Catalyst-Controlled 1,2- and 1,1-Arylboration of α-Alkyl Alkenyl Arenes

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Abstract

Two methods are reported for the 1,2- and 1,1-arylboration of α-methyl vinyl arenes. In the case of 1,2-arylboration, the formation of a quaternary center occurred through a rare cross-coupling reaction of a tertiary organometallic complex. 1,1-Arylboration was enabled by catalyst optimization and occurred through a β-hydride elimination/reinsertion cascade. Enantioselective variants of both processes are presented as well as mechanistic investigations.

Keywords

carboboration; copper; cross-coupling; homogeneous catalysis; palladium

In recent years, carboboration of alkenes has emerged as a valuable strategy for chemical synthesis due to the rapid buildup of complexity from simple components.[1] While several approaches have been described, Cu/Pd-catalyzed arylboration has been demonstrated on a variety of activated alkenes (e.g., alkenyl arenes, 1,3-dienes, vinyl silanes, strained alkenes). [2–4] These reactions operate by the general catalytic cycles illustrated in Scheme 1. Upon generation of L_nCuBpin (**II**), *syn* addition to the alkene occurs to generate $C(sp^3)$—Cu complex **III**. Transmetalation with Pd complex **VI** ensues to provide **IV**, which upon reductive elimination generates the product and Pd^0 complex **V**. As well as the difunctionalization of an alkene, the stereo-selective cross-coupling of a stereo-defined secondary $C(sp^3)$ nucleophile is achieved, which is a significant challenge in organic chemical synthesis.[5]

In all reported examples of Cu/Pd-catalyzed arylboration, terminal and 1,2-disubstituted alkenes are used, which leads to the formation of tertiary stereogenic centers via secondary $C(sp^3)$—Cu complexes.[2] Reactions to form quaternary centers through palladium-catalyzed cross-coupling of tertiary C-(sp^3)—Cu complexes have not been previously demonstrated.[6] In general, palladium-catalyzed cross-coupling reactions with tertiary

Conflict of interest

The authors declare no conflict of interest.

C(sp³) nucleophiles is challenging owing to slow transmetalation as a result of steric hindrance and a high propensity towards β-hydride elimination in the alkyl–palladium intermediate.[7] Thus, only one study has demonstrated palladium-catalyzed cross-coupling of fully substituted alkyl metals.[7,8] Herein, we describe a method for the arylboration of α-alkyl alkenyl arenes that allows for the synthesis of quaternary carbon centers, with control of enantioselectivity. These studies also led to the development of a 1,1-arylboration reaction through tuning of the Pd catalyst. With respect to the latter reaction, the only known example of 1,1-arylboration was reported by Toste and co-workers and operates on monosubstituted alkenes.[9,10] The process described herein operates on α-alkyl alkenyl arenes and leads to the controlled formation of two stereocenters.

We initiated our investigations with the arylboration of α-methylstyrene (**1**; Scheme 2). Under conditions previously disclosed by our research group for the arylboration of alkenyl arenes,[2b] the formation of product **2** with a quaternary center was observed along with 1,1-arylboration adduct **3** (> 20:1 dr). Product **2** most likely arises from reductive elimination of alkyl–palladium complex **5**. On the basis of the formation of product **3**, we propose that a β-hydride elimination/reinsertion sequence occurs to generate **6**, which then undergoes reductive elimination.[9]

The process generating **2** was optimized to the conditions shown in the reaction scheme above Table 1. Key to optimization was the identification of APhosPdG3[11,12] as a suitable catalyst that suppressed the formation of **3**. Other ligands, such as *t*-Bu₂PhP, gave rise to preferential generation of **2**, albeit in lower yield (Table 1, entry 6). Interestingly, the use of *t*-Bu₃PPdG3 and Cy₃PPdG3 led to preferential formation of the 1,1-arylboration adduct (Table 1, entries 4 and 7).

With an optimized set of conditions in hand, the scope of the method was explored (Scheme 3). The method was found to tolerate aryl bromides that bear electron-donating (product **7**) and electron-withdrawing groups (product **8**). In the case of electron-rich aryl bromides, increased quantities of the 1,1-arylboration product formed, most likely due to a slower reductive elimination of Pd complexes analogous to **5**, thus allowing for β-hydride elimination to compete. Sterically demanding aryl bromides were not tolerated, presumably due to a slow transmetalation (product **10**). Whereas a Boc-protected indole was tolerated (product **11**), other hetero-cycles with more basic motifs, such as pyridines, suppressed the reaction. With respect to the alkene component, electron-donating (products **7** from 4-methoxy-α-methylstyrene and **13**) and electron-withdrawing groups (product **14**) did not impede the reaction. However, α-ethylstyrene did not function well in this reaction due to incomplete conversion and poor selectivity (product **16**). The yield and selectivity could be improved if the substituent was constrained within a ring (product **17**). Finally, an alkenyl boronic ester could serve as the alkene component to provide access to **15**.

Enantioselective variants of the reaction were achieved through the use of chiral NHC catalyst **18** to generate products **9**, **12**, and **14** (Scheme 4).[13] This Cu catalyst was previously used by our research group to promote the enantioselective arylboration of *cis*-β-alkyl alkenyl arenes.[2e,6a] Although the yields are moderate, these reactions represent a rare example of a stereoselective palladium-catalyzed cross-coupling of a tertiary alkyl metal

(e.g., **20**).[7] Based on the absolute configuration of product **13**, the mechanistic pathway most likely involves an enantioselective borylcupration via **19**, followed by stereoretentive transmetalation (Scheme 4).[14]

On the basis of the observation that the use of PdPCy$_3$G3 led to 1,1-arylboration (Table 1, entry 7), we directed our efforts towards optimizing the formation of this product (Table 2, entry 1). It was found that using less LiOt-Bu and increased Pd-catalyst loading improved yields. Evaluation of other related ligands did not enhance yields (Table 2, entries 2 and 3). An unexpected finding is that the preformed (PCy$_3$)$_2$Pd complex was not competent in the reaction (Table 2, entry 4). Upon addition of PCy$_3$ (1.0 mol%) to PdPCy$_3$G3, product formation was not observed, which further substantiated this result (Table 2, entry 5). Furthermore, phosphine-free conditions with solely PdG3 dimer functioned well (Table 2, entry 6). Based on this result, other Pd^0 precatalysts were evaluated, and it was found that the reaction proceeded in comparable yields with Pd$_2$dba$_3$ to those observed with PdPCy$_3$G3 (Table 2, entry 7). However, initial evaluation of aryl bromides bearing electron-with-drawing groups revealed Pd$_2$dba$_3$ to be less general (Table 2, entry 9). Furthermore, it appears that dba may have a slight inhibitory effect, as the use of PdG3 dimer led to slightly improved yields as compared to Pd$_2$dba$_3$ (Table 2, entry 10). Therefore, since PdPCy$_3$G3 demonstrated the highest yield and broadest initial aryl bromide scope it was used to evaluate the scope of the method.

Under the optimized conditions, a range of aryl bromides were investigated (Scheme 5). Aryl bromides that bear electron-donating (products **25** and **27**), electron-withdrawing (products **24** and **26**), and sterically demanding groups (product **27**) functioned well. Electronic modification of the aryl alkene was tolerated (products **28–30**); however, a substrate with extended conjugation resulted in poor selectivity for the 1,1-arylboration product **31**, most likely owing to formation of a stabilized π-naphthyl complex. Sterically modified α-substituted alkenyl arenes were tolerated in these conditions to provide **32–34**.

Enantioselective variants of the reaction were also probed, and whereas the reaction to generate (1S,2R)-**3** proceeded with good enantioselectivity and diastereoselectivity, the yield was moderate (Scheme 5B). Based on the absolute and relative configuration of the product, we propose the following reaction pathway: The alkyl–palladium complex **35** was most likely generated through an analogous pathway to that shown in Scheme 4. At this stage, β-hydride elimination ensued to selectively generate E-alkene Pd complex **36**. Since the enantioselectivity in the formation of (1S,2R)-**3** is similar to that in the generation of (R)-**9**, (R)-**12**, and (S)-**14** shown in Scheme 4, it is likely that the alkene does not readily dissociate.[15] Crossover experiments have also been carried out that corroborate the stability of Pd complex **36**.[16] Therefore, hydropalladation occurs selectively on the Si face of the bound alkene to provide **37** and subsequently (1S,2R)-**3** upon reductive elimination.

With respect to the catalytic cycles of the reaction, the primary avenue of inquiry regards the divergence in reactivity with different Pd catalysts. To probe this question, we investigated reactions with preformed alkyl–copper complex **39**, which was prepared from α-methyl styrene and SIMes-CuBpin (Scheme 6A). It has been shown that the reaction of (APhos)$_2$Pd or PdAPhosG4/LiOt-Bu with PhBr gives rise to the monoligated complex **38**.[17] The

reaction of Pd complex **38** with Cu complex **39** led to formation of the expected product **2** containing a quaternary center in 45% yield. It is proposed that the large APhos ligand disfavors the β-agostic interaction necessary for β-hydride elimination and promotes reductive elimination by relief of steric congestion.

Regarding the formation of the 1,1-arylboration product, since alkyl–copper complex **39** is stable and does not undergo β-hydride elimination even when heated to 50°C,[18] the divergence in reactivity appears to occur after transmetalation with ArPdL(Br). In contrast to APhos–Pd complexes, the reaction of (PCy$_3$)$_2$Pd with PhBr resulted in the formation of bis-ligated complex **41**, and the reaction of PdPCy$_3$-G4/LiOt-Bu with PhBr resulted in the generation of a mixture of Pd complexes (Scheme 6B).[19] It has been confirmed that the bis-ligated complex **41** was not catalytically competent (Table 2, entry 4); thus, L$_2$ versus L$_1$ Pd complexes cannot be the justification for the divergence in reactivity. It is suspected that one (or more) of the complexes generated from reaction of PdPCy$_3$-G4/LiOt-Bu with PhBr is responsible for catalysis. Since phosphine-free Pd catalysts also function in the reaction (see Table 2, entries 6 and 7), it is proposed that PdPh(Br)(PCy$_3$)$_n$ (**42**) complexes undergo ligand exchange to form PdPh(Br) (**43**) and PdPh(Br)-(PCy$_3$)$_{n+1}$ (**44**), and that PdPh(Br) (**43**) is the catalytically competent species. Transmetalation of Cu complex **39** with PdPh(Br) (**43**) results in the formation of **45**. The tertiary alkyl–palladium complex **45**, having vacant coordination sites (or at least coordination sites occupied with weakly coordinating ligands, such as solvent), can readily undergo β-hydride elimination to ultimately form the 1,1-arylboration product.

In summary, through the tuning of Pd catalysts a regiodivergent process for the 1,2- and 1,1-selective arylboration of α-alkyl alkenyl arenes was developed. Importantly, this method represents a rare cross-coupling of a tertiary alkyl metal. These studies also serve to showcase the subtleties of ligand–metal dynamics and their impact on reaction rates and selectivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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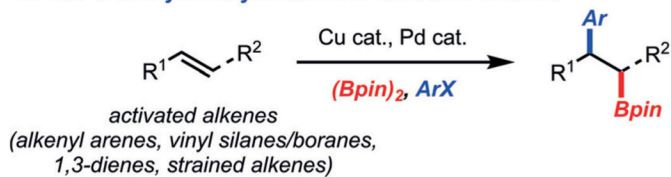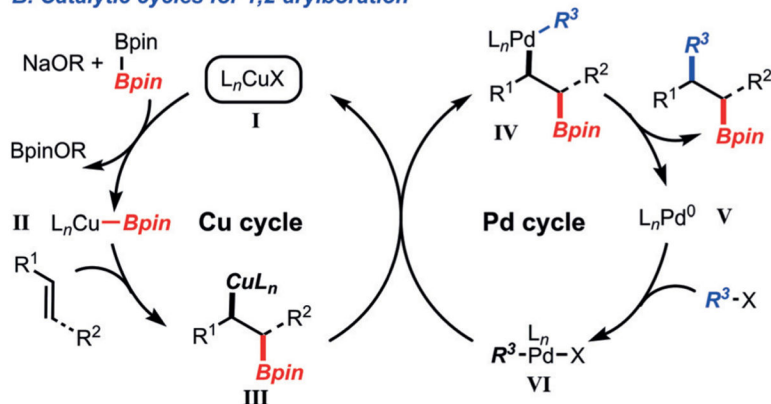
A. Cu/Pd-catalyzed arylboration of activated alkenes

activated alkenes
(alkenyl arenes, vinyl silanes/boranes,
1,3-dienes, strained alkenes)

B. Catalytic cycles for 1,2-arylboration

**C. This study: 1,2- and 1,1-arylboration**
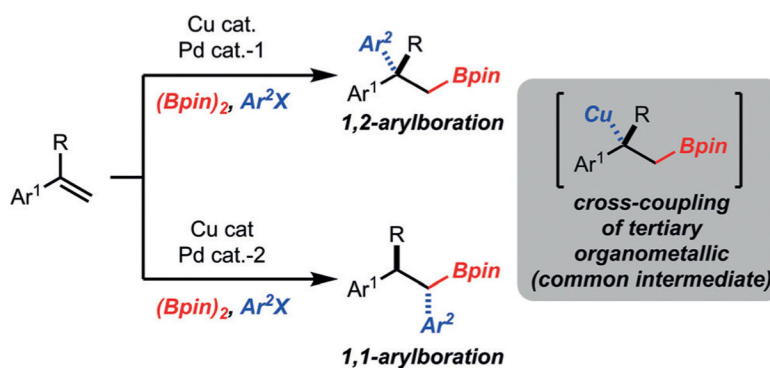
Scheme 1.
Approaches to arylboration by Cu/Pd cooperative catalysis.
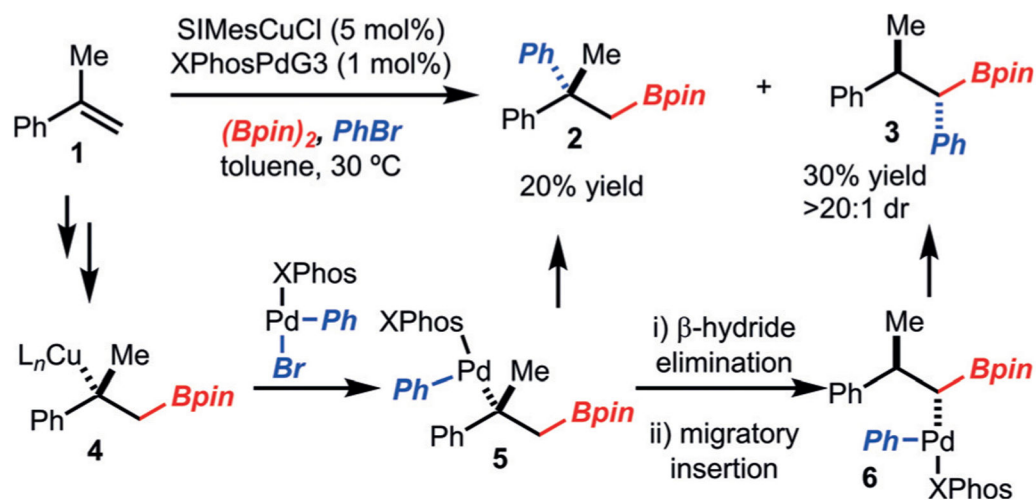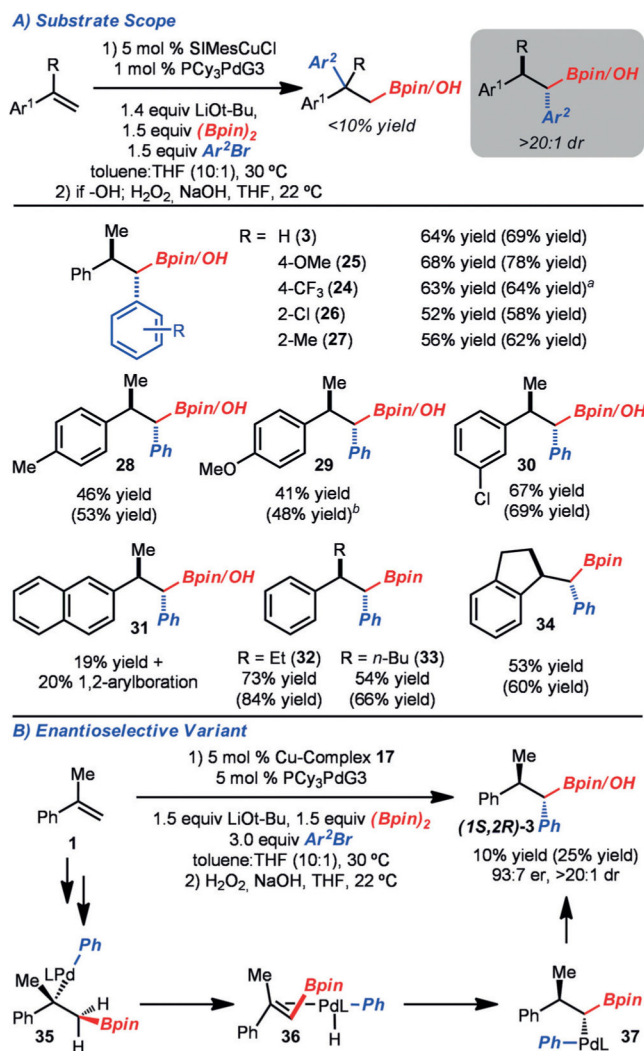
Scheme 2.
Initial investigations. SIMes= 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene, XPhosPdG3= (2-dicyclohexylphosphanyl-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium-(II) methanesulfonate.
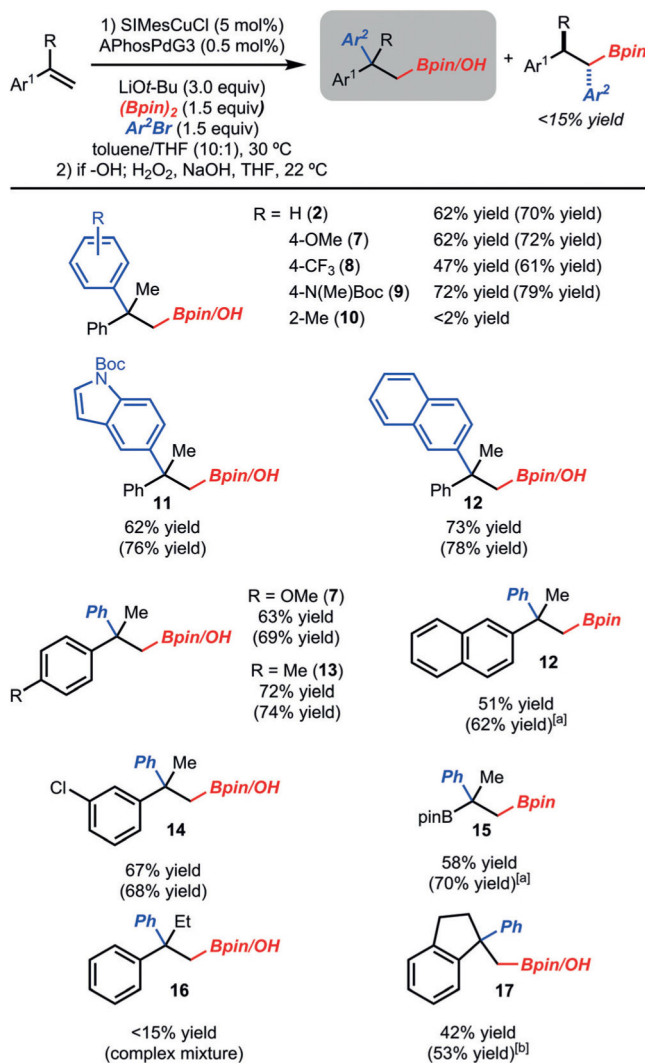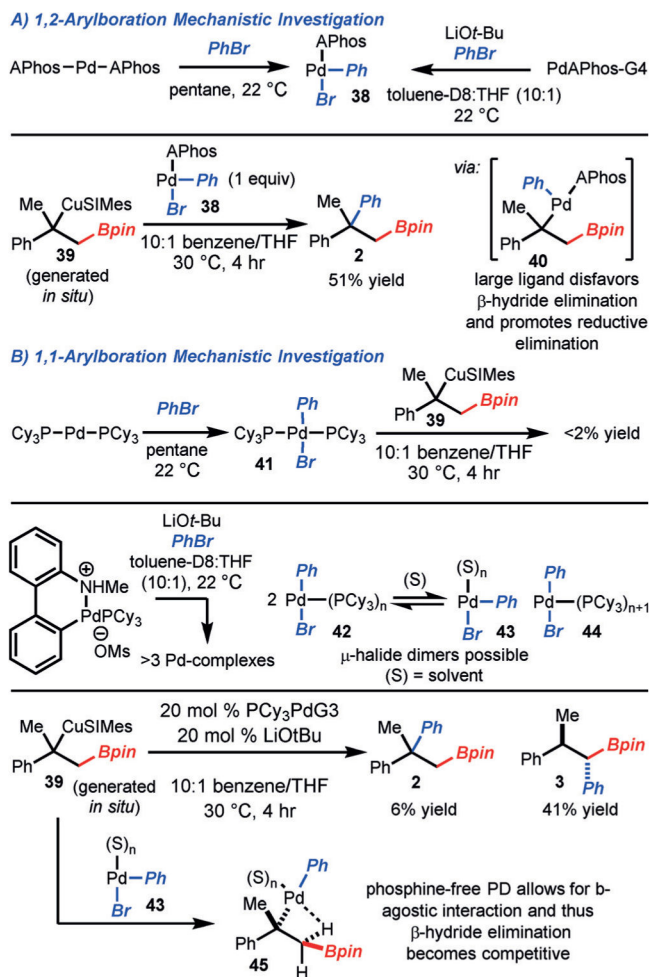
Scheme 3.

Scope of quaternary center formation. Yields are for the isolated purified alcohol product (following the oxidation step), unless noted otherwise. Yields in parentheses were determined by ^{1}H NMR analysis of the crude reaction mixture with an internal standard. [a] Isolated as the Bpin product. [b] The 1,1-arylboration product was also observed (20% yield as determined by NMR analysis). Boc= *tert*-butoxycarbonyl.
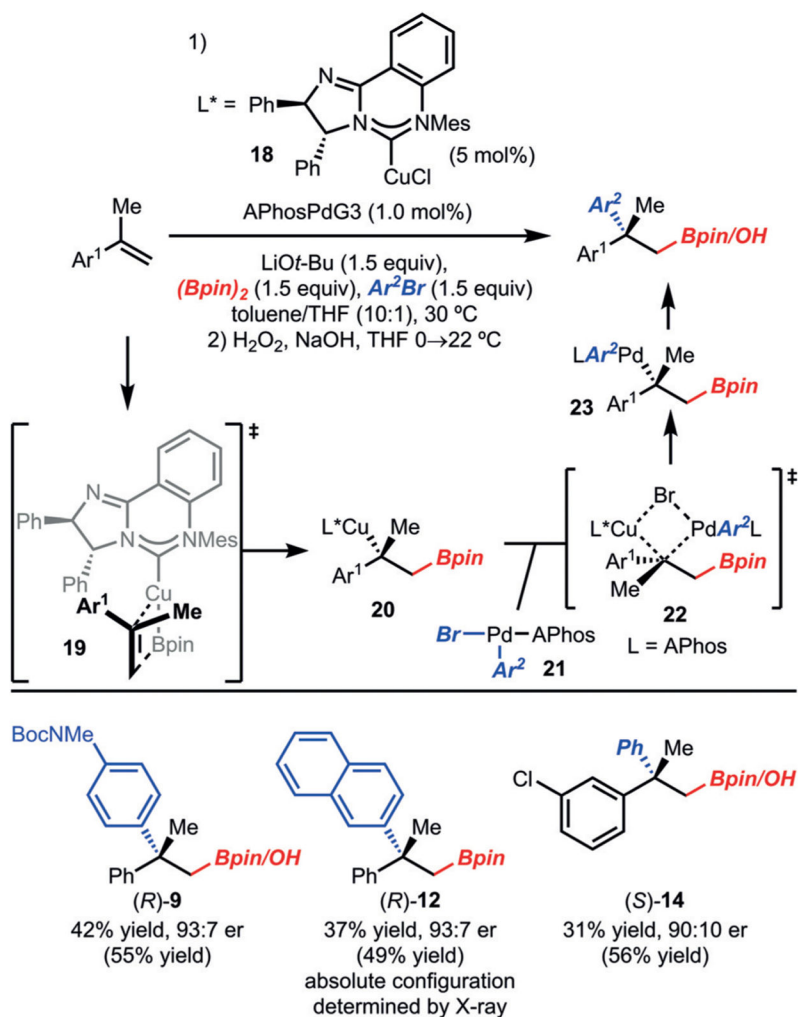
Scheme 4.
Enantioselective formation of quaternary centers. Yields are for the isolated purified alcohol product (following the oxidation step), unless noted otherwise. Yields in parentheses were determined by ^{1}H NMR analysis of the crude reaction mixture with an internal standard.

Scheme 5.
1,1-Diarylation scope. Yields are for the isolated purified alcohol product (following the oxidation step), unless noted otherwise. Yields in parentheses were determined by ^{1}H NMR analysis of the crude reaction mixture with an internal standard. [a] Isolated as the Bpin product. [b] The reaction was carried out with PhBr (3 equiv).

Scheme 6.
Mechanistic investigations. Yields were determined by ^{1}H NMR analysis of the crude reaction mixture with an internal standard.

Table 1:

Investigation of the reaction conditions.[a]
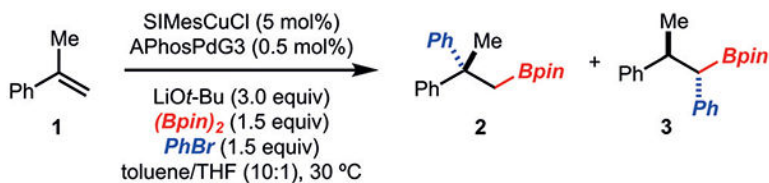
Entry	Change from standard conditions	2 [%]	3 [%]
1	none	75	12
2	1 mol% APhosPdG3 instead of 0.5 mol%	77	11
3	XPhosPdG3 instead of APhosPdG3	22	20
4	t-Bu$_3$PPdG3 instead of APhosPdG3	29	54
5	t-Bu$_2$CyPPdG3 instead of APhosPdG3	52	40
6	t-Bu$_2$PhPPdG3 instead of APhosPdG3	58	8
7	Cy$_3$PPdG3 instead of APhosPdG3	11	27
8	1.5 equiv LiOt-Bu instead of 3.0 equiv	61	3
9	toluene instead oftoluene/THF (10:1)	29	< 1

[a]Yields were determined by ^{1}H NMR analysis of the crude reaction mixture with an internal standard. Cy=cyclohexyl.
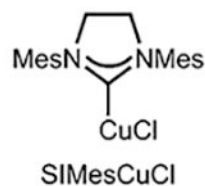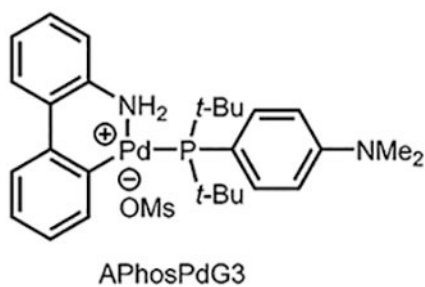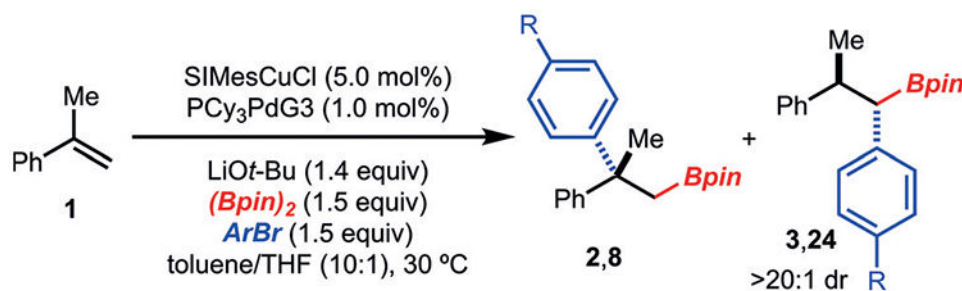

APhosPdG3

SIMesCuCl

Table 2:

Investigation of reaction conditions for the preferential formation of the 1,1-arylboration product.[a]

Entry	Change from standard conditions	R	2,8 [%]	3,24 [%]
1	no change	H (**2/3**)	3	63
2	Pi-Bu$_3$PdG3 instead of PCy$_3$PdG3	H (**2/3**)	2	39
3	Pt-Bu$_3$PdG3 instead of PCy$_3$PdG3	H (**2/3**)	21	33
4	(PCy$_3$)$_2$Pd instead of PCy$_3$PdG3	H (**2/3**)	< 2	<2
5	with 1.0 mol% PCy$_3$	H (**2/3**)	< 2	<2
6[b]	PdG3 dimer instead of PCy$_3$PdG3	H (**2/3**)	3	50
7[b]	Pd$_2$dba$_3$ instead of PCy$_3$PdG3	H (**2/3**)	3	65
8	no change	CF$_3$ (**8/24**)	4	64
9	Pd$_2$dba$_3$ instead of PCy$_3$PdG3	CF$_3$ (**8/24**)	2	24
10[b]	PdG3 dimer instead of PCy$_3$PdG3	CF$_3$ (**8/24**)	5	42

[a]Yields were determined by ^{1}H NMR analysis of the crude reaction mixture with an internal standard.

[b]Pd catalyst loading: 0.5 mol%.