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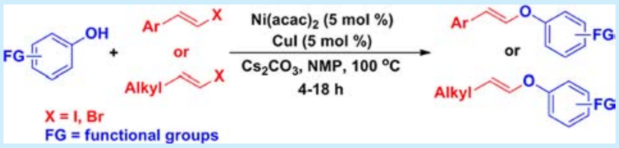
Copper-Assisted Nickel Catalyzed Ligand-Free C(sp^2)−O Cross-Coupling of Vinyl Halides and Phenols

Debasish Kundu, Pintu Maity, and Brindaban C. Ranu*

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata 700032, India

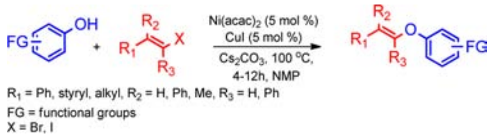
S *Supporting Information*

ABSTRACT: A convenient and efficient protocol has been achieved for the cross-coupling of phenols and vinyl halides by a unique Ni/Cu catalytic system for the first time, where the reaction is catalyzed by Ni and Cu is involved in the transmetalation process. This procedure provides an easy access to a library of aryl-vinyl and aryl-styrenyl ethers.



The vinyl C(sp^2)−O bond forming reaction is of much interest as vinyl/styrenyl ethers are employed as useful intermediates in a wide variety of reactions such as cycloaddition,[1] cyclopropanation,[2] metathesis reaction,[3] etc. They are also found as core units of several biologically active molecules and natural products.[4] In addition, vinyl groups act as efficient protecting groups for phenol derivatives.[5] Although several multistep protocols have been reported for the synthesis of vinyl ethers,[6] transition metal catalyzed cross-coupling of vinyl halides and phenols has been found to be more effective. Earlier palladium-based catalysts have been employed for vinylation of phenols.[7] However, use of expensive palladium is not cost-effective for industry. Thus use of other less expensive metals received attention. Only recently, a few reports on Cu-catalyzed vinylation of phenols and *N*-heterocycles in the presence of a variety of ligands have appeared.[8] The essential feature of all these protocols is the necessity of a ligand to activate the Cu-catalysts toward reaction. The N-containing ligands, commonly employed, are not always easily accessible and are relatively expensive when they are commercially available. Moreover, the presence of a large amount of ligands also posed difficulty in the purification of products. In addition, a couple of these methods[8a,b] required a longer reaction time (24−48 h). Recently Ni-catalysts have received much attention due to their relatively low cost and interesting catalytic features. Several Ni catalysts have been successfully used for the synthesis of important organic molecules.[9] This prompted us to explore the hitherto unreported application of a Ni-catalyst for the vinylation of phenols without using any ligand. In a preliminary experiment we found that Ni-salt alone cannot initiate the reaction of vinyl bromide and phenol. However, the presence of a Cu-salt in the system triggered the reaction. Thus, as a part of our continuing program on transition metal catalyzed reactions[10] we report here a Cu-assisted Ni- catalyzed ligand free cross-coupling of aromatic alcohols with styrenyl and vinyl halides (I and Br) (Scheme 1).

Scheme 1. Cross-Coupling of Vinyl Halides and Phenols



To standardize the reaction conditions a series of experiments were performed with variation of reaction parameters such as catalyst, solvent, base, temperature, and time for a representative coupling of 4-methoxy phenol (**1a**) and (*E*)-4-methyl styrenyl bromide (**2a**). The results are summarized in Table 1. The reaction did not proceed using NiCl$_2$, NiBr$_2$, or Ni(acac)$_2$ alone (Table 1, entries 1−3). However the presence of CuI in Ni(acac)$_2$ triggered the reaction although solvent has a significant influence. The best yield of product was obtained by using 5 mol % of Ni(acac)$_2$, 5 mol % of CuI, and 2.0 equiv of Cs$_2$CO$_3$ at 100 °C for 8 h in *N*-methylpyrrolidinone (NMP) (Table 1, entry 4). NMP was found to be more efficient compared to DMSO, dioxane, and DMF (Table 1, entries 7−9). Other nickel salts such as NiCl$_2$ and NiBr$_2$ under identical conditions are not very effective (Table 1, entries 16−17). The reaction at lower temperature (80 °C) takes a longer period (25 h) (Table 1, entry 5). At rt only a trace amount of product (5%) was isolated (Table 1, entry 6). CuBr and CuCl were found to be less active in comparison to CuI (Table 1, entries 10 and 11). Weaker bases such as K$_2$CO$_3$ and K$_3$PO$_4$ failed to initiate the reaction (Table 1, entries 12 and 13). Only a trace of product (<5%) was isolated when the reaction was carried out using CuI alone in the absence of Ni(acac)$_2$ (Table 1, entry 14). A lower catalyst loading (2%) leads to lower conversion (Table 1, entry 15). Thus, in a typical procedure a mixture of phenol and styrenyl (or vinyl) halide (I and Br) was heated at 100 °C under argon in the presence of Ni(acac)$_2$ (5 mol %) and CuI (5 mol %) for a certain period of time to complete the reaction (TLC). A series of diversely substituted styrenyl and vinyl halides underwent coupling with a variety of phenols by this procedure to produce the corresponding styrenyl aryl

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Table 1. Standardization of Reaction Conditions[a]

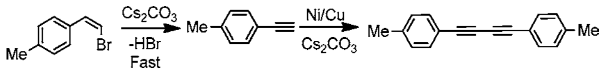
entry	catalyst	solvent	temp [°C]	time [h]	yield (%)[b]
1	$NiCl_2$	NMP	100	20	0
2	$NiBr_2$	NMP	100	20	0
3	$Ni(acac)_2$	NMP	100	20	0
4[c]	$Ni(acac)_2$/CuI	NMP	100	8	92
5[c]	$Ni(acac)_2$/CuI	NMP	80	25	60
6[c]	$Ni(acac)_2$/CuI	NMP	rt	30	0
7[c]	$Ni(acac)_2$/CuI	DMSO	100	16	25
8[c]	$Ni(acac)_2$/CuI	Dioxane	100	16	trace
9[c]	$Ni(acac)_2$/CuI	DMF	100	16	55
10[c]	$Ni(acac)_2$/CuBr	NMP	100	18	71
11[c]	$Ni(acac)_2$/CuCl	NMP	100	18	45
12[c]	$Ni(acac)_2$/CuI	NMP	100	15	0[d]
13[c]	$Ni(acac)_2$/CuI	NMP	100	15	trace[e]
14[f]	CuI	NMP	100	15	trace
15[g]	$Ni(acac)_2$/CuI	NMP	100	15	20
16[c]	$NiCl_2$/CuI	NMP	100	20	trace
17[c]	$NiBr_2$/CuI	NMP	100	20	trace
18	$NiCl_2$/CuI	NMP	100	12	40[h]

[a] Reaction conditions: A mixture of **1a** (1.0 mmol), **2a** (1.0 mmol), and Cs_2CO_3 (2.0 mmol) was heated under an argon atmosphere. [b] Yields of isolated pure products. [c] 5 mol % of Ni and Cu catalysts were used. [d] K_2CO_3 was used as base. [e] K_3PO_4 was used as base. [f] 10 mol % CuI was used. [g] 2 mol % of Ni and Cu catalyst were used. [h] 20 mol % of Zn powder was used as an additive.

ethers (Scheme 3, Scheme 5) and vinyl aryl ethers (Scheme 4). All the products were obtained with high stereoselectivity.

The (*E*)-styrenyl halides produced the corresponding (*E*)-styrenyl aryl ethers. However the reaction of (*Z*)-styrenyl bromide did not produce the corresponding (*Z*)-styrenyl aryl ethers; instead the corresponding 1,3-diyne was obtained. Possibly, the (*Z*)-styrenyl bromide underwent rapid E2 type elimination[11] in the presence of a strong base such as Cs_2CO_3 to form the aryl acetylene which is then converted to the 1,3-diyne *via* homocoupling by the Ni/Cu catalytic system (Scheme 2).

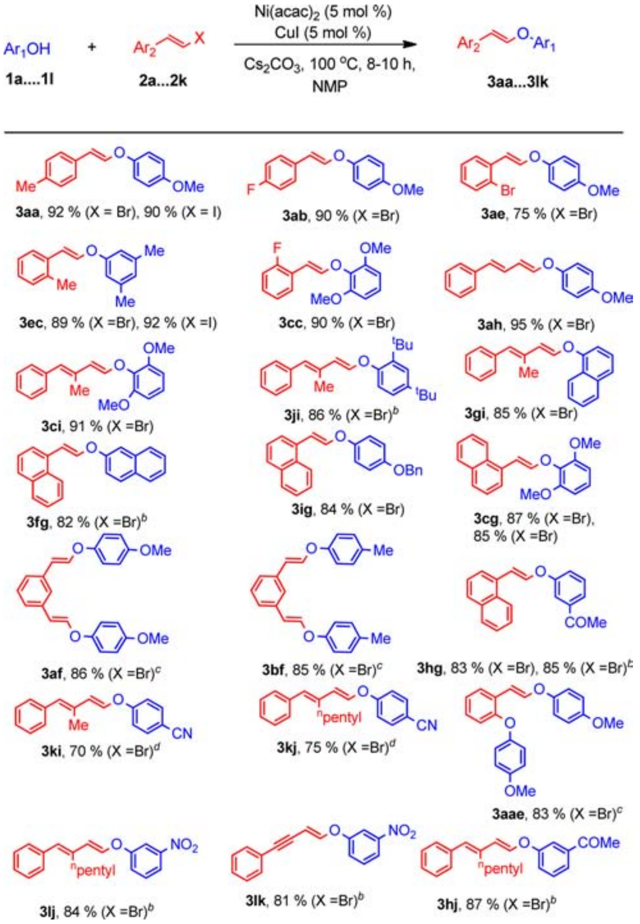
Scheme 2. Outcome of Reaction of (*Z*)-Styrenyl Bromide



A variety of functionalized styrenyl aryl ethers bearing important functionalities such as F, Br, and OMe were obtained by this procedure (Scheme 3, **3aa**, **3ae**, **3cc**). The naphthyl vinyl aryl ethers were also accomplished without any difficulty (Scheme 3, **3fg**, **3ig**, **3cg**, **3hg**). The efficiency of this protocol for the synthesis of sterically hindered styrenyl and vinyl aryl ethers by the coupling of 2,6-dimethoxy phenol and 2,4-di-*tert*-butyl phenol is noteworthy (Scheme 3, **3cc**, **3ci**, **3ji**; Scheme 4, **5jb**). Several 1-phenyl-1,3-butadienyl aryl ethers were also obtained (Scheme 3, **3ah**, **3ci**, **3ji**, **3gi**). The synthesis of these conjugated dienyl ethers were not addressed earlier by other procedures using this reaction.

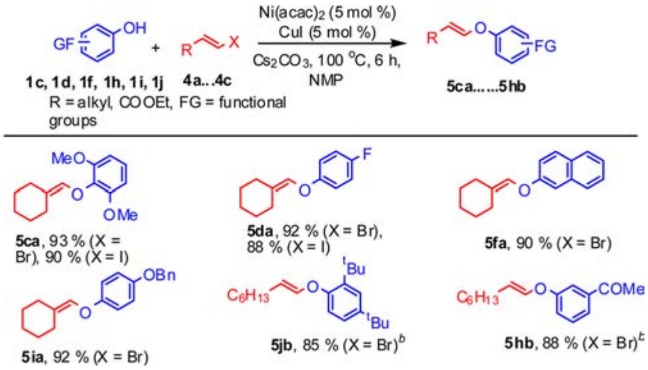
Moreover, these compounds possess great potential in organic synthesis.[12] A couple of bis-styrenyl aryl ethers (Scheme 3, **3af** and **3bf**) which are of biological importance[13] were also synthesized. Although poor reactivity from acidic phenols in Ullmann type coupling is quite common[14] this protocol is successfully employed for the synthesis of vinyl ethers by the reaction of substituted vinyl halides with acidic and electron-deficient phenols such as 3-nitrophenol, 3-hydroxy acetophenone, and 4-hydroxy benzonitrile (Scheme 3, **3hg**, **3hj**, **3ki**, **3kj**, **3lj**, **3lk**, **3hj**; Scheme 5, **3km**, **3hm**, **3lm**). Significantly,

Scheme 3. Ni–Cu Catalyzed *O*-Styrylation[a]



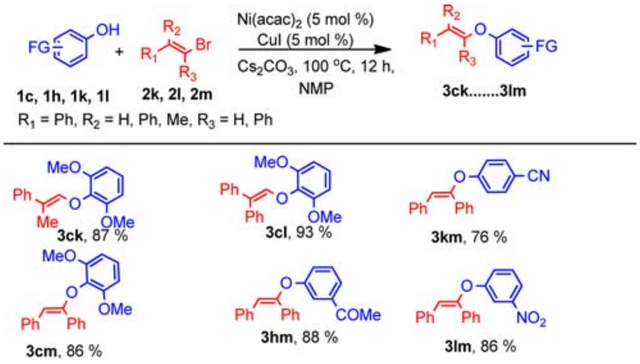
[a] Reaction conditions: aryl alcohol (1.0 mmol), styrenyl halide (1.0 mmol), $Ni(acac)_2$ (0.05 mmol), CuI (0.05 mmol), Cs_2CO_3 (2.0 mmol), NMP (3.0 mL), 100 °C, 8 h, under argon. [b] 10 h. [c] 2.0 mmol of aryl alcohols used. [d] Reaction conditions: aryl alcohol (1.5 mmol), styrenyl halide (1.0 mmol), $Ni(acac)_2$ (0.1 mmol), CuI (0.1 mmol), K_3PO_4 (2.0 mmol), NMP (3.0 mL), 100 °C, 24 h, under argon.

Scheme 4. Ni–Cu Catalyzed *O*-Vinylation[a]



[a] Reaction conditions: aryl alcohol (1.0 mmol), vinyl halide (1.0 mmol), $Ni(acac)_2$ (0.05 mmol), CuI (0.05 mmol), Cs_2CO_3 (2.0 mmol), NMP (3.0 mL), 100 °C, 6 h, under argon. [b] 10 h.

Scheme 5. Ni–Cu Catalyzed *O*-Styrylation with Trisubstituted Halo-olefins[a,b]

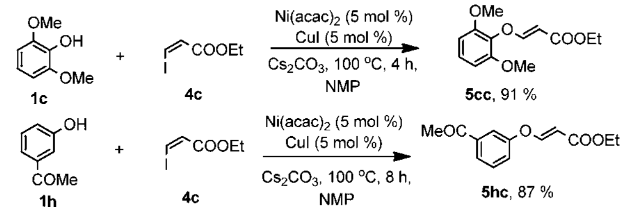


[a]Reaction conditions: aryl alcohol (1.0 mmol), vinyl halide (1.0 mmol), Ni(acac)$_2$ (0.05 mmol), CuI (0.05 mmol), Cs$_2$CO$_3$ (2.0 mmol), NMP (3.0 mL), 100 °C, 12 h, under argon. [b] Reaction conditions: aryl alcohol (1.5 mmol), vinyl halide (1.0 mmol), Ni(acac)$_2$ (0.1 mmol), CuI (0.1 mmol), K$_3$PO$_4$ (2.0 mmol), NMP (3.0 mL), 100 °C, 24 h, under argon (for **3km**).

the coupling of 4-hydroxy benzonitrile with *E*-bromostilbene (Scheme 5, **3km**) furnished the corresponding (*E*) isomer in better (76%) yield compared to that (56%) reported by Limberger et al.[8c] The more challenging reactions of vinyl halides bearing substituents at the α- and β-positions relative to the halide are also successful by this protocol (Scheme 5). All of these compounds are obtained in single stereoisomers with an (*E*)-configuration as revealed by the NOE, NOESY, and COSY experiments (see SI) of a representative molecule, **3lm**, and authentication of **3km** with a reported one.[8c]

Interestingly, the reaction of 2,6-dimethoxyphenol with (*Z*)-ethyl-3-iodo-acrylate (Scheme 6) provided the corresponding (*E*)-vinyl ether with an inverted *trans* configuration. The identity of this compound was satisfactorily established by IR, ^{1}H NMR, ^{13}C NMR, and HRMS. The coupling constant (*J* value) for the olefinic protons adjacent to $-$CO$_2$Et is found to be 12.2 Hz which is characteristic for a *trans* configuration. This value is in good agreement with *trans* coupling (*J* = 12.0–12.4 Hz) observed in closely related molecules.[15] On the other hand the *cis* olefinic protons in analogous (*Z*)-compounds show a coupling constant (*J*) of 6.8 Hz.[16] In contrast, Cook et al. reported complete retention of stereochemistry in a similar Cu-catalyzed coupling of (*Z*)-ethyl 3-iodo-acrylate with phenols to provide (*Z*)-vinyl ethers even though all of these vinyl ethers showed a coupling constant of 12 Hz for olefinic protons which indicate a *trans* configuration.[8b] A controlled experiment for a reaction of (*Z*)-ethyl 3-iodo-acrylate in the absence of phenol virtually showed no isomerization (*Z*/*E* = 98:2) of the starting material, and thus it is likely that the reaction proceeds *via* the addition elimination pathway.

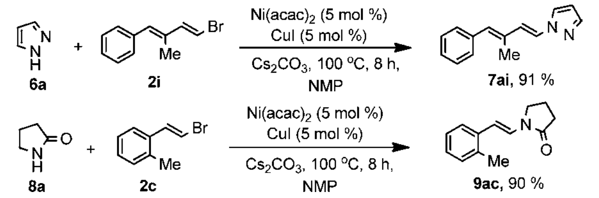
Scheme 6. *O*-Vinylation with (*Z*)-Ethyl 3-Iodo-acrylate



In general, all the reactions are clean and high yielding. The reaction is compatible with diversely substituted phenols bearing electron-donating and -withdrawing groups in the -*ortho*, -*meta* and -*para* positions of the aromatic ring. Although the products were obtained by a homogeneous metal catalysis pathway, ICP-MS studies of purified products showed the absence of any metal impurities (nickel or copper). All of these products are reported for the first time with full characterization data (IR, ^{1}H NMR, ^{13}C NMR, and HR-MS).

The *N*-heterocycles such as pyrazole and 2-pyrrolidinone also underwent coupling with vinyl halides by this catalytic system quite easily (Scheme 7).

Scheme 7. Ni–Cu Catalyzed *N*-Vinylation of Pyrazole and 2-Pyrrolidinone

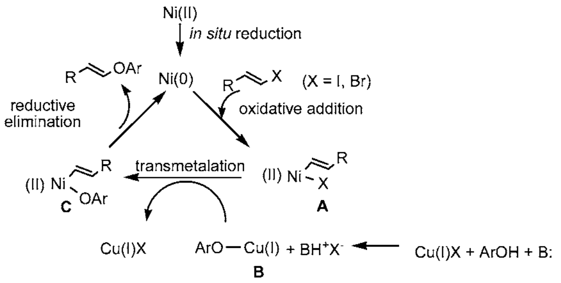


To understand the reaction mechanism we considered the possibility of a radical as well as an ionic pathway. It was observed that the reaction rate and yield remained unaffected when the reaction was performed in the presence of nitroarene (electron acceptor) or THF (electron trapper)[17] or TEMPO (radical quencher). Moreover, high stereoselectivity in *O*-styrenylation and vinylation reactions achieved in this process does not support the radical mechanism, as vinyl radicals undergo rapid inversion of configuration.[17] Thus, involvement of a radical pathway is unlikely. We observed a decreasing rate of reaction with the enhancement of steric hindrance and acidity of phenols. This is usually indicative of an oxidative addition–reductive elimination pathway.[17]

As the reaction did not proceed in the presence of either Ni(acac)$_2$ or CuI alone under ligand-free conditions it is likely that each of these two metals has its specific role in the oxidative–reduction process. Thus we focused our attention to find the primary catalytic species in this reaction. If we consider the reaction to be catalyzed by Cu the involvement of Cu^{I}/Cu^{III} in oxidative addition appears very unlikely due to the high redox potential of the Cu^{I}–Cu^{III} system in ligand-free conditions.[18a] Usually in the presence of a *N*-containing ligand the coordination of the ligand with the Cu^{I}-center leads to a sharp decrease in Cu^{I}–Cu^{III} redox potential and facilitates the process.[18b] Next we considered the catalysis by Ni. We have observed that NiCl$_2$ alone cannot initiate the reaction (Table 1, entry 18). However when the reaction was performed in presence of Zn the reaction proceeds to the extent of 40% (unoptimized).

Thus it may be suggested that the active species in this process is Ni(0) which is generated in situ in the presence of a base under the reaction conditions. To obtain more convincing evidence we performed a few UV experiments. A solution of Ni(acac)$_2$ in NMP at 100 °C (reaction temperature) shows a peak at 298 nm, whereas when Cs$_2$CO$_3$ was added into the solution immediately a new peak appeared at 376 nm which corresponds to that of Ni(0) nanoparticles.[19] This proves the formation of Ni(0) from Ni(II) in the presence of Cs$_2$CO$_3$ in the reaction mixture. The UV studies of the vinylation reaction also show the appearance of the same Ni(0) peak just after 1 min which remains until the end of the reaction (see SI).[20] The Ni(0) undergoes fast oxidative addition with styrenyl and vinyl halides leading to the intermediate **A**. In the other cycle, it is most likely that CuI interacts with a nucleophile, phenol in the presence of base (Cs_2CO_3), to form the intermediate **B** (Scheme 8) and subsequently the nucleophile is transferred from Cu^I to Ni^{II} through transmetalation leading to the formation of intermediate **C** which on reductive elimination provides the product.

Scheme 8. Possible Mechanistic Pathway for Ni−Cu Catalyzed *O*-Vinylation



In conclusion, we have developed a convenient and efficient protocol for the synthesis of vinyl aryl ether catalyzed by a unique Ni−Cu homogeneous catalytic system. The significant feature of this protocol is the catalysis by Ni and participation of Cu in the transmetalation process under ligand-free conditions. We are not aware of any C−O bond formation catalyzed by Ni metal salt, and thus this report of $C(sp^2)$−O cross-coupling is the first one. The other advantages of this protocol are broad functional group tolerance including strong electron-withdrawing functionality, high stereoselectivity, use of an inexpensive and relatively benign catalyst with low loading, ligand-free conditions, operational simplicity, and high yields. This concept of catalysis by Ni with the assistance of another transition metal such as Cu is of high potential, and further investigation for other useful cross-coupling reactions is currently in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Typical experimental procedure and characterization data of all products and copies of their ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ocbcr@iacs.res.in.

Notes

The authors declare no competing financial interest.

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