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LETTERS

Vinyl aryl ethers from copper-catalyzed coupling of vinyl halides and phenols☆

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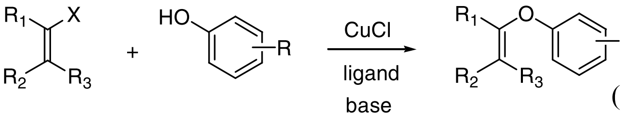
Abstract—A general procedure for vinyl aryl ether bond formation by direct coupling of vinyl halides and phenols under mild Ullmann-type reaction conditions has been developed. Using copper chloride as the catalyst and cesium carbonate as the base, vinyl bromides or iodides were reacted with phenols in refluxing toluene to produce vinyl aryl ethers in good to excellent yields.

Vinyl aryl ethers are important intermediates or building blocks in organic synthesis[1] as well as raw materials for polymers.[2] Methods for their syntheses include alcohol addition to acetylene under high pressure (20 ~ 50 atm) and high temperature (180 ~ 200°C),[3] Michael-type addition–elimination processes,[4] transition metal catalyzed vinyl transfer[5] and allyl ether isomerization.[6] Harsh reaction conditions or substrate limitations prohibit the practical application of these methods.

In recent years, great progress has been made in both palladium- and copper-catalyzed Ullmann-type diaryl ether formation.[7] To our knowledge, there are no reports on the corresponding vinyl aryl ether formation from vinyl halides and phenols under Ullmann-type conditions in the literature.[8,9] Mechanistically, vinyl aryl ether formation should be similar to Ullmann-type diaryl ether formation, and thus the reaction depicted below (Eq. (1)) should be an efficient method to access vinyl aryl ethers from vinyl halides and phenols.



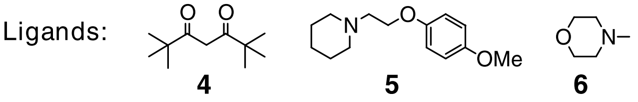
(1)

Our investigation began with the reaction of bromotriphenylethylene **1** with 4-methoxyphenol **2** utilizing literature reported conditions for Ullmann-type ether formation.[7a] As illustrated in Scheme 1, reagents **1** and **2** were combined with CuCl (25 mol%), Cs_2CO_3 and the THMD ligand **4** in refluxing toluene for 5 h to afford the ether product **3** in 92% isolated yield. In an attempt to find the optimum ligand for generalization of the reaction, ligands **5** and **6** were compared to ligand **4**. Our previous work indicated that amino ethyl ethers were efficient ligands in copper-catalyzed Ullmann diaryl ether synthesis.[10] We were interested in exploring the use of amino ethyl ethers as ligand for Ullmann vinyl–aryl ether formation. Surprisingly, all three ligands performed about the same, and interestingly even in the absence of a ligand the reaction was completed in less than 5 h (Table 1).

Table 1. Ligand effect on percent of vinyl bromide consumed[a]

Ligand	Reaction time			
	0.5 h	1.0 h	2.0 h	4.0 h
None	30.0	19.0	3.0	0
4	6.2	1.8	0.5	0
5	5.0	2.2	0.4	0
6	5.4	2.5	0.4	0

[a] Relative area% of vinyl bromide remaining determined by HPLC.



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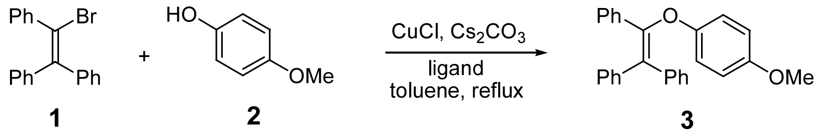
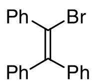
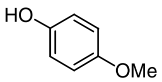
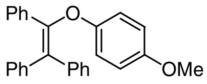
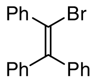
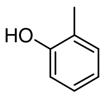
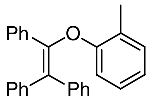
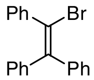
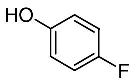
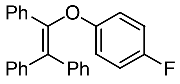
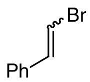
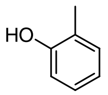
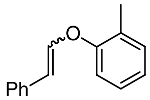
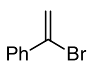
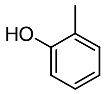
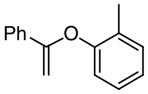
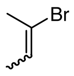
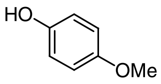
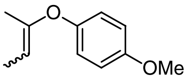
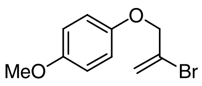
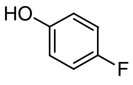
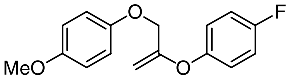
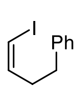
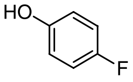
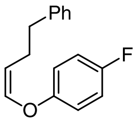
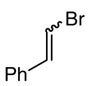
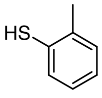
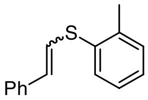


Scheme 1.

Table 2. Copper-catalyzed coupling of vinyl halides to phenols

Entry	Vinyl halide	Phenol	Product	Reaction time (h)	Isolated yield (%)
1				5	94
2				5	86
3				5	92
4				5	81[a]
5				5	71[b]
6				15	41[c]
7				5	85[b]
8				5	71
9				8	41[a]

a. A 9:1 ratio E/Z mixture corresponding to the starting viny bromide E/Z ratio by ^{1}HNMR.
b. A 1:1 ratio mixture of 1- and 2- ethers by ^{1}HNMR
c. A 1:1 ratio E/Z mixture corresponding to the starting viny bromide E/Z ratio by ^{1}HNMR.

To explore the generality of the vinyl coupling reaction, tri-substituted, vicinal, and geminal olefinic bromides were examined in combination with various phenols including the electron deficient 4-fluorophenol, the electron rich 4-methoxy phenol and the sterically demanding 2-methylphenol. Table 2 shows that the reaction proceeded smoothly regardless of the steric or electronic properties of the reactants. With few exceptions, the reactions were generally completed in less than 5 h and in good to excellent yields. Even thio ethers (Table

2, entry 9) could be formed utilizing this reaction method, albeit in lower yield.[11] The lower yield with 2-butene (Table 2, entry 6) is most likely due to the substrates volatility. It also is important to note that the *E*/*Z* stereochemistry of the vinyl aryl ether bond corresponds to the starting vinyl halide (Table 2, entries 4, 6, 8, and 9). Geminal olefinic bromides produced a 1:1 mixture of 1- and 2-ethers as determined by ^{1}H NMR (Table 2, entries 5 and 7). Mechanistic investigation for an explanation of this phenomenon was not pursued.

In conclusion, copper-catalyzed vinyl halide–phenol coupling is an efficient method for vinyl aryl ether formation. Generally, vinyl bromides and iodides, phenols and thiols are all suitable substrates. Compared to Ullmann diaryl ether formation reactions, the construction of the vinyl aryl ether bond appears to be more facile and the ligand effects are less significant.

General Method: The following general method was used for all substrates in Table 2. 1.0 equiv. vinyl halide, 1.5 equiv. phenol, 0.25 equiv. CuCl and 0.25 equiv. ligand **5**, 2.0 equiv. Cs_2CO_3 and toluene (5.0 mL/mmol) were combined in a round-bottom flask and allowed to reflux until complete consumption of the vinyl halide as determined by HPLC. After reaction completion, the mixture was diluted with MTBE and filtered through a plug of diatomaceous earth. The filtrate was washed with 28% aqueous ammonium hydroxide then dried over K_2CO_3. The crude products were purified by Kugelrohr distillation under high vacuum or chromatography on either triethylamine deactivated silica gel or neutral aluminum oxide.

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