Cross-Coupling

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Copper/Palladium Synergistic Catalysis for the *syn*- and *anti*-Selective Carboboration of Alkenes**

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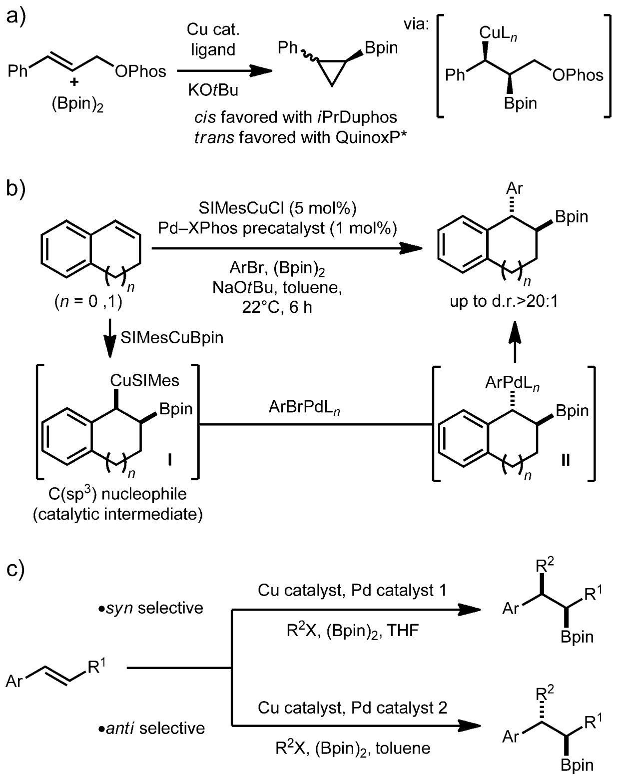
Abstract: *A method for the diastereoselective carboboration of 1,2-disubstituted styrenes with aryl/vinyl bromides and* $(Bpin)_2$ *is reported. High diastereoselectivities and yields are observed for the formation of either diastereomer of the product from a single alkene isomer. These reactions provide access to a diverse range of structures from simple starting materials.*

In recent years, carboboration reactions of π bonds have been established as important methods for the conversion of simple hydrocarbon starting materials to synthetically useful products that incorporate an organoborane. The vast majority of these methods involve the carboboration of alkynes or allenes under Pd, Ni, or Cu catalysis.[1] The carboboration of alkenes has received much less attention, but has been achieved under Pd,[2] Cu,[3] or Pd/Cu catalysis.[4] For reactions with 1,2-disubstituted alkenes, diastereocontrol becomes an additional challenge. While excellent levels of selectivity have been achieved, the preferential formation of only one isomer of the product is common.[3a–c,f,4b] Methods that can control the formation of either diastereomer are much more challenging. The only example with which this has been achieved in a carboboration was reported by Ito and Sawamura, who demonstrated that either diastereomer of a cyclopropane product could be generated by judicious choice of the ligand (Scheme 1 A).[3c] These reactions likely proceeded by initial formation of a C(sp^3)–Cu complex by borometalation of an alkene with a Cu–Bpin complex, followed by intramolecular stereoinvertive or stereoretentive electrophilic capture.

Our group[4b,5] and that of Semba and Nakao[4a] independently reported a new approach toward the intermolecular carboboration of alkenes by Pd/Cu synergistic catalysis[6] (e.g., Scheme 1 B) that allows the use of aryl and vinyl halides. These reactions likely function by borometalation with a Cu–Bpin complex across an alkene to generate a C(sp^3)–Cu complex (**I**),[7] which then undergoes transmetalation with an XPdAr complex to provide a new C(sp^3)–Pd complex (**II**). Reductive elimination of **II** provides the product and regenerates a Pd^0 complex.

These reactions are significant because they constitute a difunctionalization of vicinal alkenes with the potential for controlling the relative stereochemistry. Additionally, we envisioned using these reactions as a platform to develop methods for the stereoselective cross-coupling of stereodefined C(sp^3) nucleophiles (e.g., Cu complex **I**, Scheme 1 B),[4] which is a recognized problem in chemical synthesis.[8–10] Accordingly, in our initial disclosure, we demonstrated highly diastereoselective reactions with cyclic styrene derivatives, however, extension of this methodology to acyclic systems resulted in low levels of diastereoselectivity. Herein, we report highly diastereoselective reactions with acyclic 1,2-disubstituted styrenes, and, most notably, the synthesis of either diastereomer of the product from a single alkene isomer through a simple change of the reaction conditions (Scheme 1 C).[11]



Scheme 1. Cross-coupling with catalytically generated nucleophiles. Previous work: a) intramolecular tunable carboboration, and b) diastereoselective carboboration of cyclic alkenes. This work: c) intermolecular tunable carboboration.

We initiated our investigation by examining reactions of *trans*-β-methylstyrene (**1**). Under the previously identified optimal conditions,[4b] a 1:1 mixture of diastereomers **2** and **3** was obtained, albeit in good yield (Table 1, entry 1). Further

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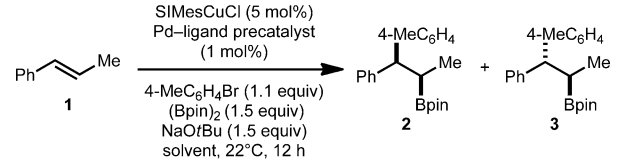
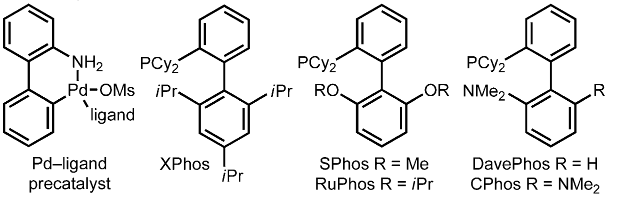
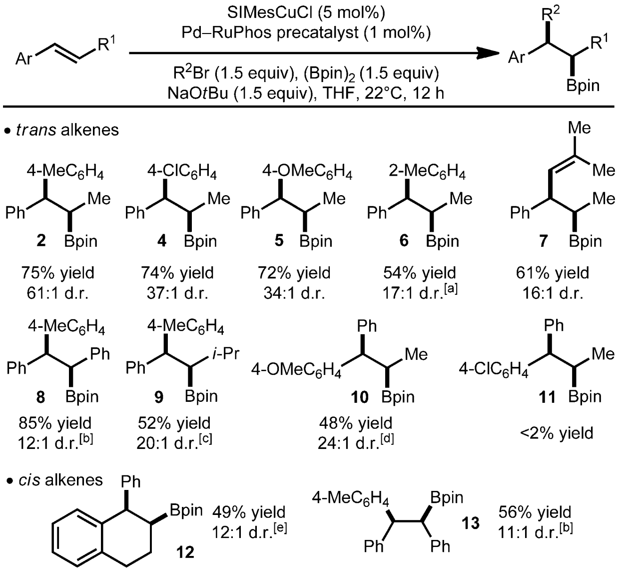
Table 1: Optimization of reaction conditions.



Entry	Ligand	Solvent	Yield [%][a]	d.r. (**2**:**3**)[b]
1	XPhos	toluene	83	1:1
2	XPhos	THF	68	6:1
3	SPhos	THF	>98	20:1
4	**RuPhos**	**THF**	**98**	**62:1**
5	DavePhos	THF	80	12:1
6	CPhos	THF	53	6:1

[a] Yields determined by GC analysis with a calibrated internal standard. [b] Diastereomeric ratios (d.r.) determined by GC analysis. Entry in bold marks optimized reaction conditions.





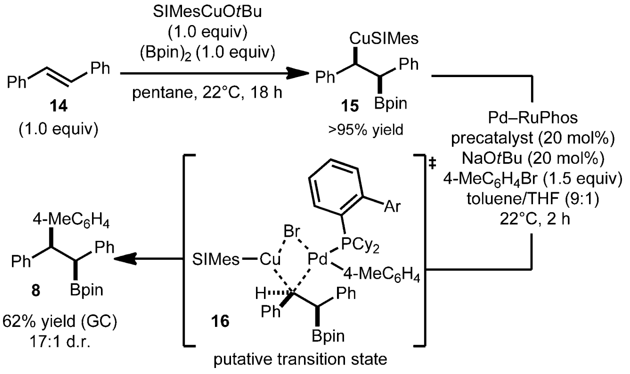
Scheme 2. *syn*-selective carboboration of alkenes. Yields reported as the average of at least two experiments. Diastereomeric ratios (d.r.) determined by GC analysis of the unpurified reaction mixture. [a] With 3 mol% Pd–RuPhos and run for 24 h. [b] Toluene/THF = 9:1 instead of THF for 24 h. [c] With 2 mol% Pd-RuPhos precatalyst, 5 mol% SIMesCuCl, 2.0 equiv NaO*t*Bu, 2.0 equiv (Bpin)$_2$, 2.0 equiv 4-MeC$_6$H$_4$Br, for 24 h. [d] 2 mol% Pd–RuPhos precatalyst, 10 mol% SIMesCuCl, 2.0 equiv NaO*t*Bu, 2.0 equiv (Bpin)$_2$, 2.0 equiv PhBr, for 24 h. [e] LiO*t*Bu used instead of NaO*t*Bu in toluene/THF = 10:1.

evaluation of the reaction conditions led to the discovery that use of THF instead of toluene as solvent provided diastereomer **2** in 6:1 d.r. (Table 1, entry 2). The assessment of related ligand scaffolds led to the identification of RuPhos as the best ligand, which furnished the product with excellent levels of diastereoselectivity and yield (Table 1, entry 4).[12] Use of other structurally similar phosphines afforded the product in lower levels of diastereoselectivity (Table 1, compare entry 4 with entries 3, 5, and 6).[13]

With the optimized reaction conditions in hand, the scope of the process was evaluated. As illustrated in Scheme 2, electron-rich (see product **5**), electron-poor (see product **4**), and sterically hindered (see product **6**) aryl bromides undergo reaction with uniformly good levels of diastereoselectivity and yield. Furthermore, use of a vinyl bromide provided **7** in good diastereoselectivity and yield.

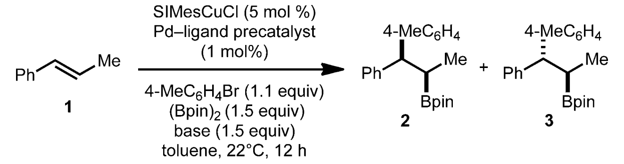
The substrate scope with respect to the alkene was also evaluated, and several points are noteworthy: 1) Electron-rich *trans*-β-methylstyrene derivatives undergo the reaction with good levels of yield and diastereoselectivity (see product **10**). Electron-deficient *trans*-β-methylstyrene derivatives fail to undergo reaction, likely because of a slow transmetalation with the more electron-poor C(sp^3)–Cu complex (product **11**). 2) Substitution of the Me group of *trans*-β-methylstyrene for either Ph or *i*Pr does not adversely affect the outcome of the reaction (see products **8** and **9**). 3) We have also investigated reactions with *cis* alkenes. Reactions of both 1,2-dihydronaphthalene and *cis*-stilbene provided the expected products (**12** and **13**) with good levels of diastereoselectivity. 4) For select cases, the use of a mixture of toluene and THF instead of THF as the sole solvent led to significantly improved yields with an acceptable decrease in selectivity. For example, preparation of **8** in THF occurred in only 23% yield (GC) but 60:1 d.r. (compare with the reaction in toluene/THF = 9:1, which resulted in the formation of **8** in 85% yield, 12:1 d.r.).

The mechanism was investigated by carrying out the reaction in a stepwise manner (Scheme 3). Treatment of *trans*-stilbene (**14**) with SIMesCuO*t*Bu and (Bpin)$_2$ in pentane provided C(sp^3)–Cu complex **15** in d.r. > 20:1 and more than 95% yield. Because of the poor stability of this complex in solution over extended periods of time, full characterization was not possible. However, the identities of closely related complexes have been confirmed by X-ray crystallography.[7a] Complex **15** was then treated with 20 mol% of the Pd–RuPhos precatalyst (activated with 20 mol% NaO*t*Bu) and 4-MeC$_6$H$_4$Br to provide **8** in 62% yield and 17:1 d.r. We suspect that the stereoretentive transmetalation proceeded through



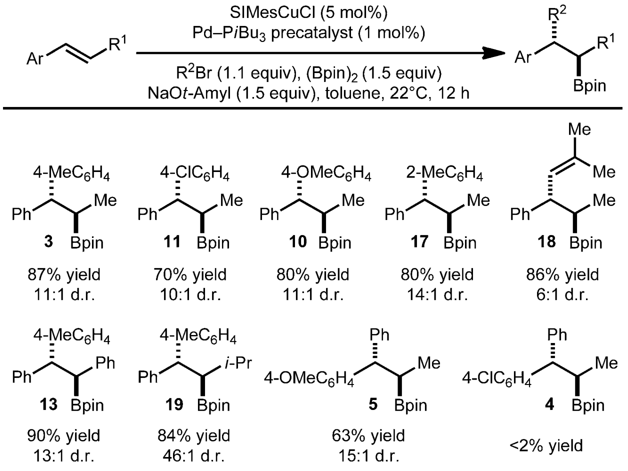
Scheme 3. Study of the reaction mechanism under *syn*-selective conditions.

Table 2: Optimization of conditions for *anti*-selective reaction.



Entry	Ligand	Solvent	Yield [%][a]	d.r. (**2**:**3**)[b]
1	XPhos	NaO*t*Bu	83	1:1
2	PCy$_3$	NaO*t*Bu	98	1:4
3	P*n*Bu$_3$	NaO*t*Bu	50	1:4
4	P*i*Bu$_3$	NaO*t*Bu	98	1:9
5	**P*i*Bu$_3$**	**NaO*t*-Amyl**	**98**	**1:11**
6[c]	P*i*Bu$_3$	NaO*t*-Amyl	45	1:3
7	RuPhos	NaO*t*Bu	68	2:1
8[d]	P*i*Bu$_3$	NaO*t*Bu	47	4:1

[a] Yields determined by GC analysis with a calibrated internal standard. [b] Diastereomeric ratios (d.r.) determined by GC analysis. [c] With 20 mol% Pd–P*i*Bu$_3$ precatalyst. [d] Reaction carried out in THF. Entry in bold marks optimized reaction conditions.



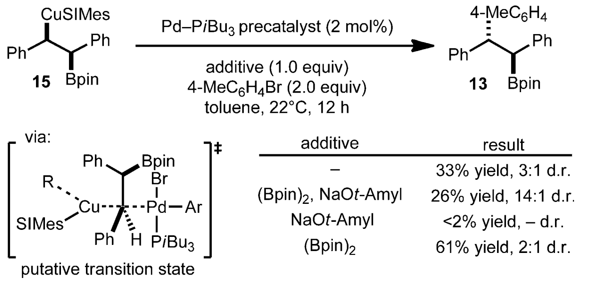
Scheme 4. Substrate scope for *anti*-selective reaction. Isolated yield reported as the average of at least two experiments except where noted. Diastereomeric ratio (d.r.) was determined by GC analysis of the unpurified reaction mixture. [a] Yield determined by GC analysis with a calibrated internal standard.

transition state **16**. This model is based on previously reported stereoretentive transmetalation processes.[11,14,15]

Based on the low selectivity observed with reactions promoted by Pd–Xphos in toluene (Table 2, entry 1) and our success in identifying *syn*-selective reaction conditions, we reasoned that the carboboration reaction might also be tuned to be an *anti*-selective process. An evaluation of ligands showed that PCy$_3$ ligated to Pd led to the formation of diastereomer **3** in 4:1 d.r. (Table 2, entry 2). Examination of related trialkylphosphines led to the finding that P*i*Bu$_3$ provided **3** in 9:1 d.r. (Table 2, entry 4). The selectivity could be improved to 11:1 d.r. if NaO*t*-Amyl was used in place of NaO*t*Bu (compare Table 2, entries 4 and 5). Thus, conditions have been identified that lead to the formation of diastereomeric products from a single alkene isomer.

Several points regarding this process are noteworthy: 1) P*i*Bu$_3$ is inexpensive and seldom used in cross-coupling reactions.[16] In addition, while P*i*Bu$_3$ is highly air-sensitive, the Pd–P*i*Bu$_3$ precatalyst was found to be air-stable. 2) Increased Pd catalyst loading resulted in lower diastereoselectivity, likely resulting from Pd^0 nucleophilic displacement of the putative C(sp^3)–Pd complex (Table 2, entry 6).[17] 3) This reaction exhibits a similar substrate scope to that demonstrated with the *syn*-selective conditions (compare Scheme 2 and Scheme 4). In all cases, the product of an *anti*-selective carboboration occurred with good levels of diastereoselectivity. 4) As with the *syn*-selective conditions, the primary limitation is the reaction with electron-deficient *trans*-β-methylstyrene derivatives (product **4**, Scheme 4). Additionally, reactions of *cis* alkenes were also investigated (e.g., *cis*-stilbene, 1,2-dihydronaphthalene), however, with Pd–P*i*Bu$_3$ as the catalyst, low levels of diastereoselectivity were observed (d.r. < 2:1). This data suggests that the existing stereogenic center bearing the C–Bpin motif can affect the selectivity of the putative transmetalation event. However, as previously reported, reactions with cyclic alkenes are highly *anti*-selective using Pd–XPhos as the catalyst.[4b] 5) In general, the *syn*-selective conditions provided the product with higher levels of diastereoselectivity, yet lower yield compared to the *anti*-selective conditions. 6) Reactions with Pd–RuPhos in toluene led to the formation of diastereomer **2** in 2:1 d.r. (Table 2, entry 7). In addition, the reaction with Pd–P*i*Bu$_3$ in THF provided diastereomer **2** as the major product in 4:1 d.r. (Table 2, entry 8). Thus, the reversal in diastereoselectivity is a combination of both solvent and ligand effects.[18]

The mechanism of the *anti*-selective carboboration was also investigated with isolated C(sp^3)–Cu complex **15** (Scheme 5). However, much lower selectivity was observed for the stoichiometric reaction versus the catalytic reaction (compare, Scheme 5, formation of **13** in 3:1 d.r., and Scheme 4, formation of **13** in 13:1 d.r.). The diastereoselectivity of the catalytic reaction was only reproduced when (Bpin)$_2$ and NaO*t*-Amyl were added to the stoichiometric reaction.[19] This effect can be rationalized by inspection of the putative transition state for the stereoinvertive transmetalation illustrated in Scheme 5.[11,15,20] A likely requirement of this model is the coordination of the Cu atom with an external nucleophile (e.g., R = Na$^+$(Bpin)$_2$O*t*-Amyl$^-$) to facilitate transmetalation. In the absence of this precoordination, a high-energy SIMesCu$^+$ would be generated. Full evaluation



Scheme 5. Study of reaction mechanism for *anti*-selective conditions.

of the reaction mechanism is necessary but will have to await further study.

In summary, we have developed a new method for the diastereoselective carboboration of 1,2-disubstituted styrene derivatives. Through the identification of two sets of conditions, either diastereomer of the product can be formed from a single alkene isomer. Further studies aim to understand the mechanism of these processes as well as extend the scope to related systems.

Keywords: carboboration · copper · cross-coupling · palladium · synergistic catalysis

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[18] Under either set of conditions, *trans*-vinyl silanes and aliphatic alkenes are unreactive.

[19] See the Supporting Information for more details. It should also be noted that the low yield is due to competitive formation of 4-MeC_6H_4Bpin.

[20] For examples of stereoinvertive transmetalation, see: a) ref. [9g]; b) ref. [11].

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