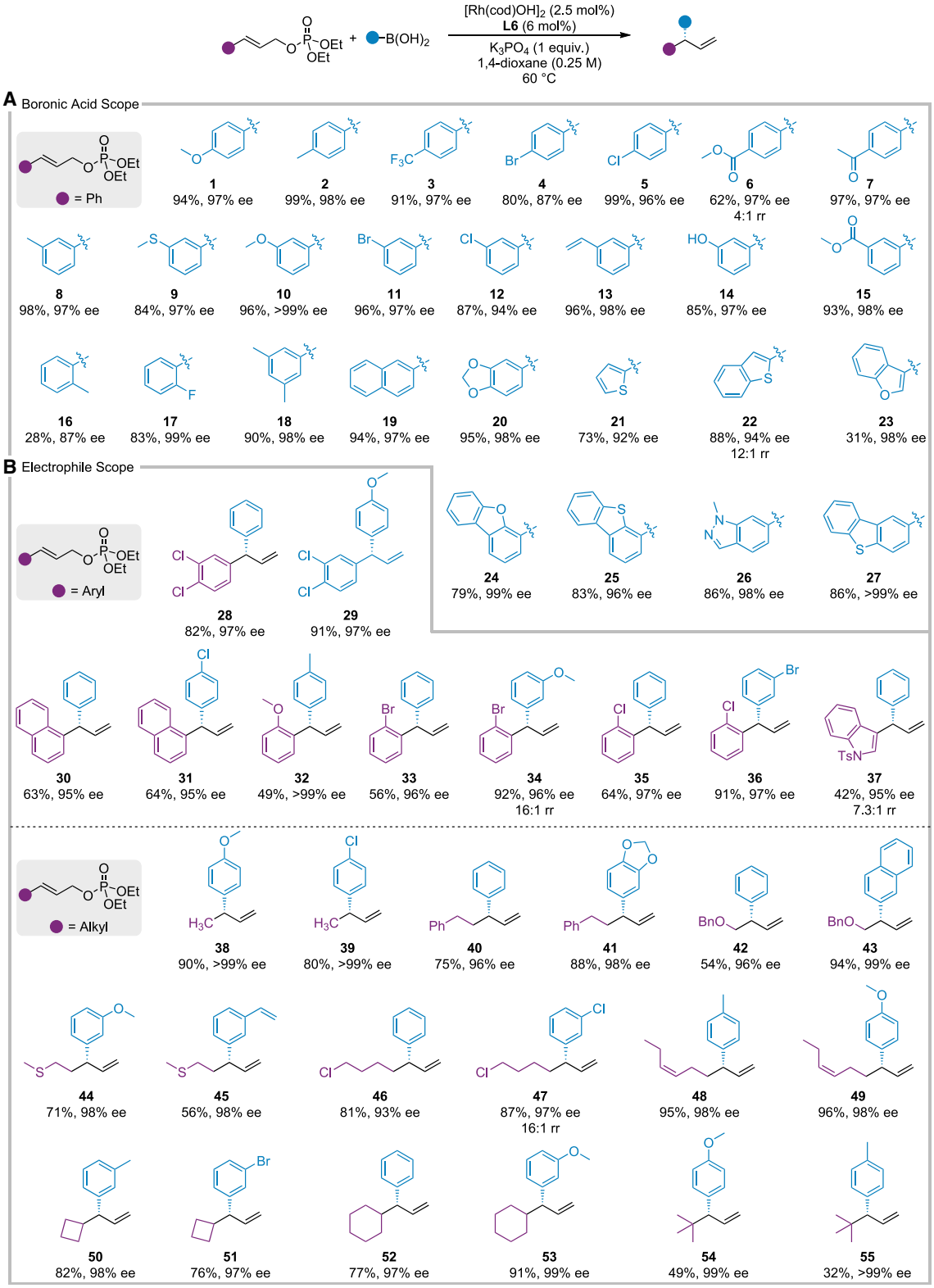

Figure 2. Substrate scope

(A and B) Reaction conditions: electrophile (0.4 mmol, 1 equiv), boronic acid (1.2 mmol, 3 equiv), $[Rh(cod)OH]_2$ (0.01 mmol, 2.5 mol %), L6 (0.024 mmol, 6 mol %), K_3PO_4 (0.4 mmol, 1 equiv), 1,4-dioxane (1.6 mL, c = 0.25 M), 60°C, 16 h. Unless stated otherwise, all compounds were isolated as single regioisomers (rr > 20:1).

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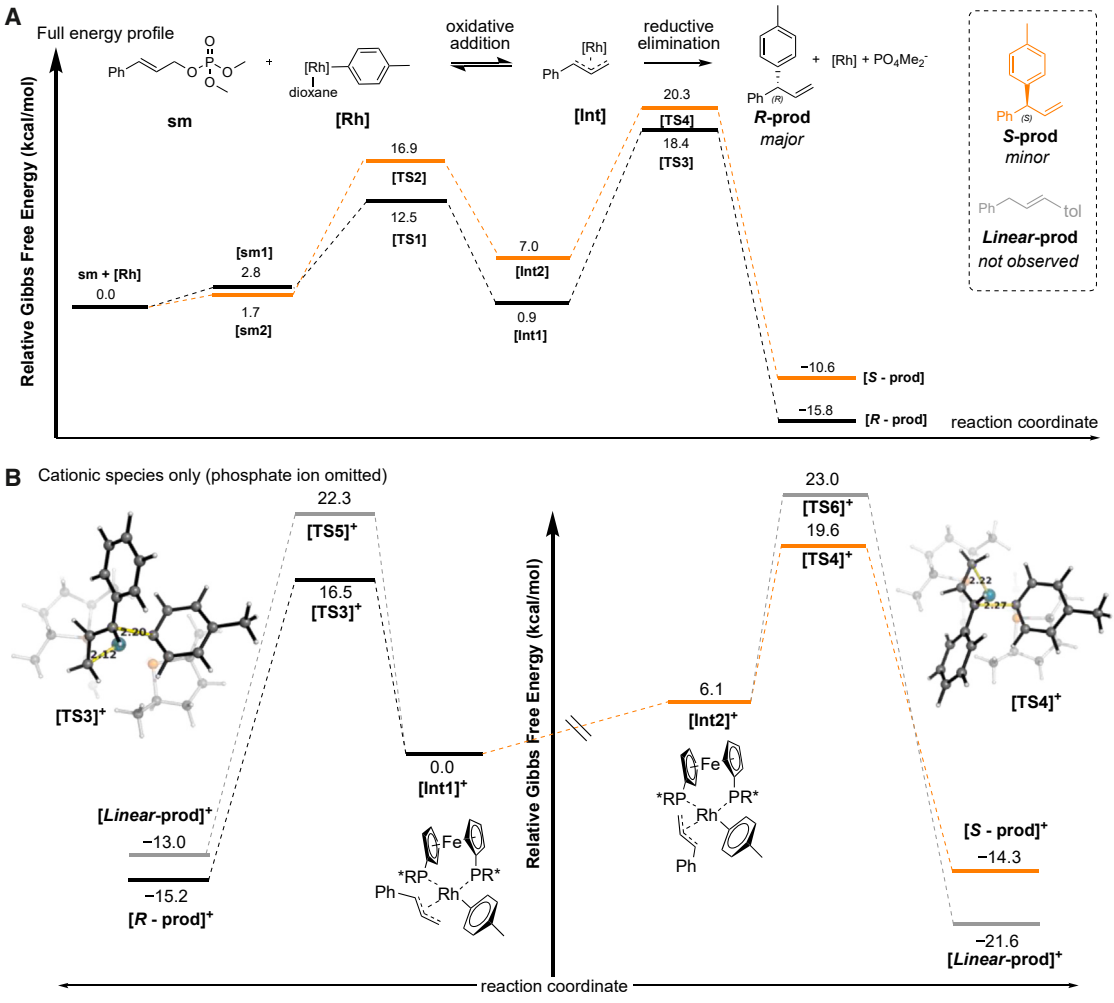

Bond length	TS3	TS4	TS5	TS6	TS3tBu	TS4tBu
C-C	2.2	2.27	2.06	2.17	2.26	2.37
Rh-C (a)	**2.12**	2.22	2.26	2.33	**2.11**	2.18
b/c	1.05	1.05	0.98	1.03	1.04	1.04
Product	*R*	*S*	*linear*	linear	*R*	*S*
$\Delta\Delta G^{\ddagger}$	0	3.1	5.8	6.5	0	6.6
ee/rr Predicted	*R*	98.2%	99.9%		*R*	99.9%
Expt.	*R*	98%	Not observed		*R*	>99%

Figure 3. Computational studies

(A) Calculated energy profile for oxidative addition—reductive elimination steps to afford product 2.

(B) Calculated energy profile reductive elimination of cationic species.

(C) Stereo-determining reductive elimination step: TS bond lengths (Å), relative free energies (kcal/mol), and product ratios for 2 (R = Ph) and 55 (R = ^{t}Bu) for competing pathways.

intermediates **int-1** and **int-2** can occur from a prochiral starting material.

The C2-chiral environment of **L6** can be represented by a quadrant diagram, in which the regions where the ligand's methyl groups are oriented toward the substrate are highlighted in gray (Figure 3C, structures displayed in supplemental information). In **TS3**, C–C bond formation between allyl and tolyl groups occurs via rotational motion of these groups into a less hindered quadrant (Figure 3C, black arrow), whereas for **TS4**, the opposite is true (Figure 3C, orange arrow). The opposite sense of motion required for each TS relative to the catalyst's chiral pocket gives rise to the enantioselectivity.

In terms of regioselectivity, we observe that the cationic η^3-coordinated Rh-center shows much stronger coordination to the terminal allylic position, with terminal vs. internal Rh–C distances of 2.08 vs. 2.91 Å (in **Int1**). In the RE TSs that form linear products, this coordination is necessarily disrupted (2.26 and 2.33 Å in **TS5** and **TS6**), compared with the more favorable

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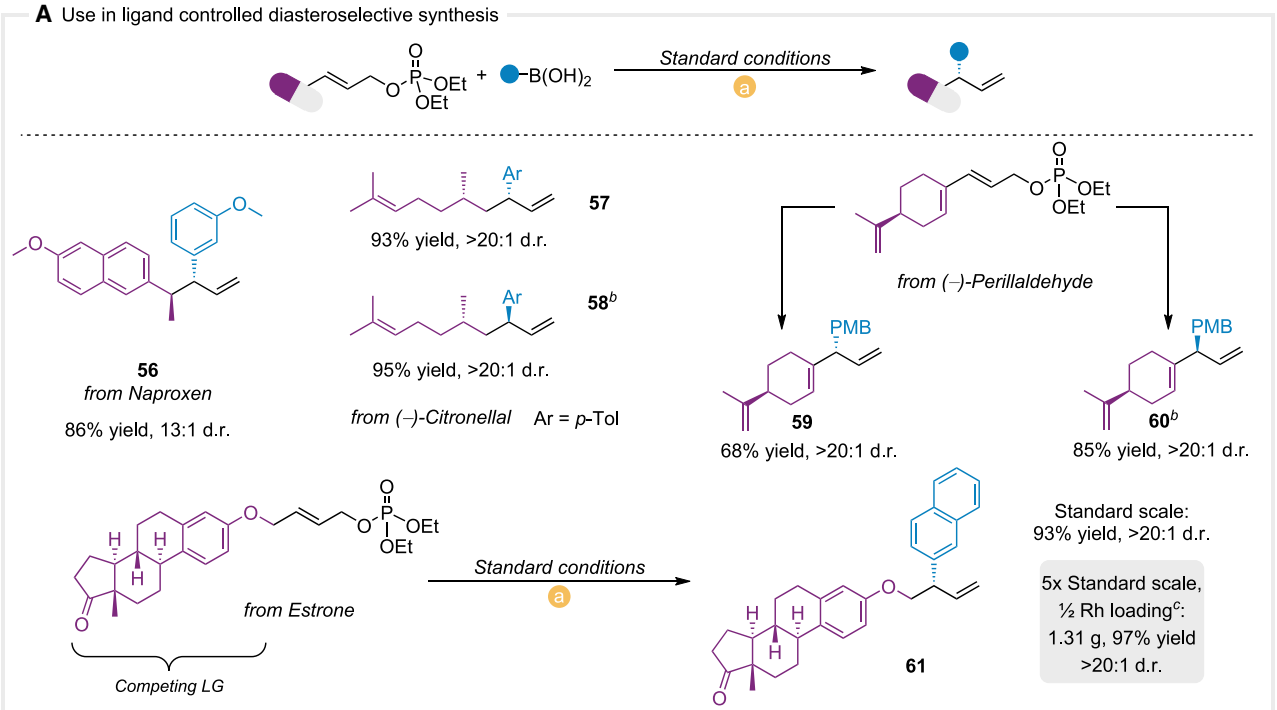

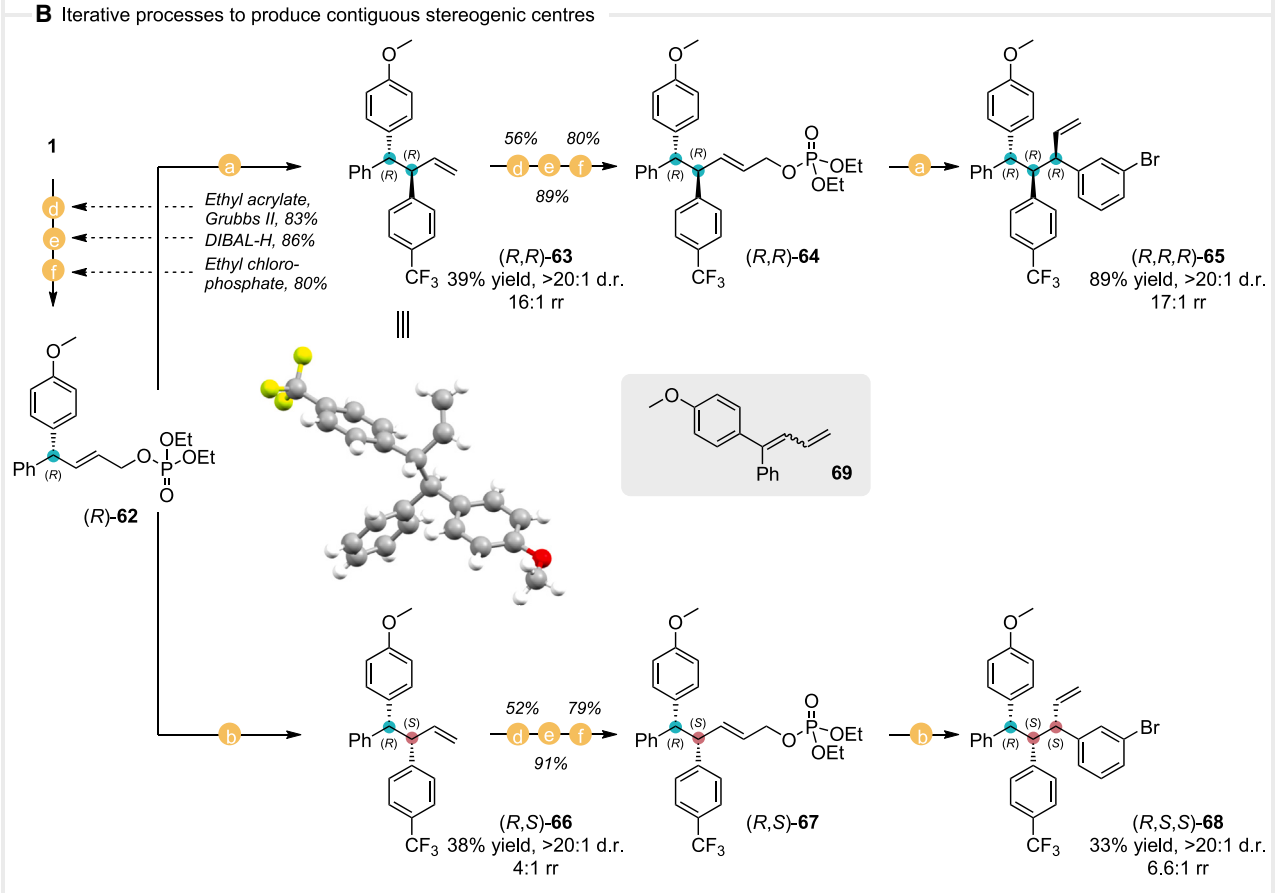

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Figure 4. Applications

(A) Standard conditions.

(B) ent-**L6** was used.

(C) 1.25 mol % $[Rh(cod)OH]_2$ and 3 mol % **L6** were used.

(D) Olefin metathesis: ethyl acrylate (3.0 equiv), Grubbs cat. 2nd gen (4 or 10 mol %), CuI (6 or 12 mol %),[45] DCM, reflux, 16 h.

(E) Reduction: DIBAL-H, hexane/Et_2O, 0°C, 1 h.

(F) Phosphorylation: diethyl chlorophosphate, DMAP, NEt_3, DCM, 0°C, 1 h. Unless stated otherwise, all compounds were isolated as single regioisomers (rr > 20:1).

branched pathway (2.12 Å in **TS3**). The TS geometries at RE revealed that the bulk of allylic part (R = Ph, ^{t}Bu; Figures 3B and 3C) pointed away from the metal center and the ligand, consistent with the transformation showing high regioselection and enantioselection across a wide range of allylic substrates, including ones bearing ^{t}Bu group such as **54** and **55**. Computed RE TSs with **55** show similar geometries to those shown above (see supplemental information), suggesting a common enantiocontrol mechanism among these substrates.

Having established an enantioselective S_N2'-like addition to prochiral molecules, we turned our attention to the selective arylation of molecules with preexisting stereogenic centers. This would establish a method that would be useful in complex molecule synthesis, beyond providing starting-material-type building blocks with a single stereogenic center. As an initial test of this approach, we first performed asymmetric addition on a naproxen derivative, and we were delighted to obtain **56** featuring two contiguous stereogenic centers in 86% yield as a 13:1 ratio of diastereoisomers (Figure 4A).

We were able to generate linear 1,3-stereogenic centers with complete control over which diastereoisomer is formed simply by choosing the appropriate ligand as demonstrated by the synthesis of **57** and **58** in excellent yield (>20:1 dr in each case) from a (−)-citronellal derivative.

Complete ligand control over newly formed centers can also be observed in much more complex starting materials—for example, either 1,5-diastereomer (**59** and **60**) can be generated from an allylic diene derived from (−)-perillaldehyde. The exquisite regioselectivity and chemoselectivity observed deserve comment, as the polyene in which the overall S_N2'-like pathway is observed could have given the linear product or undergone an S_N2'-like process to add to the olefin in the ring. The higher yield for **60** (68 vs. 85%) is likely due to a matched/mismatched effect between the substrate's preexisting stereochemistry and the ligand, because although the stereogenic centers are separated by 5 carbons, the 6-membered ring significantly affects the overall shape of the starting material. Similarly, we were able to demonstrate the compatibility of the method with a reasonably complex natural product derivative featuring multiple stereogenic centers by attaching an allylic phosphate to the female sex hormone estrone. This example also features a bis-allylic alcohol where diethyl phosphate leaves preferentially to a phenol-based group. Complete chemoselectivity and regioselectivity was observed in the formation of white solid **61** (93% yield), with almost identical results on a 3-mmol scale at half the catalyst loading to give 1.31 g (97%) of **61**.

We next explored the possibility of transforming the Rh-catalyzed asymmetric allylic arylation into an iterative process[46] to generate 1,2-polyaryl chains with precise enantiocontrol and diastereocontrol (Figure 4B). Developing such a stereoselective method would not only set a definitive benchmark for ligand-controlled diastereoselective synthesis but would also address a long-standing challenge in organic synthesis, since to the best of our knowledge, no stereoselective iterative methods for synthesizing contiguous aryl-substituted stereogenic centers have been established.

The design of our iterative sequence is facilitated by the S_N2'-type reactivity observed, which enables sequences where linear allyl-phosphate units yield branched products; the significant steric bulk of the structures in Figure 4B suggests that preparing the corresponding branched allylic alcohol-derived electrophiles would be challenging.

The sequence involves generating an allylic phosphate in three steps from the branched alkene arylation products: olefin metathesis, reduction, and phosphorylation (see supplemental information). Applying this sequence to **1** produces allylic phosphate (*R*)-**62**, where the site adjacent to where the next C–C bond will be formed is sterically hindered and contains two electronically active phenyl groups. Arylation of (*R*)-**62** using **L6** or *ent*-**L6**, gave (*R*,*R*)-**63** (see Data S3 for X-ray structure) and (*R*,*S*)-**66**, respectively, with excellent diastereoselectivities (>20:1). Regioselectivity was somewhat dependent on the diastereoisomer formed: (*R*,*R*)-**63** was obtained in a 16:1 ratio, while (*R*,*S*)-**66** formed in a 4:1 ratio, indicating variability in reactivity depending on the stereochemical combination of the substrate and ligand. In both cases, moderate yields (~38%) were observed, likely due to competitive formation of the conjugated elimination product **69**, as suggested by ^{1}H NMR spectroscopy of the crude reaction mixtures. The presence of strongly electron-donating groups, such as *p*-MeO-Ph in **62**, may promote this side reaction, as *p*-CF_3 was well tolerated above (**3**, Figure 2), and no such reduction in yield was observed in a subsequent iteration to form (*R*,*R*,*R*)-**65**. A full examination of substituent effects in these poly-arylated alkenes will be necessary to understand their impact. Both (*R*,*R*)-**63** and (*R*,*S*)-**66** were subjected to the phosphate-regenerating sequence, yielding (*R*,*R*)-**64** and (*R*,*S*)-**67**.

We then investigated the arylation reactions of both (*R*,*R*)-**64** and (*R*,*S*)-**67** with the Rh/**L6** complex, observing a major matched/mismatched effect. The reaction with (*R*,*R*)-**64** yielded (*R*,*R*,*R*)-**65** with excellent yield (89%) and diastereoselectivities and regioselectivities, but (*R*,*S*)-**67** gave only the undesired linear regioisomer (not shown in the figure). Switching to Rh/*ent*-**L6** enabled successful arylation of (*R*,*S*)-**67** so that (*R*,*S*,*S*)-**68** was obtained in >20:1 dr but moderate yield and regioselectivity (6.1:1 rr). These results suggest that a wide variety of 1,2-polyaryl arrays will be synthetically available via this sequence, although much further work is needed to determine the range of accessible structures. It is likely that 1,3- and 1,4-polyaryl linear products will

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also be achievable using this method in appropriately designed iterative sequences, where steric and matched/mismatched effects may be less impactful. Understanding which polyaryl arrays can be synthesized will guide our future efforts in this area.

In summary, we present a modular Suzuki-type cross-coupling approach for constructing sp^3 stereogenic centers through regioselective and stereoselective allylic arylation. A broad range of (hetero)aromatic boronic acids can be used in combination with electrophilic allylic alcohol derivatives. The method enables preparation of a wide range of branched allylic building blocks for organic synthesis with high levels of ee, as well as stereoselective elaboration of natural product and drug derivatives, and new strategies for the synthesis of stereogenic arrays of linear molecules. Mechanistic studies suggest that the overall S_N2' reactivity derives from reversible anti-OA followed by irreversible RE, where regioselectivities and enantioselectivities are controlled by energy disparities in competing pathways. Notably, the substituent of the allylic electrophile orients away from the metal center in the transition state of the RE step, enabling the use of sterically hindered allylic substrates, including those containing multiple aryl rings and ^{t}Bu groups.

METHODS

Further details regarding the methods can be found in the supplemental information.

RESOURCE AVAILABILITY

Lead contact

Requests for further information and resources should be directed to and will be fulfilled by the lead contact, Stephen P. Fletcher (stephen.fletcher@chem.ox.ac.uk).

Materials availability

This study did not generate new unique materials.

Data and code availability

Crystallographic data for (*R*,*R*)-**63** have been deposited in the Cambridge Crystallographic Data Center (CCDC) under accession numbers CCDC: 2406423. Data can be obtained free of charge from the CCDC at https://www.ccdc.cam.ac.uk/structures/ as of date of publication. All other generated data are available in the supplemental information.

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AUTHOR CONTRIBUTIONS

K.L. and S.P.F. conceived the project, and S.P.F. guided the research. K.L and D.E.-A. performed experimental work. R.A. and R.S.P. performed the computational studies. K.E.C. performed X-ray analysis and structure elucidation of **63**. K.L., D.E.-A., R.A., R.S.P., and S.P.F. wrote the manuscript. All authors participated in data analysis.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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