Cross-Coupling

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Copper-Catalyzed Cross-Coupling of Boronic Esters with Aryl Iodides and Application to the Carboboration of Alkynes and Allenes**

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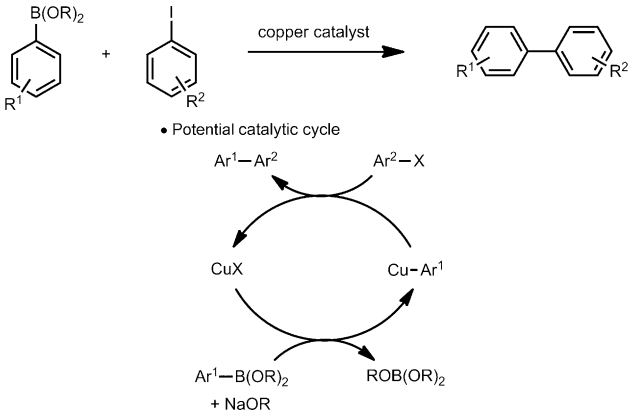
Abstract: *Copper-catalyzed Suzuki–Miyaura-type cross-coupling and carboboration processes are reported. The cross-couplings function well with a variety of substituted aryl iodides and aryl boronic esters and allows for orthogonal reactivity compared to palladium-catalyzed processes. The carboboration method includes both alkynes and allenes and provides access to highly substituted and stereodefined vinyl boronic esters. The alkyne carboboration method is highlighted in the simple one-pot synthesis of Tamoxifen.*

Copper-catalyzed cross-coupling reactions are valuable reactions for chemical synthesis.[1,2] A variety of methods are known for the preparation of C–C,[3–7] C–O,[8] C–N,[9,10] C–S,[11] and C–X bonds.[12] Despite these advances, generally effective and mild copper-catalyzed Suzuki–Miyaura-type cross-couplings,[13,14] especially with C(sp^2) electrophiles, are lacking.[3]

Herein we disclose a method for mild copper-catalyzed Suzuki–Miyaura-type cross-couplings. Introduction of this method allows the identification of orthogonal reactivity relative to palladium-catalyzed Suzuki–Miyaura cross-couplings and has led to the development of novel carboboration processes. Therefore, our interest in this area is driven both by the low cost and low toxicity[15] associated with copper, as well as by the discovery of new reactivity that will lead to the synthesis of important molecules which were previously difficult to access.

Li and co-workers have developed copper-catalyzed Suzuki–Miyaura-type processes, however high temperatures (125 °C in DMF) are needed and the reaction does not work with sterically hindered or electron-poor aryl boronic acids.[3c,d] Other systems involve the use of copper nanoclusters[3a,b] or copper powder in polyethylene glycol solvents.[3f] Recent studies by Liu and co-workers have demonstrated that CuCl can promote the reaction of a variety of aryl and alkyl boronic esters with unhindered C(sp^3) electrophiles, and is likely to proceed through an S_N2-type pathway.[3f]

To develop a copper-catalyzed Suzuki–Miyaura-type cross-coupling, we envisioned an initial reaction between $ArB(OR)_2$ and CuX. We hypothesized that the resulting nucleophilic Ar-Cu^{I}[16] species could react with an electrophilic aryl halide, perhaps proceeding through a Cu^{III} intermediate (Scheme 1).[17] This type of cross-coupling, while not unprecedented,[18] differs significantly from traditional processes involving palladium complexes in which reaction with the ArX precedes that with $ArB(OR)_2$.[13]



Scheme 1. Overall reaction scheme for copper-catalyzed cross-coupling and generalized putative catalytic cycle.

We initiated our studies by examination of the cross-coupling reaction between the *p*-tolylphenyl boronic ester **1** and iodobenzene (**2**). Initial success was achieved with IMes/CuCl in the presence of 1.2 equivalents of NaO*t*Bu at 80 °C (Table 1, entry 1). Reaction optimization was achieved primarily through the evaluation of the ligand. Xantphos was identified to be the optimal ligand for this system in combination with 2–3 equivalents NaO*t*Bu (Table 1, entries 7 and 8). Reactions at lower temperature (60 °C versus 80 °C) or with a reduced reaction time (8 h versus 15 h) provided the product in diminished but acceptable yields (compare entry 8 with entries 9 and 10, Table 1).[19] Finally, it should be noted that the coupling reaction in the absence of a ligand or copper does not proceed (Table 1, entries 11 and 12).[20]

With an optimized set of reaction conditions in hand we explored the scope and limitations of this process. Several points learned from these studies are noteworthy (Table 2): 1) electron-deficient and electron-rich aryl boronic esters and aryl iodides undergo cross-coupling in good yield. 2) Sterically hindered aryl boronic esters undergo cross-coupling in good yield, however [Cy_3PCuCl] was necessary for this process (Table 2, entries 4 and 16). For example, the reactions

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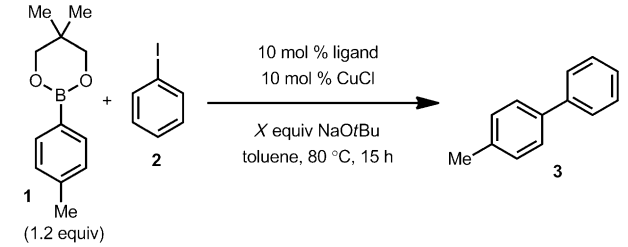
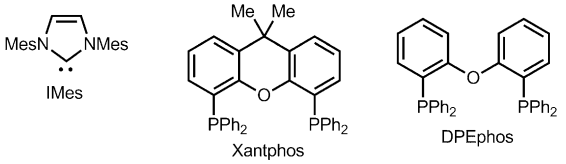
Table 1: Optimization studies.[a]



Entry	Ligand	*T* [°C]	*X* equiv NaO*t*Bu	Yield [%][b]
1	IMes	80	1.2	28
2	DPEPhos	80	1.2	6
3	dppb	80	1.2	8
4	dppf	80	1.2	29
5	PCy_3	80	1.2	56
6	Xantphos	80	1.2	82
7	Xantphos	80	2.0	96
8	Xantphos	80	3.0	99
9	Xantphos	60	3.0	72
10	Xantphos	80	3.0	88[c]
11	none	80	3.0	< 2
12	Xantphos (no CuCl)	80	3.0	< 2

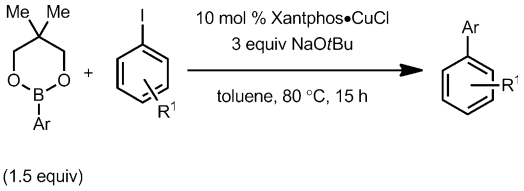
[a] See the Supporting Information for experimental details. [b] Yield determined by GC analysis using *n*-dodecane as an internal standard. [c] Reaction run for 8 h. dppb = 1,4-bis(diphenylphosphino)butane, dppf = 1,1′-bis(diphenylphosphino)ferrocene.



presented in entries 4 and 16 of Table 2, promoted by Xantphos/CuCl provided the product in 55 and 65% yield, respectively. 3) Reactions with aryl bromides resulted in complete recovery of the starting materials. 4) Boronic acids are not suitable substrates for the process because of rapid protodemetallation of the putative aryl copper intermediate. 5) Boronic esters derived from pinacol can be used in this process, however reduced yields were observed. For example, cross-coupling of PhBpin with 4-iodochlorobenzene promoted by 10 mol% Xantphos/CuCl at 80°C provided the desired product in 44% yield (compare with Table 2, entry 1).

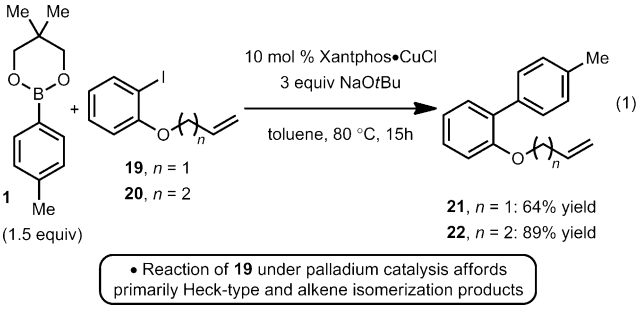
The alkene-substituted aryl iodides **19** and **20** were investigated to probe the mechanistic question of whether or not radical intermediates are generated [Eq. (1)].[21] Under the optimized reaction conditions, cross-coupling of **19** and **20** with **1**, catalyzed by Xantphos/CuCl, proceeded smoothly to generate **21** (64%) and **22** (89%), respectively, without the formation of any cyclized products (< 2%). This data suggests that radical intermediates are not involved in the cross-coupling.[21] In addition, these reactions also demonstrate that orthogonal reactivity compared to that of palladium-catalyzed reactions may be achieved. For example, the analogous reaction between **1** and **19** promoted by palladium catalysts leads not to the formation of **21** but rather to the formation of Heck-type products.[22]

Table 2: Copper-catalyzed cross-coupling: Substrate scope.[a]



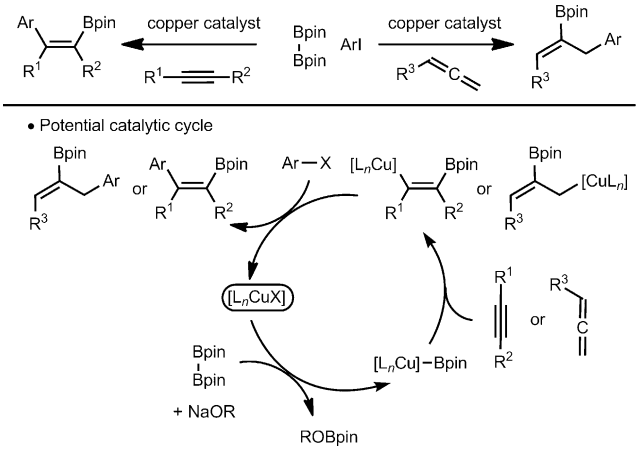
Entry	Ar	ArI	Product	Yield [%][b]
1	C_6H_5	4-ClC_6H_4I	**4**	94
2	4-MeC_6H_4	4-ClC_6H_4I	**5**	90
3	3,4-$Cl_2C_6H_3$	4-ClC_6H_4I	**6**	92
4	1-napht	4-ClC_6H_4I	**7**	82[c]
5	2-napht	4-ClC_6H_4I	**8**	89
6	4-$OMeC_6H_4$	4-ClC_6H_4I	**9**	96
7	4-$CF_3C_6H_4$	4-ClC_6H_4I	**10**	76
8	Ph	4-ClC_6H_4I	**11**	70
9	4-MeC_6H_4	C_6H_5I	**3**	90
10	4-MeC_6H_4	4-MeC_6H_4I	**12**	70
11	4-MeC_6H_4	4-$CF_3C_6H_4I$	**13**	90
12	4-MeC_6H_4	4-$OMeC_6H_4I$	**14**	76
13	4-MeC_6H_4	2-MeC_6H_4I	**15**	71
14	4-MeC_6H_4	4-iodopyridine	**16**	80
15	4-$CF_3C_6H_4$	2,6-$Me_2C_6H_3I$	**17**	71[d]
16	1-napht	2,6-$Me_2C_6H_3I$	**18**	75[c]

[a] See the Supporting Information for experimental details. [b] Yield of the isolated product after silica gel column chromatography. [c] Reactions run with 10 mol% Cy_3PCuCl at 120°C. [d] Reaction carried out at 120°C.



The cross-coupling reactions presented above likely involve the intermediacy of RCu^I (R = aryl or vinyl), which is generated by a transmetalation process. We hypothesized that if RCu^I intermediates could be generated through a migratory insertion across C–C π bonds and then subjected to reaction with aryl halides, useful three-component reactions could be developed.

The addition of Cu^I/Bpin complexes across alkynes and allenes has been established to be an efficient process for the generation of vinyl– and allyl–copper bonds, respectively (Scheme 2).[23] Typically, the organocopper bond is subject to protonation and thus constitutes a hydroboration process.[24,25a–d,26] Much less developed are examples where the organocopper bond is intercepted with a carbon-based electrophile.[25e,27–29] Furthermore, trapping of the organocopper with aryl halides is unknown and development of such a process would establish a straightforward and useful method



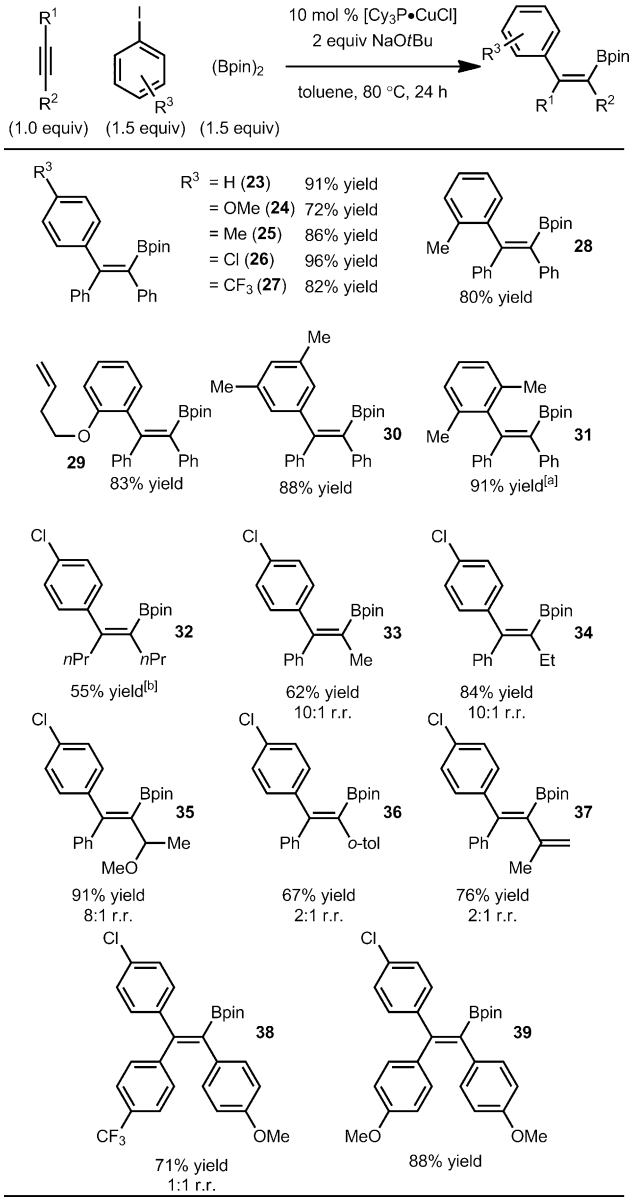
Scheme 2. Overall reaction scheme for carboboration and potential catalytic cycle. pin = pinacol.

for carboboration. Described below is the development of carboboration reactions with alkynes and allenes.

We have discovered that the vinyl–copper bond generated through a migratory insertion of a Cu/Bpin complex across an alkyne could be subjected to cross-coupling with an aryl iodide (Scheme 3). This method is important because it provides access to highly substituted alkenes, which is a challenging problem in chemical synthesis.[30,31] The optimal catalyst for these reactions was determined to be the readily available and inexpensive [Cy_3PCuCl], and the reaction proceeded under relatively mild reaction conditions (80 °C). Premature reaction of an in situ generated Cu/B intermediate with the aryl iodide was slow relative to reactions with an alkyne.[32] The process was tolerant of a variety of aryl iodide substitution patterns and provided the product as a single alkene isomer (**23**–**32** and **39**; Scheme 3). With unsymmetrical alkynes, regioisomers were often generated (**33**–**38**). For example, reactions with aryl/alkyl alkynes led to formation of **33**–**35** with high levels of regioselectivity ($\geq$8:1) while reactions with unsymmetrical alkynes bearing two different C(sp^2)-derived substituents resulted in formation of the desired products in low regioselectivity ($\leq$2:1; **36**–**38**). Reactions with terminal alkynes led to low yields of the desired product, with formation of the disubstituted vinylborane as the major product. This product likely arises by protonation of the vinyl copper intermediate with the terminal alkyne hydrogen.[33].

The utility of the carboboration process was highlighted in the rapid synthesis of the estrogen receptor antagonist Tamoxifen [Eq. (2)]. Copper-catalyzed carboboration of the commercially available alkyne **41** with the aryl iodide **40** (prepared in one step) resulted in the formation of **42** (which can be isolated if necessary in 80% yield and 10:1 r.r.). Iodobenzene and additional NaO*t*Bu and [Cy_3PCuCl] were then added and the reaction mixture heated for an additional 24 hours to provide Tamoxifen, after isolation, in 36% yield (>10:1 d.r.). This strategy constitutes a simple two-step synthesis of Tamoxifen.[34]

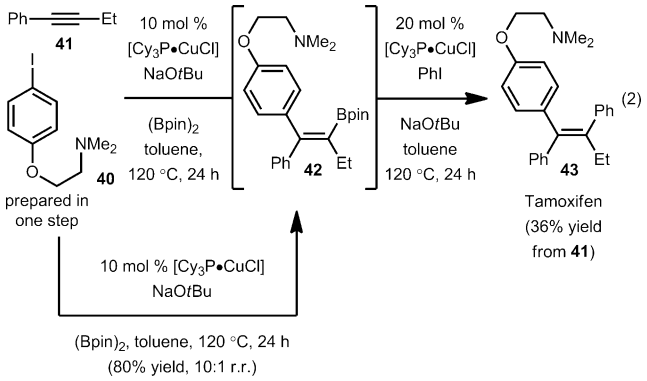
We have investigated the mechanism of the carboboration of alkynes by preparation of a putative intermediate [Eq. (3)].

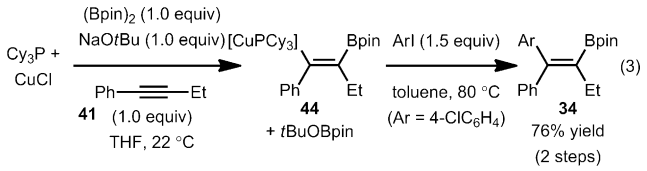


Scheme 3. Copper-catalyzed carboboration of alkynes. See the Supporting Information for experimental details. Yield refers to yield of isolated product after silica gel column chromatography. A >20:1 d.r. is observed in all cases as determined by ^{1}H NMR analysis of the unpurified reaction mixture. Regioisomeric ratios (r.r.) determined by ^{1}H NMR analysis of the unpurified reaction mixture. [a] Reaction carried out at 120 °C [b] Reactions run with 10 mol% [IMesCuCl] at 120 °C.

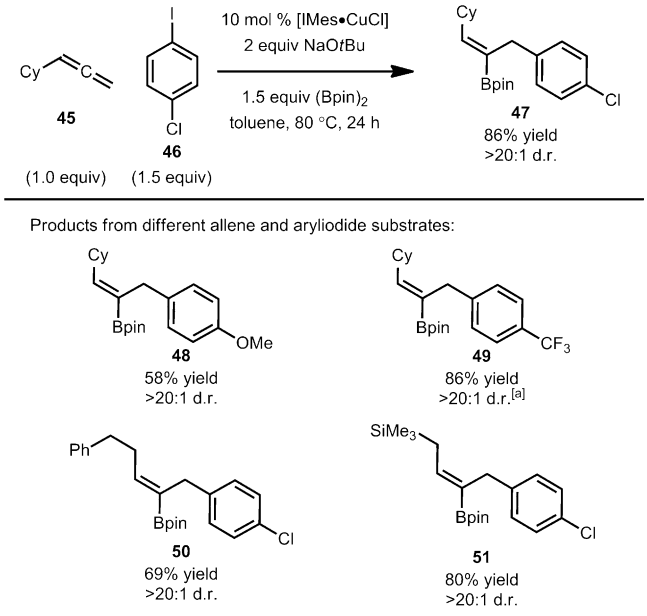
Thus, treatment of in situ generated [Cy_3PCuCl] with NaO*t*Bu, $(Bpin)_2$, and **41** leads to the formation of the vinyl copper intermediate **44**. The selectivity of the migratory insertion of the putative intermediate, pinB–$CuPCy_3$, is in complete agreement with previous reports.[24,27] The reaction of **44** with 4-ClC_6H_4I led to formation of **34** in 76% yield with 10:1 d.r., thus confirming that vinyl copper intermediates are capable of reaction with an aryl iodide.[35]

Similarly, the carboboration of allenes functions well when [IMesCuCl] is employed as the catalyst, and leads to the formation of stereodefined vinyl boronic esters (**47**–**51**,





Scheme 4). The process is tolerant of a variety of aryl iodide substitution patterns. In all cases coupling of the generated putative allyl copper intermediate with the aryl iodide occurs at the least-substituted position. Furthermore, the *Z* alkene is generated exclusively in all cases. Thus, migratory insertion of pinB–CuIMes across the allene likely occurs from the least hindered π face to generate the least-substituted allyl copper complex, which is in accordance with prior observations.[25] These studies represent a rare example of a carboboration of an allene.[25e]



Scheme 4. Copper-catalyzed carboboration of allenes. See the Supporting Information for experimental details. Yield refers to yield of isolated product after silica gel column chromatography. A >98:2 d.r. and >98:2 r.r. observed in all cases as determined by ^{1}H NMR analysis of the unpurified reaction mixture. [a] Contaminated with ca. 7% of a protonated product. See the Supporting Information for details.

In conclusion, we have developed a copper-catalyzed Suzuki–Miyaura-type cross-coupling reaction. The process is notable for the wide substrate scope relative to known copper-catalyzed Suzuki–Miyaura-type cross-couplings.[3] Furthermore, because of the likely difference in reaction mechanism relative to related palladium-catalyzed reactions, unique reactivity can be achieved. These observations have led to the development of carboboration processes. Future efforts in this area will be directed toward expanding the scope to include less reactive aryl halides, elucidation of reaction mechanism, and development of enantioselective variants.

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