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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Diarylation of Alkenes by a Cu-Catalyzed Migratory Insertion/Cross-Coupling Cascade

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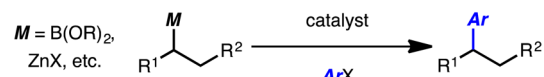
S *Supporting Information*

ABSTRACT: A strategy for the catalytic diarylation of alkenes is presented. The method involves the migratory insertion of alkenes into an Ar−Cu complex to generate a new $C(sp^3)$−Cu complex, which subsequently undergoes reaction with an aryl iodide to constitute a vicinal diarylation of an alkene. The method provides access to benzofuran- and indoline-containing products. Furthermore, highly diastereoselective examples are presented, allowing access to complex, stereochemically rich structures from simple alkene starting materials.
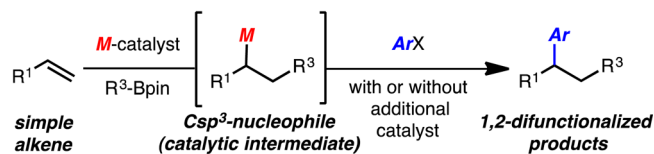
Cross-coupling reactions of $C(sp^3)$ nucleophiles have emerged as an important method for chemical synthesis.[1] The majority of these processes utilize pregenerated and often isolated nucleophiles (Scheme 1A). An alternative approach involves catalytic generation of a $C(sp^3)$ nucleophile by migratory insertion of an alkene followed by cross-coupling, according to the general reaction illustrated in Scheme 1B. A key feature of this method is that the $C(sp^3)$ nucleophile is a catalytic intermediate. *This strategy offers several advantages over traditional methods because readily available alkenes are used as the direct chemical input and both positions of the π bond are functionalized.* Thus, simple starting materials can be readily converted to significantly more complex structures in a single step.

Known methods for the general cross-coupling strategy outlined in Scheme 1B are relatively rare.[2] Cong and Fu[3] recently described a Ni-catalyzed vicinal dicarbofunctionalization of alkenes. For these reactions, a $C(sp^3)$−Ni complex was proposed to be generated by carbometalation of an Ar−Ni complex across a tethered alkene, which was followed by cross-coupling with an alkyl halide. Within the last several years, Cu-

Scheme 1. Complementary Approaches toward Cross-Coupling

A) Cross Coupling with Pregenerated Nucleophiles

B) Catalytic Migratory Insertion/Cross Coupling

catalyzed variants of this type of cross-coupling have emerged in reports from our lab[4] as well as others.[5] Ito, Sawamura, and Yoshida have demonstrated that $C(sp^3)$−Cu complexes, generated as catalytic intermediates through migratory insertion of alkenes into Cu−Bpin complexes, can be trapped with alkyl halides.[5a−c,f,i,j] We have developed two methods that allow for the cross-coupling of in situ-generated nucleophilic $C(sp^3)$−Cu complexes with aryl halides (Scheme 2A). Both of these methods
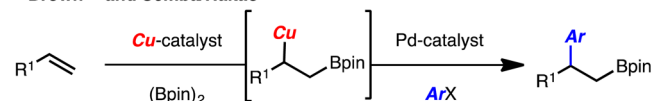
Scheme 2. Approaches toward Cu-Catalyzed Migratory Insertion/Cross-Coupling with Aryl Halides
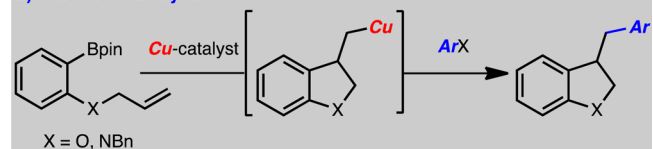
A) Previous Work: Arylboration

• *Brown[4a]*
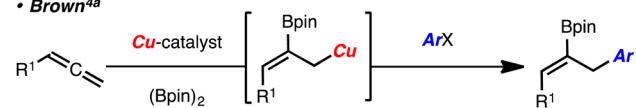
• *Brown[4b] and Semba/Nakao[5k]*

B) This Work: Diarylation

rely on the generation of the $C(sp^3)$−Cu complex by a migratory insertion of π bonds into Cu−Bpin complexes to ultimately constitute carboboration reactions. For reactions that involve allenes, the generated allyl−Cu complex can be directly trapped with an aryl halide.[4a] Carboboration of alkenes proved to be more challenging and required the use of a Pd catalyst to facilitate the reaction with the aryl halide.[4b] It should be noted that concurrent with our studies regarding the carboboration of alkenes, Semba and Nakao reported a related method.[5k]

To further extend the scope of migratory insertion/cross-coupling cascades, we sought to develop a method that could generate the $C(sp^3)$−Cu intermediate through carbometalation of a Cu−Ar complex across an alkene (Scheme 2B). After capture of the resulting $C(sp^3)$−Cu complex with an aryl halide, this process would constitute a vicinal diarylation of an alkene.[6] Diarylation reactions of alkenes are highly sought because rapid
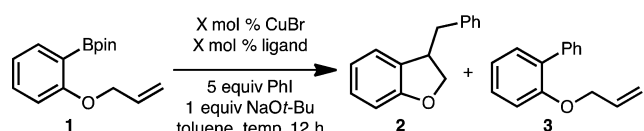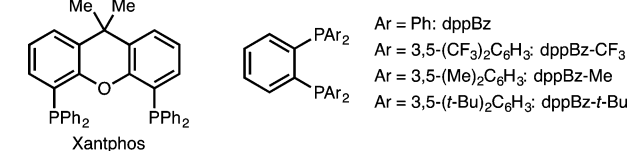
molecular complexity can be generated from simple components. Consequently, several methods have been introduced.[7] In all cases, the substrates must be designed to prevent, suppress, or in some cases take advantage of β-hydride elimination pathways. One of the benefits of the method outlined herein is that β-hydride elimination pathways are limited because C(sp³)−Cu complexes are generated.[8]

To begin our studies, we examined the cyclization of borane **1** (easily prepared in two steps) because (1) the reaction would provide an efficient synthesis of benzofuran-containing structures[9] and (2) the carbometalation of Cu−Ar across an alkene would be facilitated. This type of process is not known for Cu(I)−Ar complexes. Initial optimization studies revealed that reactions run in the absence of ligand or with monodentate ligands led to the formation of the direct cross-coupling product **3** (Table 1, entries 1 and 2). Further evaluation of ligands led to

Table 1. Optimization of the Cu-Catalyzed Diarylation Reaction[a]

| entry	X	ligand	temp (°C)	yield of 2 (%)[b]	2:3[c]
1	5	none	120	12	0.2:1
2	5	PCy₃	120	16	0.22:1
3	5	Xantphos	120	26	1.9:1
4	5	dppe	120	38	2.0:1
5	5	dppp	120	43	1.5:1
6	5	dppBz	120	34	3.8:1
7	1	dppBz	120	47	4.3:1
8	1	dppBz	140	52	5.8:1
9	1	dppBz-CF₃	140	71	4.2:1
10	1	**dppBz-Me**	140	74 (72)	7.4:1
11	1	dppBz-t-Bu	140	49	9.8:1
12	0	none	120	<2	N/A
13[d]	5	dppBz	120	<2	N/A

[a]See the Supporting Information (SI) for experimental details. [b]Determined by ¹H NMR analysis (400 MHz) with an internal standard. The value in parentheses is the yield of the isolated product. [c]Determined by ¹H NMR analysis (400 MHz). [d]NaO*t*-Bu was not used

the discovery that the use of bidentate ligands provided benzofuran **2** as the major isomer (entries 3−6). From these studies, 1,2-bis(diphenylphosphino)benzene (dppBz) was identified to be optimal because the product ratio (**2**:**3**) was the most favorable (entry 6). Increasing the temperature and reducing the catalyst loading from 5 to 1 mol % led to increases in the yield and the **2**:**3** ratio (entries 6−8). The increase in yield with a decrease in catalyst loading is unusual and is likely due to minimization of dimerization or bimolecular catalyst decomposition. On the basis of these assumptions, sterically larger catalysts were evaluated. These studies led to the identification of an optimal ligand, dppBz-Me, with which the desired product was generated in 74% yield (entry 10). Use of the even larger ligand dppBz-t-Bu led to

an increase in the **2**:**3** ratio but a decrease in the yield of **2** (entry 11). Finally, we note that using less PhI (3 vs 5 equiv) led to a decrease in the yield (59%) with a concomitant increase in the **2**:**3** ratio (19:1). However, the excess aryl iodide could be recovered in nearly quantitative yield at the end of the reaction.

With an optimized set of conditions in hand, we initially explored the scope of this method with respect to the aryl iodide (Scheme 3). A variety of electron-deficient, electron-rich, and

Scheme 3. Substrate Scope[a]
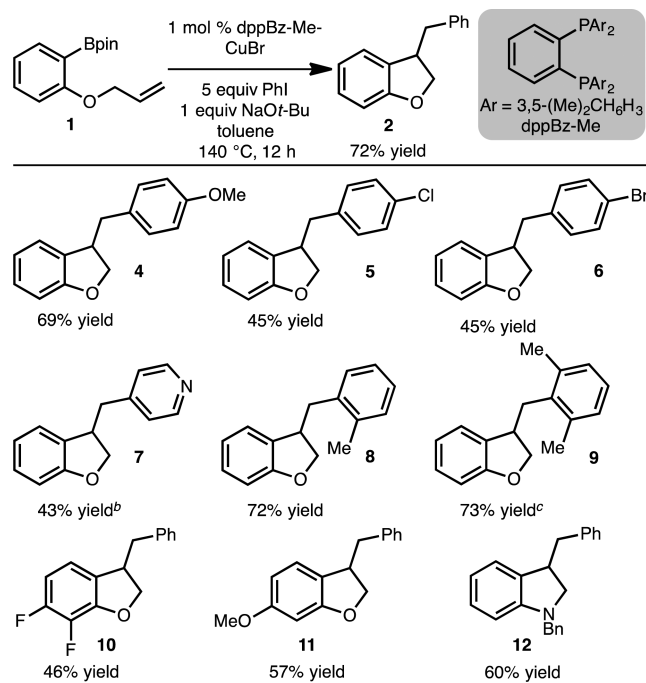
[a]See the SI for experimental details. Yields of isolated products (averages of two experiments) are shown. [b]3.0 equiv of ArI was used. [c]1.5 equiv of ArI was used.

heteroaryl iodides underwent the reaction in good yields (see products **4**−**7**). Notably, sterically hindered aryl iodides underwent the reaction to provide **8** and **9** in 72% and 73% yield, respectively. Electron-deficient and electron-rich substrates also functioned well under these reaction conditions (see products **10** and **11**, respectively). We also investigated the effect of the nature of the tether on the efficiency of the reaction. A substrate bearing an N linkage rather than an O linkage underwent reaction to provide **12** in 60% yield. Attempts to form carbocycles or six-membered rings were unsuccessful, as we observed only the products of direct cross-coupling. Finally, the moderate yields observed in some cases are primarily due to increased amounts of direct cross-coupling.[10,11]

The formation of quaternary carbons was also tolerated with this method. Thus, treatment of **13** with 5 mol % dppBz-Me−CuBr, PhI, and NaO*t*-Bu at 120 °C provided benzofuran **14** in 78% yield (Scheme 4). We also discovered that the use of PCy₃−CuCl led to formation of the direct cross-coupling product **15** (80% yield).[4a,12] Thus, differential reactivity was achieved through simple ligand selection and modest changes in the reaction conditions.

Diastereoselective variants of these reactions were also investigated. Substrate **16** bearing an additional methyl substituent in the tether underwent highly stereoselective

Scheme 4. Catalyst-Controlled Cross-Coupling
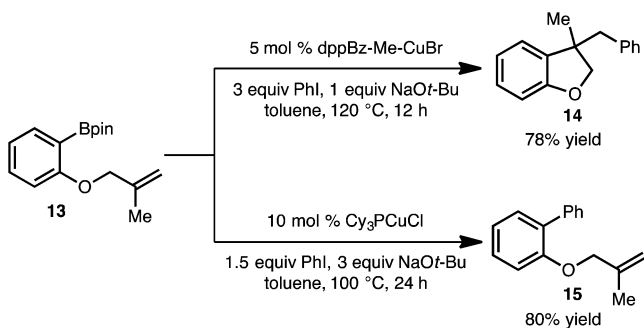
reaction (>20:1 dr) to provide **17** in 50% yield (eq 1). The reaction likely proceeded through the pre-transition-state assembly shown in eq 1, where the migratory insertion occurred from the less hindered face of the alkene.
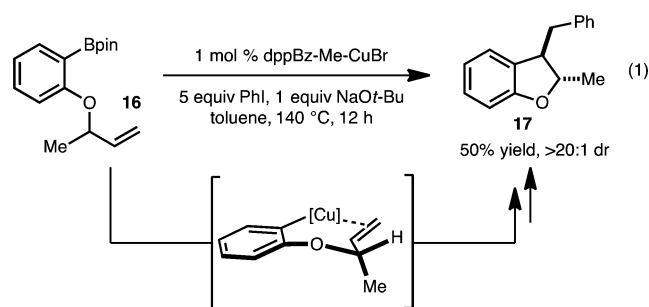

Diastereoselective reactions were also explored with 1,2-disubstituted alkenes. Since reactions with 1,2-dialkyl-substituted alkenes led only to direct cross-coupling, likely because of slow migratory insertion, styrene-derived substrates were examined (Scheme 5). Treatment of **18** with 1 mol % dppBz-CF$_3$−CuBr,

Scheme 5. Diastereoselective Cu-Catalyzed Diarylation[a]
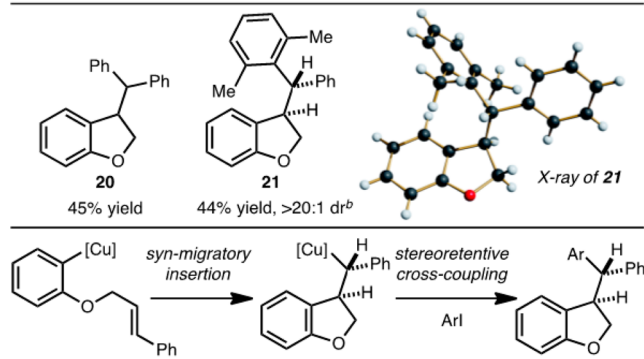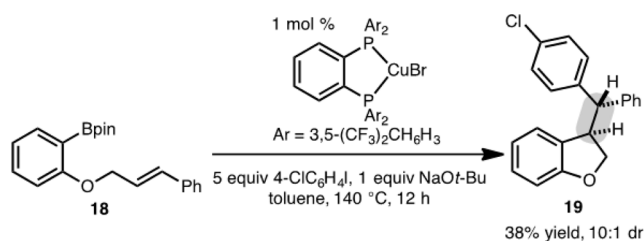
[a]See the SI for experimental details. Yields of isolated products (averages of two experiments) are shown. Diastereomeric ratios (dr) were determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [b]With 1.5 equiv of 2,6-(Me)$_2$C$_6$H$_3$I.

NaO*t*-Bu, and 4-ClC$_6$H$_4$I in toluene at 140 °C led to the formation of **19** in 38% yield with 10:1 dr.[13] Sterically hindered aryl iodides could also be used to generate **21** with high diastereoselectivity (>20:1 dr). The formation of the observed diastereomer is not likely the result of an equilibration of the putative C(sp^3)−Cu complex to a thermodynamic minimum because the use of the *Z* isomer of **18** provided the opposite diastereomer of **19** with 8:1 dr, albeit in low yield (data not shown).[10] The diastereoselectivity in these processes is intriguing because it is likely the result of syn migratory insertion followed by stereoretentive cross-coupling with ArI (Scheme 5). To the best of our knowledge, neither of these processes has been documented with Ar−Cu(I) complexes or C(sp^3)−Cu(I) complexes, respectively. These results also suggest that the reaction does not proceed via the intermediacy of radical intermediates, as low diastereoselectivity would be expected.

We carried out studies to provide further evidence for the proposed mechanism (Scheme 6). Treatment of dppBz−CuCl

Scheme 6. Mechanistic Studies[a]
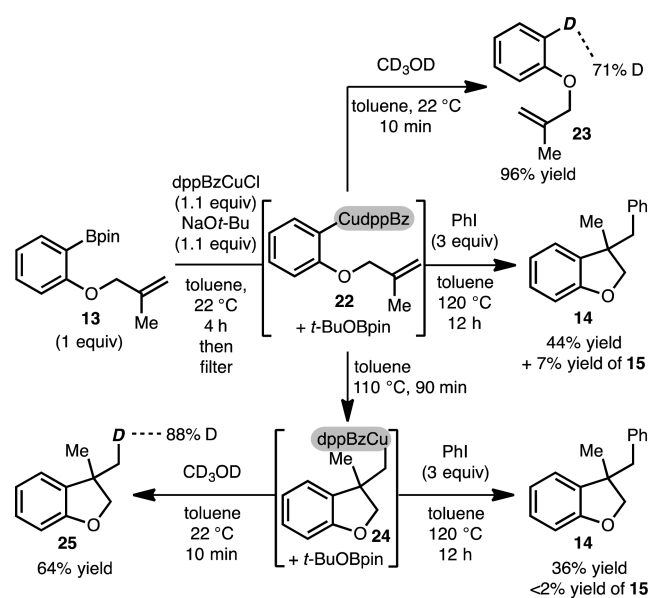
[a]See the SI for experimental details. Yields were determined by ^{1}H NMR analysis (400 MHz) of the unpurified reaction mixtures using an internal standard.

(1.1 equiv) with NaO*t*-Bu (1.1 equiv) and substrate **13** in toluene at 22 °C led to the formation of a new complex, tentatively assigned as **22**, within 4 h.[14] Treatment of **22** with CD$_3$OD led to the rapid formation of deuterated product **23** in 96% yield. Furthermore, addition of 3 equiv of PhI to **22** and warming to 120 °C provided the diarylated product **14** in 44% yield along with the direct coupling product **15** in 7% yield. Finally, when the putative Ar−Cu complex **22** was heated to 110 °C for 90 min, full conversion to a new complex, tentatively assigned as C(sp^3)−Cu complex **24**, was observed. This complex was captured with CD$_3$OD to provide deuterated product **25** in 64% yield. When PhI was added to this species and the mixture was heated to 120 °C, the diarylated product **14** was generated in 36% yield. These data (Scheme 6) are in complete agreement with the outcomes of the diastereoselective reactions shown in Scheme 5 and strongly suggest that the reaction proceeds through carbometalation of an Ar−Cu complex across an alkene followed by cross-coupling with ArI. The mechanism of the reaction of the generated

C(sp^3)−Cu complex **24** with ArI is not clear at this time but will be the subject of future investigations.

In summary, a method for the catalytic diarylation of alkenes has been presented. The method provides access to a range of heterocyclic compounds from simple starting materials. Furthermore, new reactions of organocopper complexes have also been described. Future work will focus on expanding the scope of these processes to enantioselective variants.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, analytical data for all compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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