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Pd(0)-Catalyzed Directed *syn*-1,2-Carboboration and -Silylation: Alkene Scope, Applications in Dearomatization, and Stereocontrol via a Chiral Auxiliary

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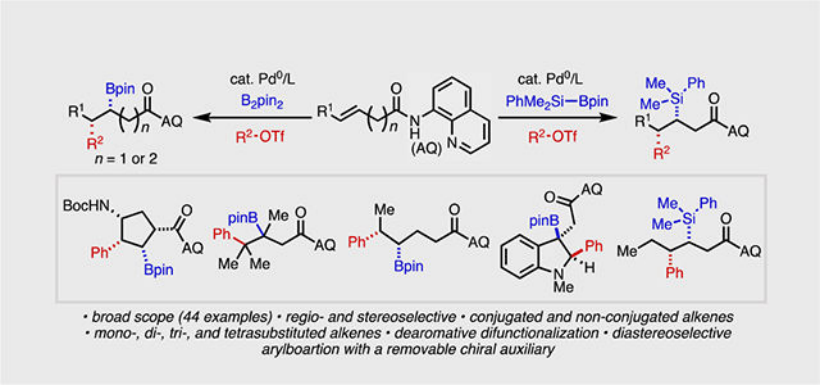
Abstract

We report the development of palladium(0)-catalyzed *syn*-selective 1,2-carboboration and -silylation reactions of alkenes containing cleavable directing groups. With B_2pin_2 or $PhMe_2Si$–Bpin as nucleophiles and aryl/alkenyl triflates as electrophiles, a broad range of mono-, di-, tri- and tetrasubstituted alkenes are compatible in these transformations. We further describe a directed dearomative 1,2-carboboration of electron-rich heteroarenes by employing this approach. Through use of a removable chiral directing group, we demonstrate the viability of achieving stereoinduction in Heck-type alkene 1,2-difunctionalization. This work introduces new avenues to access highly functionalized boronates and silanes with precise regio- and stereocontrol.

Graphical Abstract



Alkene Functionalization. A method to affect *syn*-1,2-carboboration and -silylation of alkenes and heterocycles via Pd(0)/Pd(II) catalysis is described. Strategic use of a chiral directing groups allows for stereocontrol in the key 1,2-migratory insertion step.

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Keywords

carboboration; borylation; palladium; directing group; alkene

Introduction

Metal-catalyzed 1,2-carboboration of alkenes is a powerful means of simultaneously forming a C(sp^3)–C and a C(sp^3)–B bond in a single step with multiple levels of selectivity control.[1] Indeed, successful examples of catalytic 1,2-carboboration have been developed with copper,[2] palladium,[3] nickel,[4] and dual catalyst systems[5]. Of the various coupling partners that can be engaged in 1,2-carboboration, organohalides and pseudohalides are particularly important, given the structural diversity and widespread availability of these electrophiles (Scheme 1A). In this area, classical limitations have included the scope of compatible alkenes and associated issues with regiocontrol; indeed, the vast majority of successful examples involve activated alkenes, such as styrenes[2a,f,3a,4c,d,5] or norbornenes (Scheme 1B).[2d,3b] Previously, Xiao and Fu developed a Cu-catalyzed regiodivergent 1,2-alkylboration of non-conjugated terminal alkenes containing a proximal heteroatom.[2c] Recently, Brown has developed an elegant series of nickel-catalyzed 1,2-arylboration methods capable of functionalizing mono-, di- and tri- substituted non-conjugated alkenes[4a,b] without formation of competitive chain-walking products.[6,7] These reactions are believed to proceed via a Ni^{I}–Bpin intermediate, which generally delivers the Bpin group to the less substituted carbon atom. With trisubstituted alkenes, the reactions are highly regioselective, whereas with non-symmetric 1,2-disubstituted alkenes and terminal alkenes, regiomeric ratios (r.r.) are variable and controlled by a combination of steric and electronic factors.

To complement these approaches, we reasoned that a substrate-directed strategy involving palladium catalysis could enhance reactivity with hindered substrates (e.g., tetrasubstituted alkenes[8]) and provide a means of controlling regioselectivity in a manner that is independent of the alkene substitution pattern. Previously, our lab[9] and others[10] have developed a toolkit of hydro- and difunctionalization reactions of alkenyl carbonyl compounds bearing the 8-aminoquinoline[11] (AQ) directing group. As part of this effort, we described an *anti*-selective 1,2-carboboration of alkenyl carbonyl compounds that initiates via Wacker-type carbopalladation (Scheme 1C).[3c–e] Though useful in its own right, this method is limited in terms of the carbogenic groups that can be introduced (indole-type nucleophiles) and the alkene scope (terminal and 1,2-disubstituted alkenes). We hypothesized that these issues could be overcome by developing a catalytic system that instead initiates via Heck-type 1,2-migratory insertion.[9d,f,10b,e] Based on this idea, herein we describe a Heck-type directed 1,2-carboboration that proceeds via a Pd(0)/Pd(II) redox manifold (Scheme 1D). In addition to tolerating essentially all possible alkene substitution patterns, the protocol can also be applied in directed dearomative 1,2-carboboration of electron-rich heterocycles. The generality of this directed 1,2-difunctionalization approach via Pd(0)/Pd(II) catalysis is demonstrated through the realization of a 1,2-carbosilylation method by using $PhMe_2Si$–Bpin[12] in place of B_2Pin_2. Lastly, stereoinduction by use of a chiral directing group is shown.

Results and Discussion

To initiate our study, we first selected 8-aminoquinoline (AQ)-masked 3-butenoic acid (**1a**) and (*E*)-3-hexenoic acid (**1c**) as our pilot alkene substrates, phenyl triflate (**2a**) as the electrophile, and B_2pin_2 (**3a**) as the boron-based nucleophile. We elected to use a catalyst system consisting of Pd_2dba_3 and a phosphine ligand.[10b] We hypothesized that the phosphine ligand would coordinate to Pd(0) and promote oxidative addition to the aryl triflate. After extensive screening of different ligands, bases, and reaction solvents (see SI for details), we identified an optimal combination: *i*-Pr_2NEt as base and *t*-AmylOH as solvent with a Buchwald-type ligand,[13] such as RuPhos, XPhos, or Cy-JohnPhos (**L**). Under these conditions *syn*-1,2-arylborylated products **4a** and **4c** could be isolated in nearly quantitative yield without observable formation of regio- and stereoisomers based on ^1H NMR.

We then tested the alkene scope of this Pd(0)-catalyzed 1,2-arylboration (Table 1). Pleasingly, we found that a remarkably broad collection of alkenes were reactive. For β,γ-unsaturated carbonyl compounds, which react via five-membered palladacycles, the reaction was largely insensitive to the alkene substitution pattern. Di-, tri-, and even tetrasubstituted alkenes were all competent, leading to a variety of secondary and tertiary alkyl boronates in excellent yields (**4a**–**k**). These results stand in contrast to our previously developed directed 1,2-difunctionalization reactions involving Wacker-type nucleopalladation,[3c,9b,c,e] which are highly sensitive to steric hindrance and are incompatible with tri- and tetrasubstituted alkenes. Substrate **1h**, which is derived from Vince lactam,[14] underwent arylboration smoothly to give product **4h**, which bears four substituents on the same face of the cyclopentane ring. Furthermore, from tetrasubstituted alkene **1k**, the resulting product contains two contiguous quaternary centers, a motif that is inaccessible using existing arylboration methods.

The reaction also works reasonably well for substrates containing one additional methylene spacer between the C=C bond and the carbonyl groups (**4l**–**p**), which react via six-membered palladacycles. However, with these substrates, the reaction is more sensitive to steric hindrance. With 1,2-disubstituted alkene **1m**, the product (**4m**) was obtained in 85% yield, which is slightly diminished compared to analogous earlier examples (**4b**–**4d**). With trisubstituted alkene **1r**, no reaction was observed. We attribute this pattern of attenuated reactivity to less favorable kinetics and thermodynamics for 1,2-migratory insertion to form a six-membered palladacycle versus a five-membered palladacycle. Substrates with even more distal alkenes, including terminal alkene **1s**, were unreactive under the standard conditions. Interestingly, an alkenyl amine substrate containing a picolinamide (PA) directing group also underwent 1,2-arylboration in moderate yield (**4q**). Importantly, across all of these examples, the phenyl group was reliably delivered to position distal to the AQ group, and the Bpin group moiety was installed proximal to the AQ group, irrespective of alkene substitution pattern, illustrating a unique aspect of this directed 1,2-carboboration compared to other approaches.[1–5]

Next, we investigated the compatibility of carbon electrophiles in this transformation (Table 2). An array of aryl triflates containing substituents with different electronic properties on

the *para* or *meta* positions reacted smoothly under the optimal conditions, delivering the corresponding products, **4r**–**4u**, in excellent yields. Notably heteroaryl triflates containing a Lewis basic N(sp^2) atom (**4v** and **4w**), which are incompatible in many Pd-catalyzed alkene functionalizations, are tolerated in this reaction, though slightly lower yields were obtained. Gratifyingly, when we used alkenyl triflates **2h** and **2i** as carbon electrophiles, 1,2-alkenylboration could be achieved. Both 3-butenoic acid and 4-pentenoic acid derivatives underwent alkenylboration in good to excellent yields (**4x**–**4z**).

In order to demonstrate the method's operational simplicity and practicality, we scaled up the alkene arylboration reaction using **1c** as a model substrate (Scheme 2). Under standard conditions, boronate **4c** was isolated in 91% yield (1.2 g).

Considering the relatively expensive nature of aryl triflates, we also investigated other aryl electrophiles as triflate surrogates. Aryl fluorosulfates,[15] which can be readily prepared from phenols and sulfurylfluoride (SO_2F_2), are a class of inexpensive aryl electrophiles that are used on industrial scale, making them attractive yet underutilized coupling partners in alkene functionalization. To our delight, phenyl fluorosulfate (**2j**) was found to be a highly effective electrophile in this 1,2-arylboration reaction, providing nearly quantitative yield of **4c** (Scheme 3).

Given the broad scope of this reaction and its insensitivity to alkene substitution patterns, we next questioned whether it was possible to carry out directed dearomative 1,2-difunctionalization[16] of heteroarenes (Table 3). The three-component 1,2-carboboration of heteroarenes would represent a powerful way to prepare highly functionalized heterocycles. However, this type of reaction has not been previously reported in the literature to the best of our knowledge. The envisioned transformation is challenging for several reasons, including the potential for competitive two-component Miyaura borylation, the relatively large energy barrier associated with breaking aromaticity, and the possibility of undergoing rearomatization. Taking inspiration from an elegant recent report by Jia, Lautens and coworkers on Pd(0)-catalyzed intramolecular dearomative arylboration of indoles,[17] we reasoned that the aforementioned issues could be overcome through AQ-directed Heck-type migratory insertion.

Gratifyingly, using this substrate directivity strategy, we were able to effect 1,2-carboboration of indoles and benzofurans in good yields and with excellent diastereoselectivity (**5a**–**5f**). Several benzo-fused heterocyclic products containing a tertiary boronate group could thus be prepared in a succinct manner. This dearomative transformation is not without its limitations. Aryl triflates bearing strong electron-withdrawing groups are incompatible in this reaction. With indole substrates bearing a 2-substituent (**1w**) or one extra methylene spacer (**1x**), similarly no reaction was observed. A benzothiophene derivative **1y** was also unreactive in this transformation.

To demonstrate the versatility of directed Heck-type 1,2-difunctionalization chemistry, we next sought to develop a method for three-component alkene 1,2-carbosilyation, a transformation that would be synthetically enabling yet remains underdeveloped in the literature.[18,19] To this end, we tested Suginome's $PhMe_2Si$–Bpin reagent[12] (**3b**) in place

of B_2pin_2 (**3a**). Gratifyingly, after brief optimization we identified conditions for alkene 1,2-carbosilylation (Table 4).[20] Although silyl group transfer to the Pd(II) center was generally favored over boryl group transfer, small amounts of the 1,2-carboborylated byproduct could nevertheless be detected. This competitive pathway accounts for the slightly lower product yields in this transformation. Representative examples of alkene substrates and electrophiles were examined, and yields were consistently in the moderate to good range (**6a**–**6i**). 4-Pentenoic acid derivatives (such as **1l**), however, were incompatible in this transformation. In this case, only a small amount of arylsilylated product was generated, together with alkene arylboration and hydroarylation byproducts.

To illustrate the synthetic utility of this 1,2-carboboration reaction, we performed a series of transformations on representative 1,2-carboborated products (Scheme 4). First, we carried out a 2-step transamination sequence to remove the AQ directing group, following Verho's procedure.[21] Compounds **4c**, **4j**, and **4l** were successfully transformed to the corresponding pyrrolidine amides in excellent yields. In addition, with $Ni(tmhd)_2$ as a mediator, methanolysis of **4c** was achieved in 78% yield.[22] Finally, the boronate group of **8c** was transformed to a vinyl and fluoro group, respectively (**10** and **11**), using literature methods.[23,24]

To conclude this study, we aimed to demonstrate the viability of establishing the absolute configuration of the newly installed stereocenters through use of a chiral bidentate directing group to facilitate the migratory insertion step.[25,26] After some experimentation, we eventually identified 1-(pyridin-2-yl)ethan-1-amine (as shown in substrates **1za**–**1zc**, Table 5),[27] which is commercially available in enantiopure form, as a suitable chiral directing group. Under modified conditions using increased catalyst and ligand loading, 1,2-arylboration proceeded smoothly with terminal alkene substrate **1za**, forming product **7a** in good yield with 9:1 *dr* and no epimerization of the chiral auxiliary. With internal alkene substrates **1zb** and **1zc**, this strategy could be used to establish two contiguous stereogenic centers (**7b** and **7c**). While both reactions provided similar diastereoselectivity to the terminal case, the yields were diminished (51% and 32% for the *Z*- and *E*- alkene isomers, respectively) with unreatced starting material in both cases, reflecting the sensitivity of the reaction to steric hindrance. Based on an X-ray crystal structure of the racemic form of product **7a**, we were able to assign the relative stereochemistry of the major diastereomer and hence establish the absolute configuration of the newly formed $C(sp^3)$–O bond. The stereochemistry of **7b** and **7c** was assigned by analogy assuming a *syn*-migratory insertion event. One plausible stereoinduction model is shown in Table 5 (bottom left). In this model, the directing group binds in a bidentate fashion, displacing phosphine. The bottom-facing methyl group then affects the preferred coordination mode of the alkene to the palladium center during the migratory insertion step through steric clashing. Alternatively, the directing group could be bound in a monodentate fashion, with the phosphine still coordinated (see SI for additional discussion).

Conclusion

In conclusion, we have developed highly regio- and diastereoselective carboboration and carbosilylation reactions of alkenyl carbonyl compounds using a substrate directivity

strategy. Compatible substrates include alkenes with various substitution patterns and benzo-fused heteroaromatics that react through five- and six-membered palladacycle intermediates. These methods allow direct access to carbonyl products containing boron and silicon groups at the β and γ positions. Furthermore, an array of aryl and alkenyl triflates are suitable carbon electrophiles. The reactions are scalable and operationally simple. Diversification of arylborylated products was also demonstrated, showcasing the synthetic versatility of the products. Finally, an example of diastereoselective 1,2-arylboration using a chiral directing group was shown.

Experimental Section

General procedure for aryl- and alkenylboration of alkenes.

To a 4-mL scintillation vial equipped with a Teflon-coated magnetic stir bar were added the alkene substrate (0.1 mmol), bis(pinacolato)diboron (50.8 mg, 0.2 mmol), $Pd_2(dba)_3$ (2.8 mg, 3 mol%), Cy-JohnPhos (2.2 mg, 6 mol%), and 4Å molecular sieves (~28 mg). The vial was sealed with a screw-top septum cap and was then evacuated and backfilled with N_2 (×3). Under positive N_2 pressure, aryl or alkenyl triflate (0.15 mmol), *i*-Pr_2NEt (34.8 μL, 0.2 mmol), and *t*-AmylOH (0.2 mL) were added. All needle inlets/outlets were removed, and the reaction was placed in a heating block that was pre-heated to 90 °C. After 40–44 h, the black reaction mixture was allowed to cool to room temperature and filtered through a short plug of celite. Upon purification by column chromatography with 5:1 to 3:1 hexanes:EtOAc as the eluent, the pure product was obtained.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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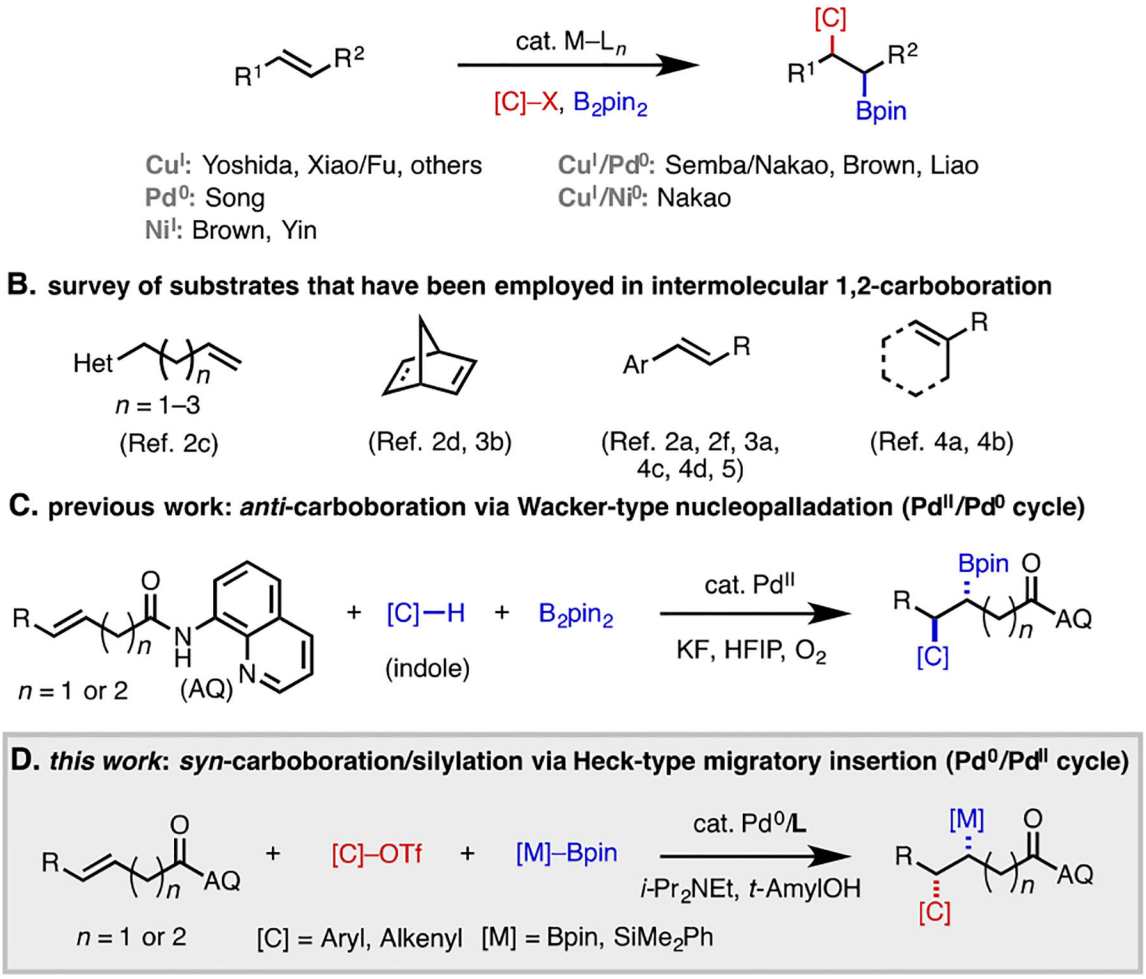
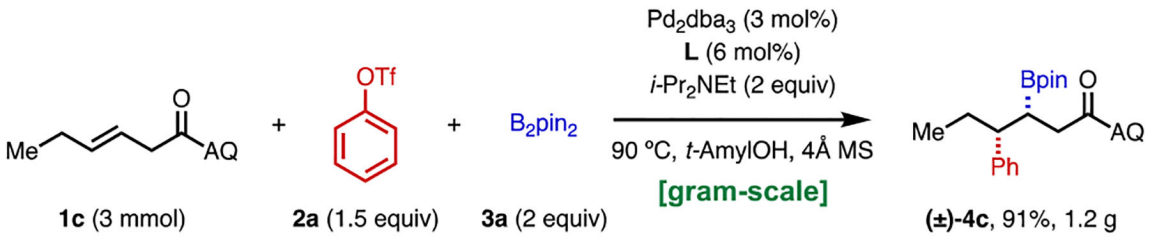
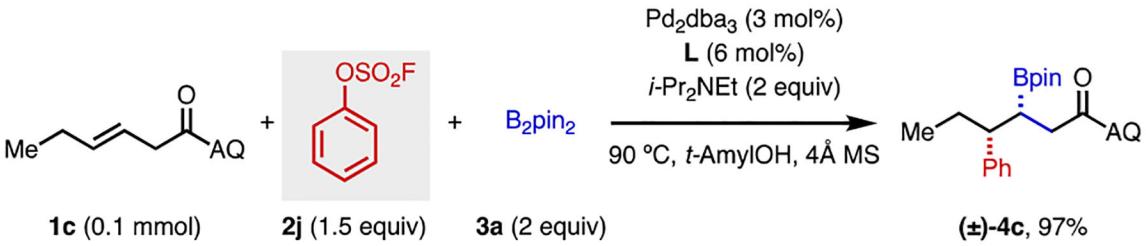


Scheme 1.
Background and Project Synopsis.

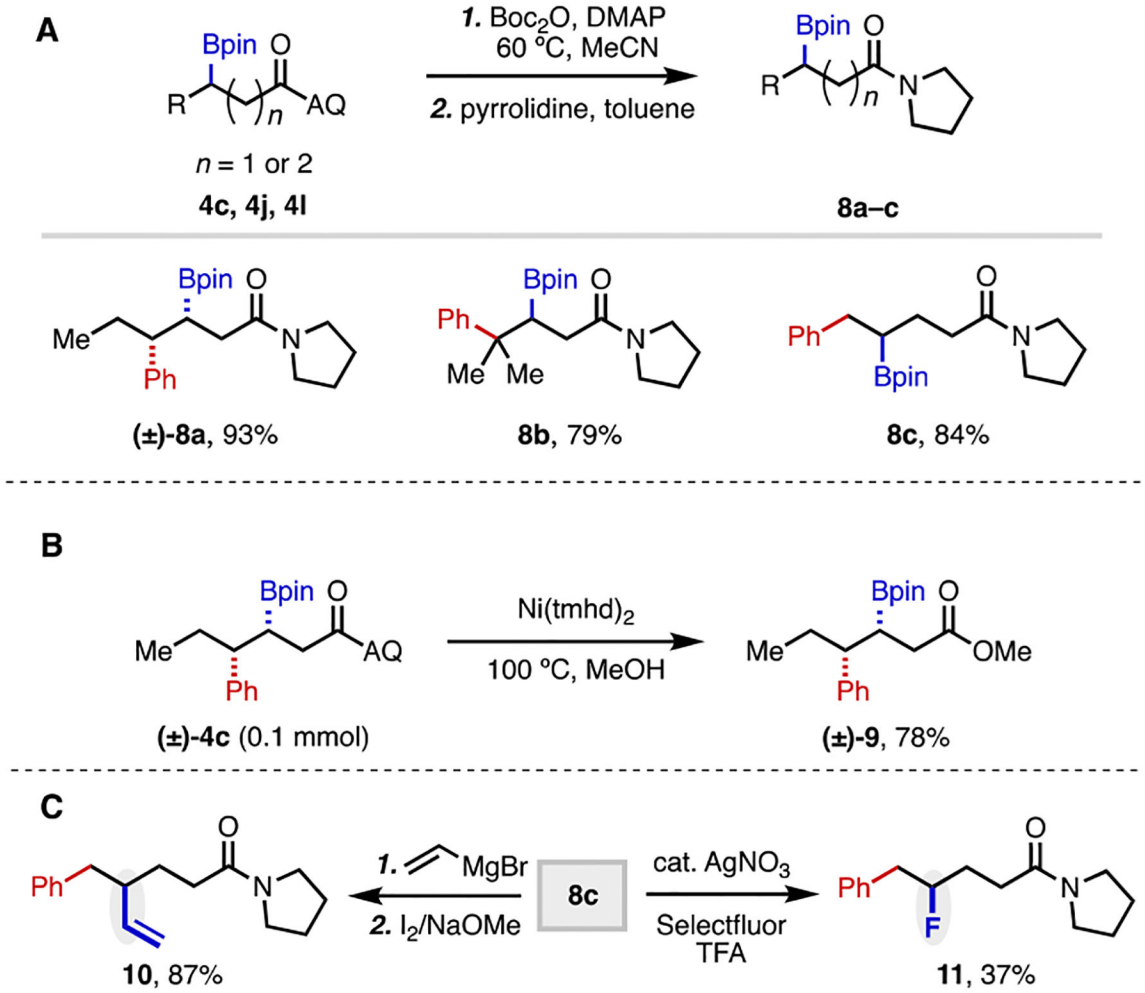


Scheme 2.
Gram-Scale 1,2-Arylboration.



Scheme 3.

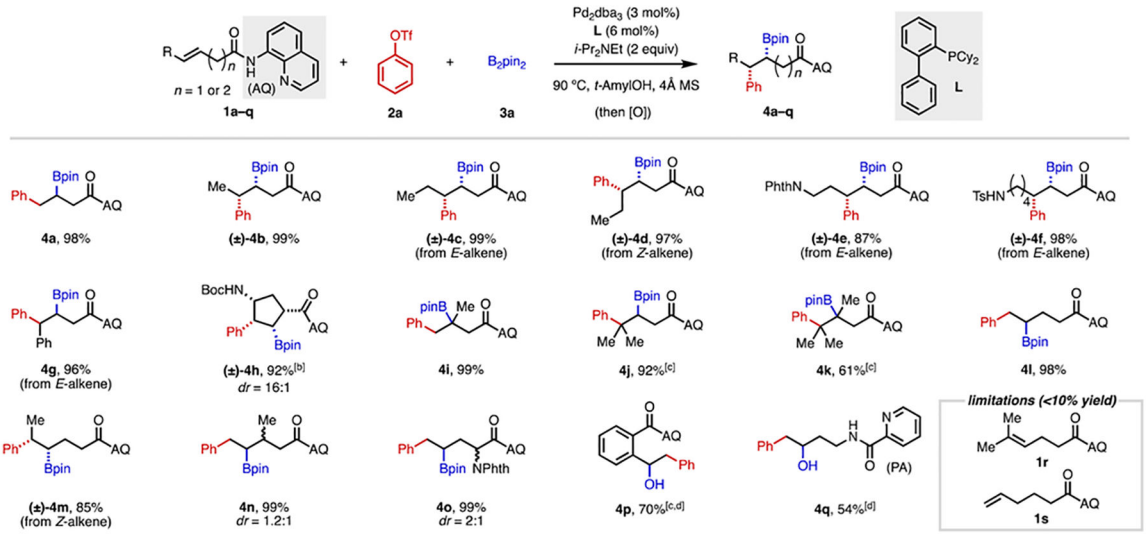
Arylboration using Phenyl Fluorosulfate as the Electrophile.



Scheme 4.
Diversification of Arylborylated Products.

Table 1.

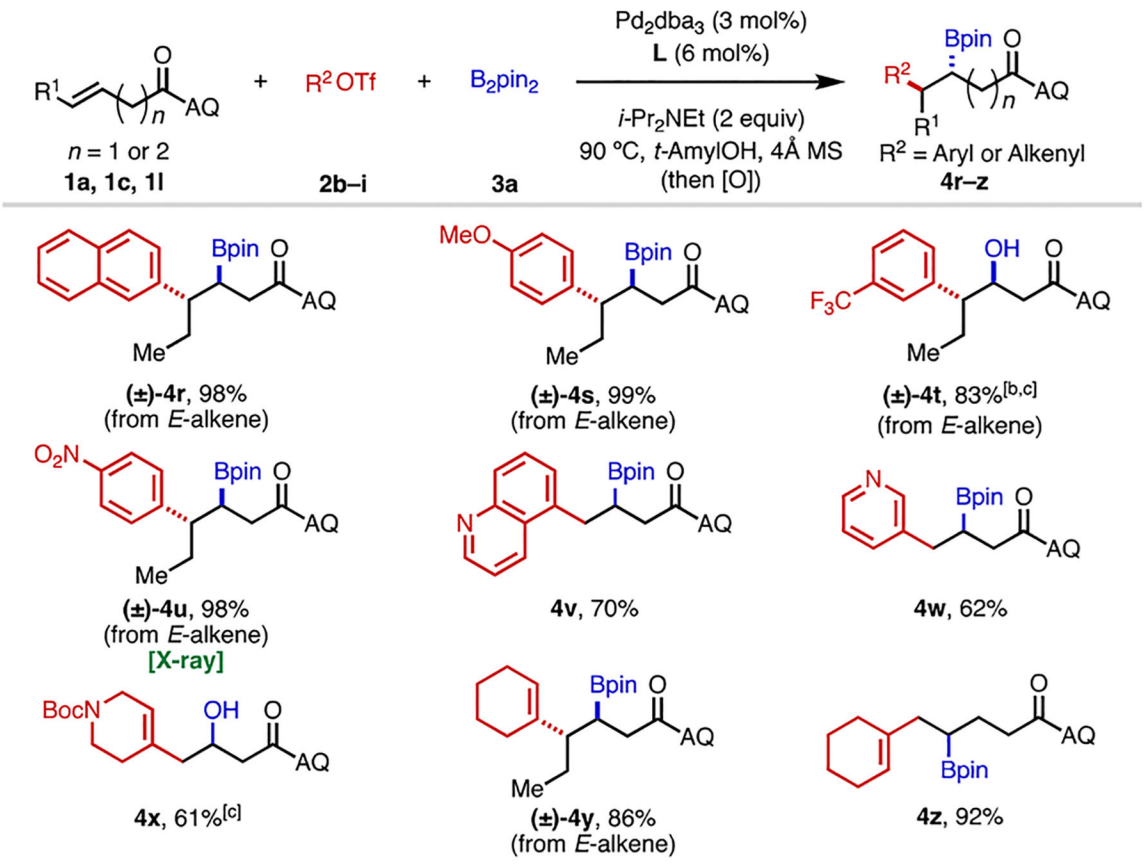
Alkene Scope of 1,2-Arylboration[a]



[a]Reaction conditions: **1a**–**q** (0.05 mmol or 0.1 mmol), **2a** (1.5 equiv), **3a** (2 equiv), Pd_2dba_3 (3 mol%), **L** (6 mol%), *i*-Pr_2NEt (2 equiv), 4Å MS (15–30 mg), 90 °C, N_2, 38–44 h. Percentages refer to isolated yields. Unless otherwise noted, diastereomeric ratio (dr) was found to be >30:1 in all cases. [b] **2a** (3 equiv), **3a** (3 equiv), Pd_2dba_3 (5 mol%), **L** (10 mol%), *i*-Pr_2NEt (3 equiv), 100 °C. [c] **2a** (2 equiv), **3a** (3 equiv), Pd_2dba_3 (4.5 mol%), **L** (9 mol%), *i*-Pr_2NEt (3 equiv). [d] The final product was oxidized to the corresponding alcohol with $NaBO_3$•$4H_2O$ (5 equiv) for ease of isolation.

Table 2.

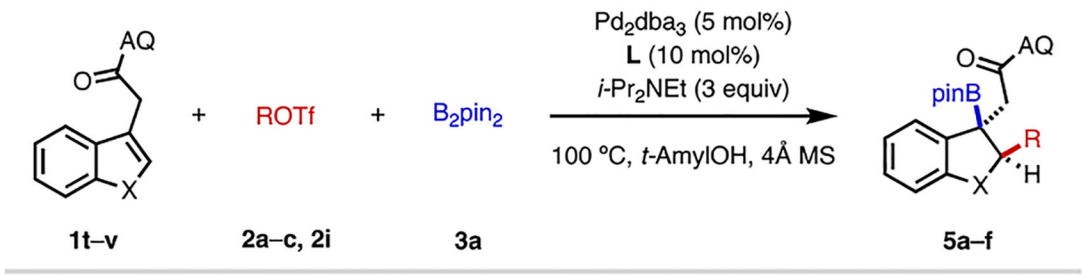
Electrophile Scope.[a]

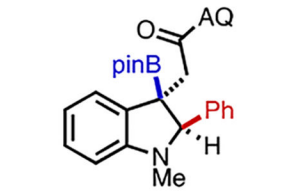


[a]Unless otherwise specified, reaction conditions were as in Table 1. dr values were found to be >30:1 in all cases. [b] **2d** (2 equiv), **3a** (3 equiv). [c] The final product was oxidized to the corresponding alcohol with $NaBO_3 \cdot 4H_2O$ (5 equiv) for ease of isolation.

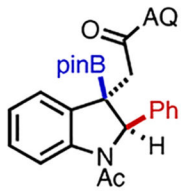
Table 3.

Dearomative Aryl/Alkenylboration of Heterocycles.[a]

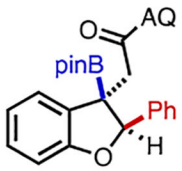




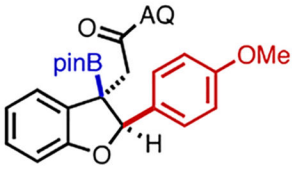
(±)-5a, 63%



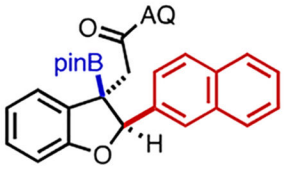
(±)-5b, 66%[b]



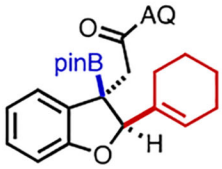
(±)-5c, 86%



(±)-5d, 73%[c]

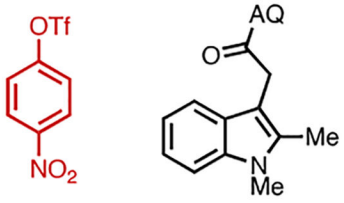


(±)-5e, 87%



(±)-5f, 72%

limitations (<10% yield)

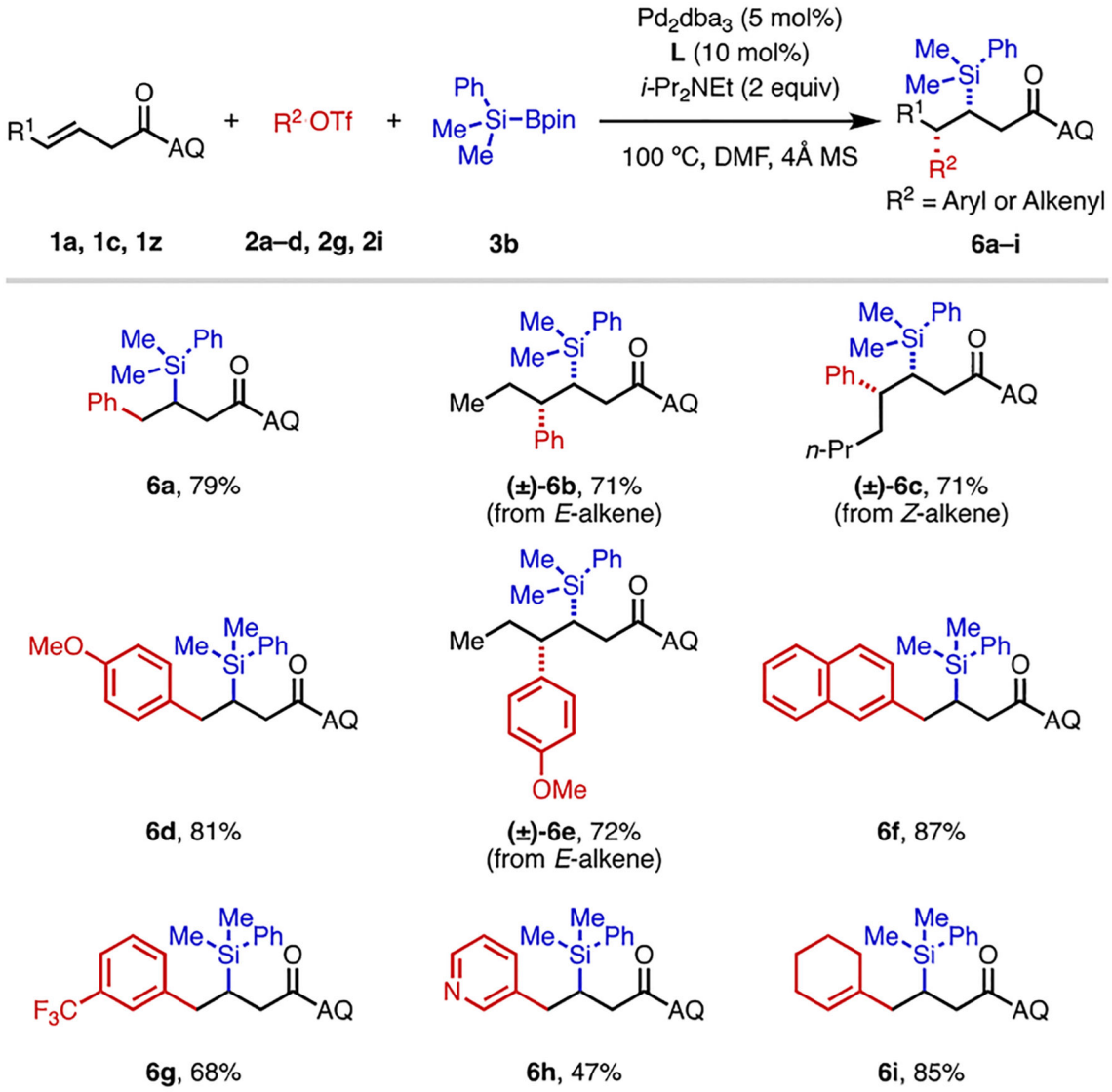


2e **1w** **1x** **1y**

[a]Reaction conditions: **1t–v** (0.05 or 0.1 mmol), **2a–c**, or **2i** (3 equiv), **3a** (3 equiv), Pd_2dba_3 (5 mol%), **L** (10 mol%), *i*-Pr_2NEt (3 equiv), 4Å MS (20–30 mg), 100 °C, N_2, 38–44 h. Percentages refer to isolated yields. The diastereomeric ratio (dr) was found to be >30:1 in all cases. [b] Reaction time of 96 h. [c] **1v** (0.1 mmol), **2c** (2 equiv), Pd_2dba_3 (4.5 mol%), **L** (9 mol%).

Table 4.

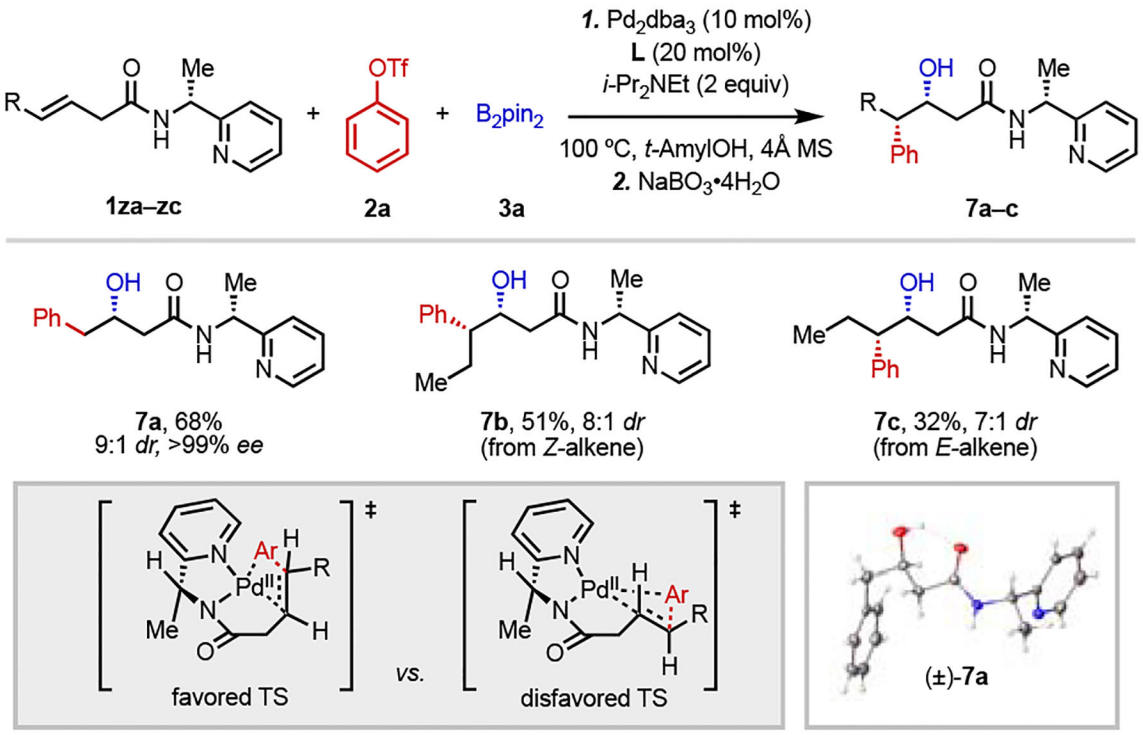
Scope of Alkene Aryl/Alkenylsilylation.[a]



[a]Reaction conditions: **1a**, **1c**, **1z** (0.1 mmol), **2a–d**, **2g**, **2i** (1.5 equiv), **3b** (3 equiv), Pd_2dba_3 (5 mol%), **L** (10 mol%), *i*-Pr_2NEt (2 equiv), 4Å MS (30 mg), 100 °C, N_2, 38–44 h. All the yields refer to the isolated yields.

Table 5.

Diastereoselective Arylboration Using a Removable Chiral Directing Group.[a]



[a]Reaction conditions: **1za**–**zc** (0.05 mmol), **2a** (1.5 equiv), **3a** (2 equiv), Pd_2dba_3 (10 mol%), **L** (20 mol%), *i*-Pr_2NEt (2 equiv), 4Å MS (20 mg), 100 °C, N_2, 44–48 h. The final products were oxidized to the corresponding alcohol with $NaBO_3$•$4H_2O$ (5 equiv) for ease of isolation. All the yields refer to the isolated yields.