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Regioselective Arylboration of Isoprene and Its Derivatives by Pd/Cu Cooperative Catalysis

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Abstract

A method for the regioselective arylboration of isoprene and its derivatives is presented. These reactions allow for the synthesis of useful building blocks from simple components. Through these studies, an unusual additive effect with DMAP has been uncovered that allows for altered reactivity and the formation of quaternary carbon centers. The utility of this method is demonstrated toward the formal synthesis of mesembrine.

Due to the large-scale production (1 million tons produced/year) and low cost of isoprene, conversion to more complex small molecules with additional functionality represents an attractive process for chemical synthesis.[1] In addition, due to the presence of isoprene units in natural products (e.g., terpenes) and biologically active molecules, isoprene-derived small molecules constitute useful building blocks for the construction of these targets. As such, numerous methods exist for the functionalization of isoprene, the majority of which are hydrofunctionalization processes.[2] Difunctionalization of isoprene is less common but significant as the products incorporate an additional group (compared to hydrofunctionalization).[3–5] At the outset of our studies, a recent report by Sigman et al. represented the current state-of-the-art for three-component couplings of isoprene (Scheme 1A).[5e]

Our group has taken an interest in carboboration processes that operate by Pd/Cu cooperative catalysis.[6–8] Accordingly, we have developed methods for the arylboration of styrene derivatives (note that Semba and Nakao independently developed a closely related process).[9,10] The reactions function by addition of a Cu–Bpin complex across an alkene followed by Pd-catalyzed cross-coupling of the generated C_{sp^3}–Cu complex. We became interested in extending this process to the arylboration of isoprene (Scheme 1B, C). Realization of such a process would allow for the formation of synthetically versatile

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Notes

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Supporting Information

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Experimental procedures and analytical data (PDF)

products. It should be noted that during the final stages of this study, two reports appeared for the carboboration of isoprene with alkylidene malonates[8a] and imines.[8e]

It was reasoned that selective arylboration for the formation of any regioisomer would be valuable; however, development of such a transformation is challenging due to the potential formation of up to four regioisomeric products (Scheme 1C). The regioselectivity of the reaction is established at two distinct stages. First, the initial addition of Cu–Bpin across isoprene can generate two possible adducts, **5** and **6**.[11] Even if this process can be controlled with judicious choice of ligand and reaction conditions, the subsequent Pd-catalyzed cross coupling can lead to the formation of up to four regioisomers. This event is undoubtedly controlled by the nature of both the Pd catalyst and Cu complex. Here we disclose a method for the regioselective arylboration of isoprene in which, with different conditions, either a 1,4-product or a 2,1-product can be generated (Scheme 1B). With respect to the latter process, we also have uncovered an unusual additive effect with 4-(dimethylamino)pyridine (DMAP).

Initial studies found that reaction of isoprene (**1**) under conditions similar to those previously identified for arylboration of styrenes led to the formation of **7**, **8**, and **9** in a 3:1:2 ratio (Table 1, entry 1).[6] It was reasoned that the formation of **7** and **8** resulted from Cu complex **5** whereas the remaining product **9** is formed from the regioisomeric complex **6**. It was reasoned that the regioselectivity could be increased if a more sterically encumbered NHC was used such that reaction at the less substituted alkene of isoprene would be favored. This ultimately led to the identification of I*t*-BuCuBr as a catalyst, which allowed for formation of only **7** and **8** suggesting that the borylcupration step could be controlled (Table 1, entry 2). Since the regioselectivity of borylcupration had been overcome, Pd catalysts were evaluated to increase the selectivity of the transmetalation. This initiative led to the discovery that Pd-QPhos-G3[12] allowed for highly selective synthesis of **7** (vs **8** or **9**) as a 9:1 mixture of *Z*- and *E*-isomers (Table 1, entry 5).

With an optimized set of conditions in hand, the scope of this process was evaluated. Several points are noteworthy (Scheme 2): (1) Electron-rich and electron-poor aryl bromides can be used (products **11**, **12** and **10**, **13**, respectively). (2) Sterically hindered aryl bromides functioned less well in this process, likely due to adverse steric interactions during the putative transmetalation (product **15**). (3) Vinyl bromides were found to be competent; however, slightly lower diastereoselectivities (*Z:E*) are observed relative to those achieved with aryl bromides (product **16**). (4) In all cases, while good yields of the allylboronic ester were observed, the reaction products were typically oxidized to allow for more facile purification. (5) The related terpene, myrcene, also functioned well under the reaction conditions (products **17** and **18)**.

During the course of our investigations, the observation was made that reactions involving pyridine derivatives, such as **19**, gave rise to small quantities of the 2,1-adduct **22** (Scheme 3). The formation of the 2,1-arylboration product **9** was observed previously with reactions promoted by IMesCuCl (Table 1, entry 1). However, optimization of the reaction for selective formation of **9** was unsuccessful. Since pyridine derivatives were clearly affecting

the selectivity of these reactions, further studies were carried out based on the result outlined in Scheme 3.

We reasoned that the Lewis basic nitrogen of the pyridine was allowing for the altered reactivity. To test this hypothesis, reactions with isoprene and PhBr were carried out under standard conditions shown in Scheme 2, except that various pyridine derivatives were added. Initially, when pyridine was used as an additive, the formation of **9** was observed, albeit in low yield as the minor isomer (Table 2, entry 1). Further evaluation of pyridine derivatives led to the finding that DMAP allowed for generation of **9** as the major product. Standard optimization of conditions and assessment of other sterically large phosphine ligands led to improved reaction yields (Table 2, entry 6). Finally, it was found that increased equivalents of DMAP (2.0 vs 1.0) allowed for formation of **9** as the exclusive product in 61% yield as judged by ^{1}H NMR analysis (Table 2, entry 8). Control experiments were also carried out that suggested DMAP is not simply replacing I*t*-Bu or P*t*-Bu$_2$CH$_2$*t*-Bu from either Cu or Pd, respectively (Table 2, entries 9 and 10).

The scope of the 2,1-arylboration reactions was investigated and found to accommodate electron-rich (products **24**, **25**, **28**), electron-poor (products **26** and **27**), and sterically hindered aryl bromides (products **23**, **24**) (Scheme 4). In addition, myrcene could also be substituted for isoprene with little loss in efficiency (products **30** and **31**). In general, the 2,1-arylboration products were formed in high selectivity (>10:1 product:other isomers); they can also be converted to other structures due to the versatility of the C–B bond.[13] Illustrated in Scheme 5 are two representative examples of C–C bond formation.

Cyclic 1,2-disubstituted diene **34** was also tolerated (Scheme 6). In this example, **36** was generated in high selectivity with formation of the *anti*-diastereomer. Boronic ester **36** could be easily converted to **37** through a hydroboration–oxidation sequence,[14] which can be transformed to mesembrine (**38**) through established protocols.[15,16] Several additional examples of arylboration (products **40** and **42**) are also shown in Scheme 6. Highly stereoselective synthesis of **40** demonstrates the effect of an existing stereocenter, while preparation of **42** showcases heterocycle functionalization.

Preliminary mechanistic investigations of the reaction have been carried out. To probe the regioselectivity of the migratory insertion, isoprene was treated with equimolar quantities of I*t*-BuCuBr, KO*t*-Bu and (Bpin)$_2$ (Scheme 7A). This reaction led to the formation of **43** and **44** in a 3:1 ratio in 98% yield. It should be noted that **43** and **44** are formed at roughly the same rate.[17] Treatment of this mixture with Pd-QPhos-G3 and PhBr gave rise to **7** and **45** in a 3:1 ratio and 75% yield (also note that **7** and **45** are produced at approximately the same rate).[17] This result is surprising as under the optimized catalytic reaction conditions, <2% of isomer **45** is formed. The above data suggests that either **43** and **44** undergo interconversion, or **43** is formed selectively under the catalytic reaction conditions. With respect to the former we have not been able to provide evidence of this interconversion through crossover experiments (this scenario is also unlikely as qualitative rate measurements for formation and consumption of **43** and **44** are nearly the same, as mentioned previously).[17] Regarding the latter, we probed the transient formation of **43** and **44** by running the catalytic reaction in the presence of *t*-BuOH, as protonation of allylcopper intermediates is known to be rapid.[18]

In this case only the expected arylboration product **7** and the protoboration adduct (**46**) derived from **43** were observed. This suggests that **44** was not generated under the catalytic reaction conditions. The apparent divergence in selectivity for the stoichiometric and catalytic reactions is unclear at this time.

With respect to the mechanism of the 2,1-arylboration reaction, DMAP was found to not inhibit or alter in any way the stoichiometric formation of **43** and **44**. Furthermore, the mixture of **43** and **44** could not be converted to the 2,1-arylboration products, despite numerous attempts (Scheme 7A).[17] In addition, a protoboration experiment in the presence of DMAP (Scheme 7B) also resulted in the exclusive formation of **46**. This data suggests that **43** was generated under the 2,1-arylboration reaction conditions; however, its potential role as a catalytic intermediate on the pathway to product **9** remains unclear. Altogether, it is evident that the mechanisms of the both 1,4- and 2,1-arylboration reactions are quite complex and further investigations are in progress.

Finally, for formation of *Z*-crotyl metal Cu complexes **43** and **44**, two possibilities are proposed: (1) it has been established that *Z*-crotyl metal complexes are more stable relative to the *E*-crotyl metal complexes,[19] and (2) insertion of 1,3-dienes into organometal bonds occurs preferentially in the *s*-cis conformation to give rise to *Z*-crotyl metal complexes.[20]

In conclusion, a process for the regioselective arylboration of isoprene and its derivatives is presented. DMAP has been shown to alter the normal reactivity of the system. Future efforts aim to further investigate the role of DMAP and develop enantioselective variants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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16. Diene 34 did not lead to arylboration products under conditions outlined in Scheme 2.

17. See the Supporting Information for details.

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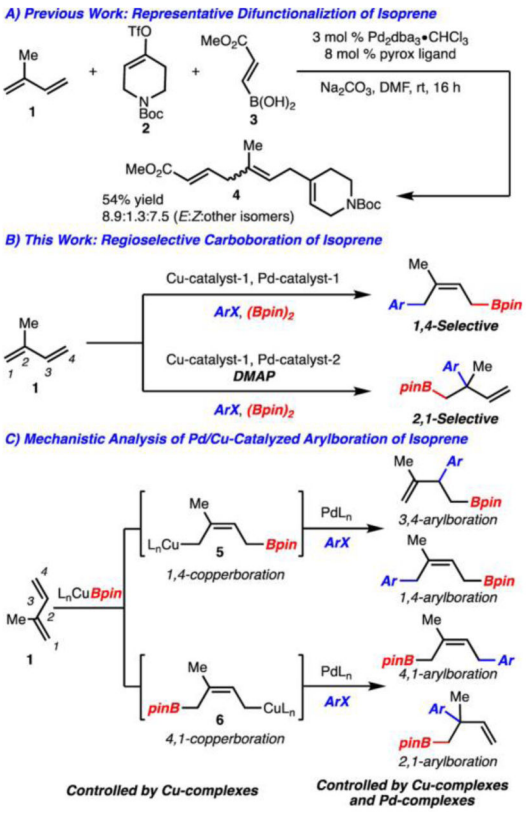
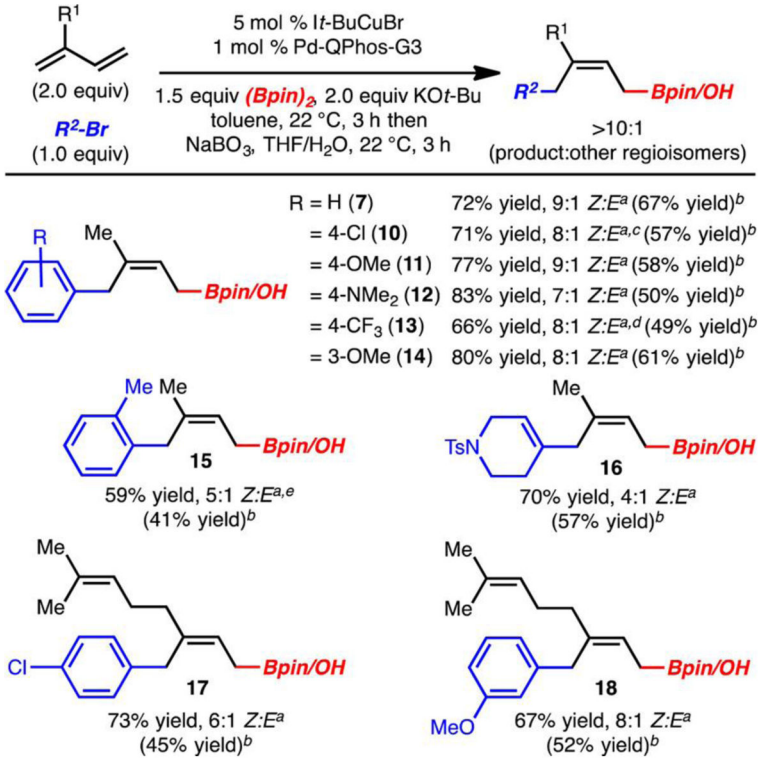
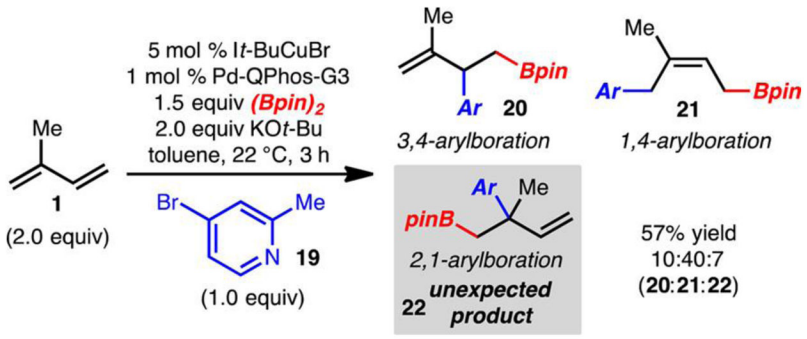


Scheme 1.
Difunctionalization of Isoprene



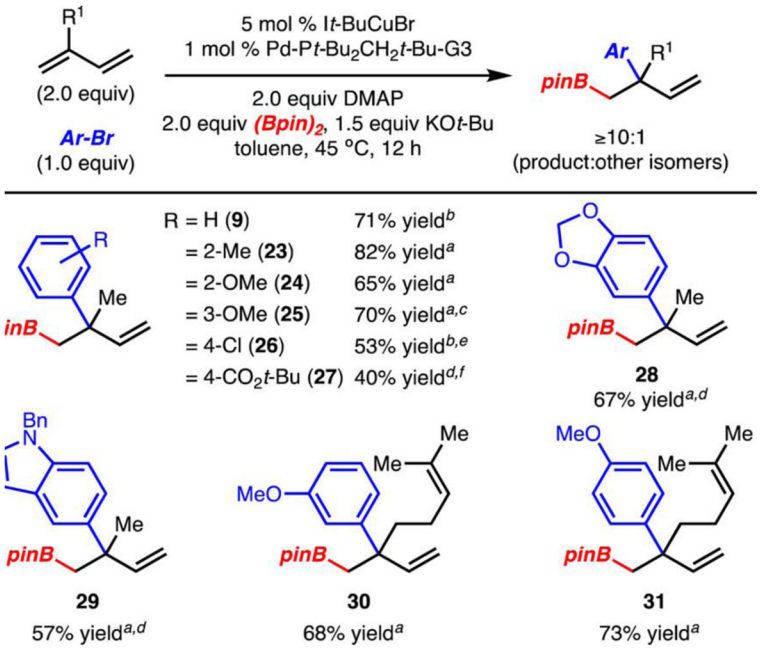
Scheme 2. Substrate Scope

[a] Yield and selectivity of the allylboronate determined by analysis of the crude ^{1}H NMR with an internal standard. [b]Yield (two steps from R^2Br) of isolated alcohol after oxidation (only a mixture of alkene isomers). [c]9:1 product:other isomers. [d]8:1 product:other isomers. [e]4.4:1 product:other isomers.



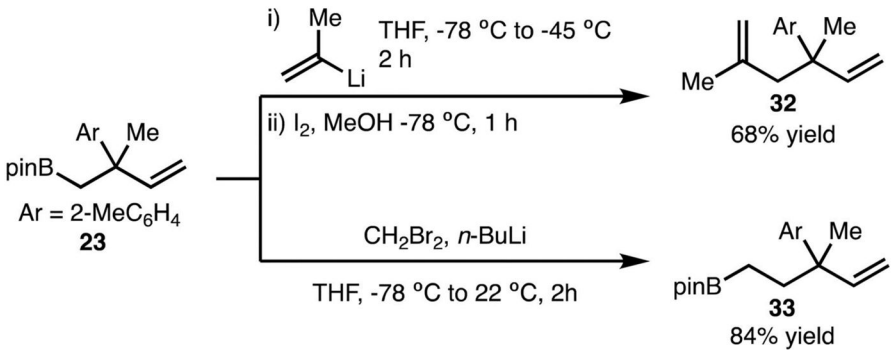
Scheme 3.

Formation of 2,1-Arylboration Product with Bromopyridine

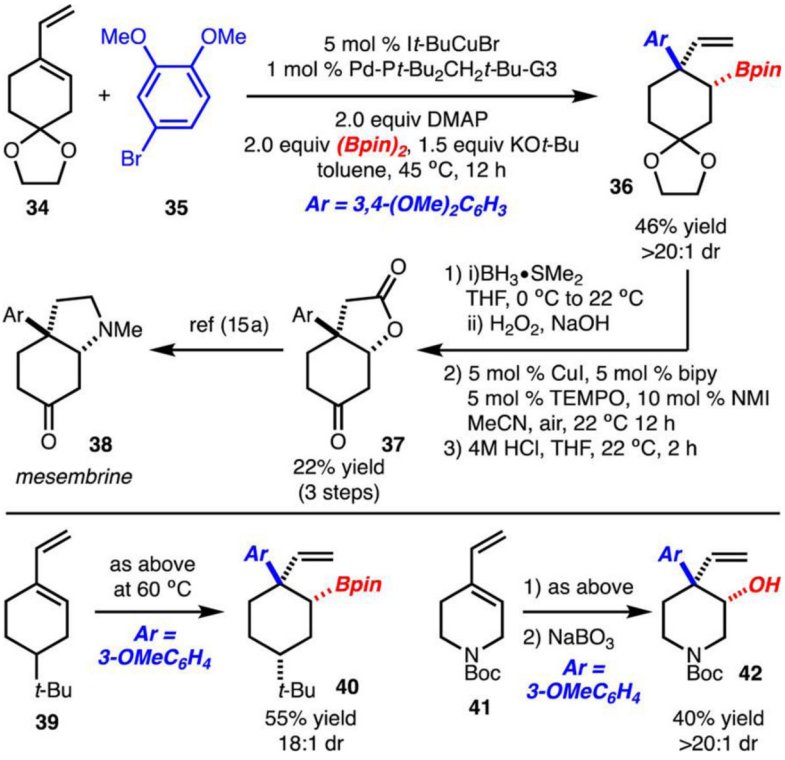


Scheme 4. Substrate Scope

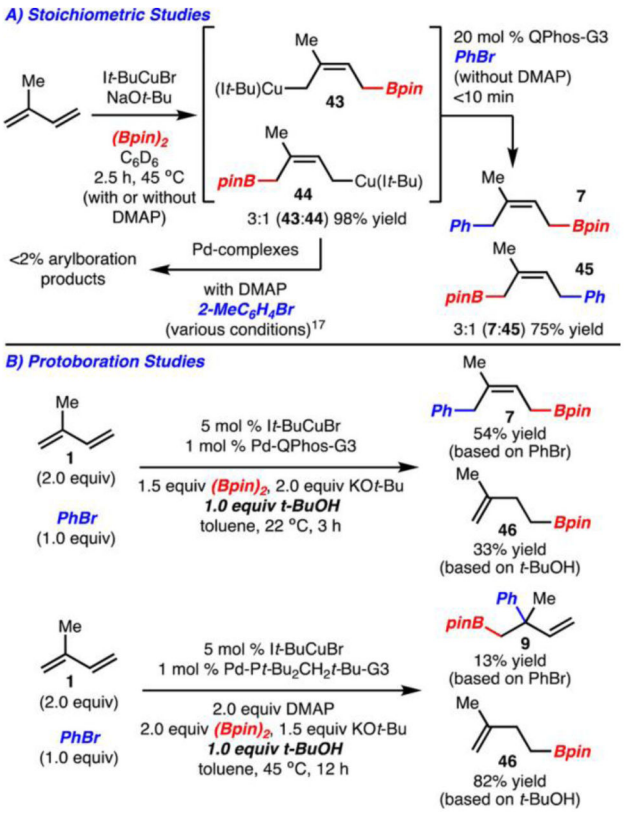
[a] Yield of isolated product (>20:1 product:other isomers) after silica gel column chromatography. [b]Yield determined by ^{1}H NMR analysis of the crude reaction mixture with an internal standard. [c]8:1 product:other isomers. [d]9:1 product:other isomers. [e]2:1 product:other isomers. [f]Yield reported for two steps after oxidation to alcohol, 16:1 product:other isomers, see the SI for details.



Scheme 5.
Representative Functionalizations



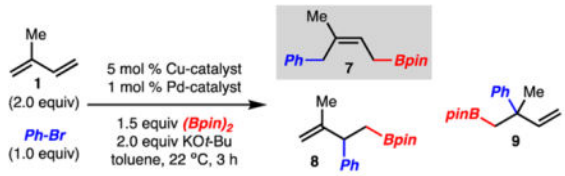
Scheme 6.
Stereoselective Arylboration



Scheme 7.
Mechanistic Studies

Table 1

Optimization of Reactions Conditions

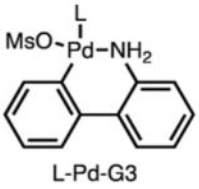


entry	Cu catalyst	Pd catalyst	7:8:9	yield of 7 (%)[a]
1[b]	IMesCuCl	Pd-P*t*-Bu$_3$-G3	3:1:2	24
2[b]	I*t*-BuCuBr	Pd-P*t*-Bu$_3$-G3	11:1:<0.1	42
3	I*t*-BuCuBr	Pd-P*t*-Bu$_3$-G3	11:1:<0.1	57
4	I*t*-BuCuBr	Pd-P*t*-Bu$_2$CH$_2$*t*-Bu-G3	3:1:< 0.1	47
5	I*t*-BuCuBr	Pd-QPhos-G3	15:1:<0.1	77
6[c]	I*t*-BuCuBr	Pd-QPhos-G3	10:1:<0.1	58

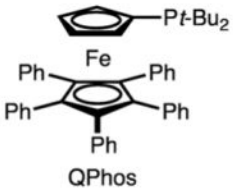
[a]Yield and product ratios determined by ^{1}H NMR analysis of the crude reaction mixture with an internal standard.

[b]Reaction run with 1.5 equiv of KO*t*-Bu instead of 2 equiv.

[c]Reaction run with NaO*t*-Bu instead of KO*t*-Bu.



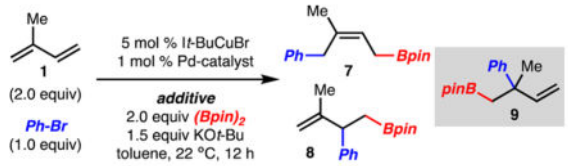
L-Pd-G3



QPhos

Table 2

Evaluation of Pyridine Derivatives as Additives



entry	additive/equiv	Pd catalyst	7:8:9[a]	yield of 9 (%)[a]
1	pyridine/1.0[b]	Pd-QPhos-G3	6:1:1	5
2	DMAP/1.0[b]	Pd-QPhos-G3	1:1:4	17
3	DMAP/1.0	Pd-QPhos-G3	2:1:3	34
4	DMAP/1.0	Pd-P*t*-Bu_3-G3	4:1:2	14
5	DMAP/1.0	Pd-APhos-G3	1:1:5	27
6	DMAP/1.0	Pd-P*t*-Bu_2CH_2*t*-Bu-G3	1:1:11	68
7	DMAP/1.0[c]	Pd-P*t*-Bu_2CH_2*t*-Bu-G3	2:1:13	67
8	DMAP/2.0[c]	Pd-P*t*-Bu_2CH_2*t*-Bu-G3	1:1:>20	61
9	DMAP/2.0[c]	$[Pd\text{-}G3]_2$	n.d.	<2
10	DMAP/2.0[c,d]	Pd-P*t*-Bu_2CH_2*t*-Bu-G3	n.d.	<2

[a]Yield and (1,2):(1,4) determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

[b]Reaction run with 1.5 equiv of $(Bpin)_2$ and 2.0 equiv of KO*t*-Bu.

[c]Reaction run at 45 °C instead of 22 °C.

[d]Reaction run with 5 mol% CuBr instead of 5 mol% I*t*-BuCuBr. n.d. = not determined