CuI/*N*,*N*-Dimethylglycine-Catalyzed Cross-Coupling Reaction of Vinyl Halides with Phenols and its Application to the Assembly of Substituted Benzofurans

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Abstract: CuI-catalyzed coupling reaction of vinyl halides and phenols occurs at 60–90 °C with *N*,*N*-dimethylglycine hydrochloride as the additive, giving vinyl aryl ethers in good yields. The cross-coupling products formed from *o*-iodophenols and vinyl iodides are converted into substituted benzofurans via an intramolecular Heck reaction.

Key words: cross-coupling, vinyl aryl ethers, vinyl halides, benzofuran

Vinyl aryl ethers have found considerable applications as monomers in materials chemistry[1] and as key intermediates in organic synthesis.[2] The conventional methods to elaborate these chemicals include addition of alcohols to acetylene under high pressure and temperature,[3] transition metal-catalyzed vinyl transfer,[4] and allyl ether isomerization.[5] However, these processes are applicable only to a limited number of substrates or use very harsh reaction conditions. Consequently developing a more efficient method is highly required.

Over the past number of years, great progress has been made in both palladium- and copper-catalyzed aryl C–O bond formation,[6,7] which shed new light on methods for the elaboration of vinyl aryl ethers. Quite recently, two groups have disclosed their attempts toward this goal. Wan and co-workers reported that the CuCl-catalyzed coupling of vinyl halides and phenols in refluxing toluene using 2,2,6,6-tetramethylheptane-3,5-dione (THMD) or amino ethyl ethers as ligands provided vinyl aryl ethers.[8] Willis and co-workers found that cross-coupling of vinyl triflates with phenols occurred at 100 °C in toluene with Pd_2dba_3/2-(di-*tert*-butylphosphino)biphenyl as a catalyst.[9] In addition, a CuI-catalyzed cross-coupling reaction of aliphatic alcohols with vinyl halides was also reported recently.[10]

In the course of exploring amino acid-promoted Ullmann-type coupling reactions,[7b,11,12] we have observed that *N*,*N*-dimethylglycine was an useful ligand for CuI-catalyzed diaryl ether formation[7b] and for coupling vinyl halides with amides[12] which proceeds under relatively mild conditions. These successes prompted us to test our catalytic system in the coupling reaction of vinyl halides and phenols, which is described here.

As demonstrated in Table 1, our experiments were first conducted by coupling 1-iodocyclohexene with phenol under the catalysis of 10 mol% CuI and 30 mol% *N*,*N*-dimethylglycine hydrochloride. This reaction proceeded well at 60 °C in 1,4-dioxane in the presence of Cs_2CO_3 as base to produce 1-phenoxycyclohexene in 88% yield (Table 1, entry 1). The use of Cs_2CO_3 is crucial as was observed in diaryl ether formation[7b] because yields of only 20–30% were obtained when K_2CO_3 or K_3PO_4 was employed, and no desired product was observed when Na_2CO_3 or Et_3N was utilized.

With 1-iodocyclohexene as a model substrate, several substituted phenols were tested in the coupling reaction. It was found that the reaction proceeded well with an electron-rich phenol under the standard conditions (Table 1, entry 2). While with the electron-deficient phenol, a higher reaction temperature was required to ensure good conversion (Table 1, compare entries 3 and 4). A similar phenomenon was observed when 2-methoxyphenol, a sterically hindered phenol was used (Table 1, compare entries 5 and 6). Noteworthy, is 3-aminophenol, the desired coupling product was isolated in 64% yield (Table 1, entry 7), which implied that the free amino group did not influence the reaction.

For vinyl iodides, both 1-iodocyclopentene and iodomethylenecyclohexane were compatible with the standard conditions, providing the corresponding coupled products in satisfactory yields (Table 1, entries 8–10). When (*Z*)-1-iodo-1-heptene and (*Z*)-3-iodo-2-heptenoic acid ethyl ester were used, only moderate yields were observed, when the reaction was carried out at 60 °C for 24 hours due to incomplete conversion (Table 1, entries 11 and 12). This problem might result from the greater steric hindrance present in these two substrates. The stereochemistry of the C–C double bond was retained, as determined by ^1H NMR spectroscopy. Raising the reaction temperature to 70 °C did increase conversion but led to some isomerization of the C–C double bond (data not shown). Similarly, the reaction of β-bromostyrene with phenol at 60 °C gave the corresponding coupled product in 65% yield with almost full retention of stereochemistry (Table 1, entry 13), while

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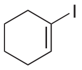
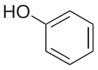
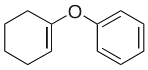
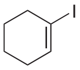
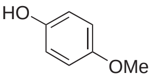
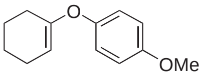
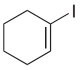
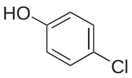
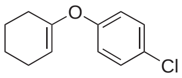
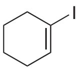
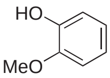
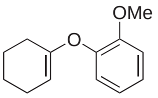
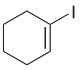
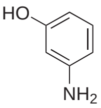
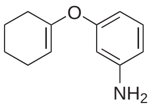
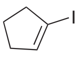
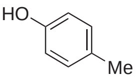
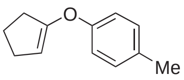
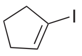
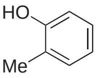
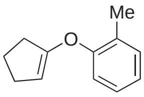
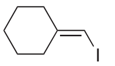
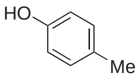
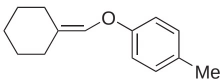
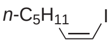
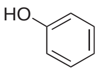
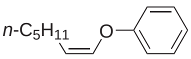
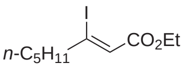
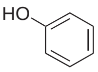
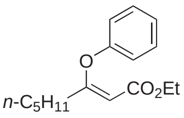
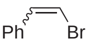
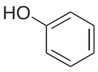
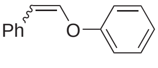
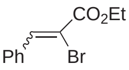
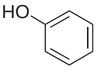
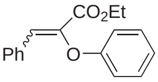
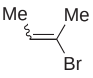
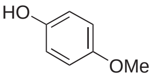
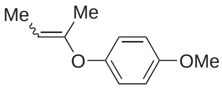
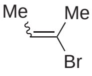
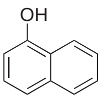
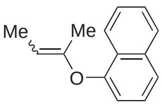
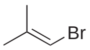
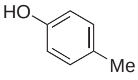
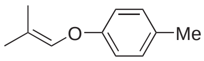
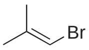
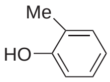
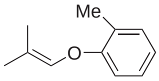
Table 1 CuI/*N*,*N*-Dimethylglycine-Catalyzed Cross-Coupling Reaction of Vinyl Halides with Phenols[a]

Entry	Vinyl halide	Phenol	Product	Temp (°C)	Time (h)	Yield (%)[b]
1				60	24	88
2				60	24	80
3 4				60 70	24	55[c] 82
5 6				60 70	24 14	62 81
7				60	24	64
8				60	24	75
9				60	24	64
10				60	24	71
11				60	24	48[c]
12				60	24	50[c]
13 14	 *Z*/*E* = 6:1			60 70	24 24	65 (*Z*/*E*, 5:1) 77 (*Z*/*E*, 2:1)
15	 *E*/*Z* = 5:1			70	20	70 (*Z*/*E*, 1:1)
16	 *Z*/*E* = 5:1			90	20	65 (*Z*/*E*, 3.5:1)
17	 *Z*/*E* = 5:1			90	20	67 (*Z*/*E*, 4.4:1)
18				90	24	90
19				90	24	80

[a] Reaction conditions: vinyl halide (1.0 mmol), phenol (1.5 mmol), Cs_2CO_3 (2.1 mmol), CuI (0.1 mmol), *N*,*N*-dimethylglycine hydrochloride (0.3 mmol), 1,4-dioxane (2 mL).

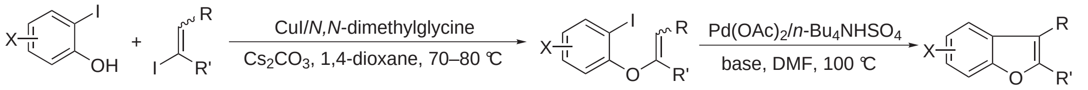
[b] Isolated yield, the *Z*/*E* ratio was determined by ^{1}H NMR.

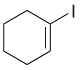
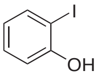
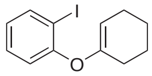
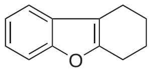
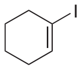
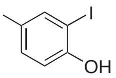
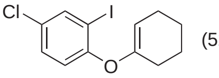
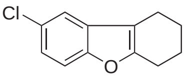
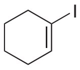
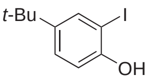
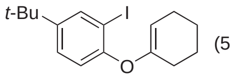
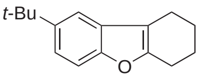
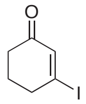
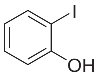
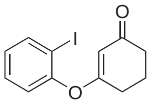
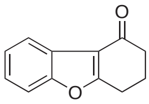
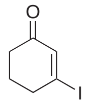
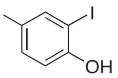
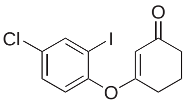
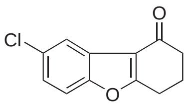
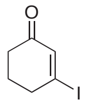
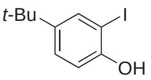
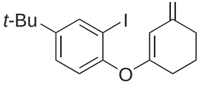
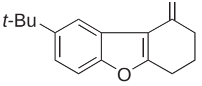
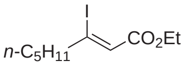
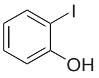
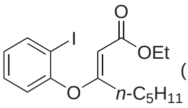
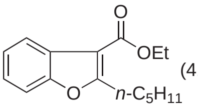
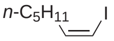
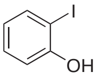
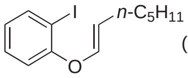
[c] Vinyl iodide was recovered in about 20% yield.

at 70 °C this reaction provided a 2:1 mixture of *Z*- and *E*-isomers in a 77% combined yield (Table 1, entry 14). These results clearly showed that the lower reaction temperature was essential for retention of stereochemistry. For other vinyl bromides examined, good yields were obtained, although in most cases a higher reaction temperature (90 °C) was required (Table 1, entries 15–19).

With this new method for the preparation of vinyl aryl ethers in hand, we next addressed its synthetic applications. The benzofuran ring-system is found in many naturally occurring and designed molecules that possess a wide range of biological activities. Consequently this moiety has become the target for many synthetic methodologies.[13] In 1997, Henke and co-workers mentioned that a vinyl aryl ether derived from *o*-bromophenol and ethyl propiolate underwent an intramolecular Heck reaction to afford 3-ethoxycarbonyl benzofurans in 40% yield.[2c] For this process only propiolate could be used because the other substituted conjugated alkynoates were found to be poor acceptors for the Michael addition of phenols. Our method may provide an opportunity for assembling more diverse benzofurans using this strategy. To this end, the coupling reaction of *o*-iodophenols with vinyl iodides and subsequent cyclization reactions were studied, and the results are summarized in Table 2. We were pleased to find

Table 2 Synthesis of Substituted Benzofurans via CuI/*N*,*N*-Dimethylglycine-Catalyzed Cross-Coupling Reaction of Vinyl Halides with *o*-Iodophenols and Subsequent Intramolecular Heck Reaction[a]



Entry	Vinyl iodide	Phenol	Cross-coupling product (yield)[b]	Benzofuran (yield)[b]
1			 (66%)	 (42%)[c] (88%)
2			 (52%)	 (70%)
3			 (59%)	 (85%)
4			 (76%)	 (0%)[d] (65%)
5			 (54%)	 (60%)
6			 (71%)	 (52%)
7			 (11%)[e]	 (41%)
8			 (0%)[f]	–

[a] Reaction conditions for cross-coupling: vinyl iodide (1.0 mmol), phenol (1.5 mmol), Cs_2CO_3 (2.1 mmol), CuI (0.1 mmol), *N*,*N*-dimethylglycine hydrochloride (0.3 mmol), 1,4-dioxane (2 mL), 70–80 °C; intramolecular Heck reaction: vinyl aryl ether (1 mmol), $Pd(OAc)_2$ (0.05 mmol), base (2.5 mmol, $NaHCO_3$ (entries 1–3), Et_3N (entries 4–7), n-Bu_4NHSO_4 (1 mmol), 4 Å molecular sieves (0.4 g, crashed into a powder before use), anhyd DMF (1 mL).

[b] Isolated yield.

[c] Without addition of n-Bu_4NHSO_4.

[d] Using $NaHCO_3$ as base.

[e] Vinyl iodide was recovered in about 80% yield.

[f] Vinyl iodide was recovered in about 90% yield.

that the coupling of 1-iodocyclohexene with three selected *o*-iodophenols delivered the corresponding coupled products, which were subjected to Heck reaction[14] to produce tricyclic benzofurans (Table 2, entries 1–3). Addition of *n*-Bu_4NHSO_4 in the Heck reaction was important, a low yield was observed in the absence of this reagent (Table 2, entry 1).[15] Further exploration demonstrated 3-iodo-2-hexen-1-one was compatible with the above process to give the corresponding tricyclic benzofurans (Table 2, entries 4–6). In this case Et_3N was used as the base in the Heck reaction step because no product was obtained when $NaHCO_3$ was used. However, poor conversion was encountered when two acyclic vinyl iodides were employed mainly due to steric hindrance (Table 2, entries 7 and 8). It is notable that a moderate yield was obtained from the coupling of (*Z*)-3-iodo-2-octenoic ethyl ester with 2-iodophenol to a 2,3-disubstrated benzofuran (Table 2, entry 7).

In conclusion, a new catalytic system for the coupling of vinyl halides with phenols was described, and this process allowed a considerable range of substrates to react under relatively mild reaction conditions. The use of this method was illustrated by the conversion of coupled products benzofurans via an intramolecular Heck reaction to potentially biologically interesting molecules. Further optimization of the reaction conditions, as well as some synthetic applications, are in progress and will be reported in due course.

Cross-coupling: A mixture of vinyl halide (1.0 mmol), phenol (1.5 mmol), Cs_2CO_3 (2.1 mmol), CuI (0.1 mmol), *N*,*N*-dimethylglycine hydrochloride (0.3 mmol) in 1,4-dioxane (2 mL) was heated at 60–90 °C under a nitrogen atmosphere. The cooled solution was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed to afford the corresponding vinyl aryl ether.

Formation of benzofurans via the Heck reaction: A dried Schlenk tube equipped with a magnetic stir bar and a rubber stopper was charged sequentially with aryl vinyl ether (1.0 mmol), $NaHCO_3$ (2.5 mmol, if indicated), *n*-Bu_4NHSO_4 (1.0 mmol), 4 Å molecular sieves (400 mg, crushed into a powder before use), and $Pd(OAc)_2$ (0.05 mmol). The tube was evacuated and backfilled with argon (4 times). Et_3N (2.5 mmol, if indicated) was injected, followed by anhyd DMF (1.0 mL). The tube was heated to 100 °C until the starting material had disappeared (monitored by TLC). The cooled solution was partitioned between ethyl acetate and saturated aqueous NH_4Cl. The organic layer was washed with brine, dried, filtered, and concentrated on a rotary evaporator. The material thus obtained was purified by silica gel chromatography to give the corresponding benzofuran.

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