N,*N*-Dimethylglycine-Promoted Ullmann-Type Coupling Reactions of Aryl Iodides with Aliphatic Alcohols

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Abstract: The Ullmann-type coupling reactions of aryl iodides and aliphatic alcohols occur at 110 °C with *N*,*N*-dimethylglycine as the ligand, giving aryl alkyl ethers in good to excellent yields.

Key words: cross-coupling, aliphatic alcohols, catalysis, ligands, aryl iodides

Aryl alkyl ethers are important solvents and synthetic building blocks for the production of fragrances, cosmetics, pharmaceuticals and materials.[1] The copper-mediated Ullmann ether synthesis is a classical method for the synthesis of these compounds.[2] However, harsh reaction conditions, such as high reaction temperature, the usual requirement of strong bases, stoichiometric quantities of the copper catalysts, and the low to moderate yields, have greatly reduced the synthetic scope of this reaction. Although recent progress in palladium-catalyzed ether formation reactions has been made in this area,[3] the drawbacks of the catalyst systems, such as air sensitivity, high cost and toxicity, limit their applications. Thus, copper-catalyzed systems still hold the advantage of low cost for large-scale industrial applications and have become attractive due to the mild reaction conditions realized in the recent years.[4–6] For example, Buchwald and co-workers found a simple and mild method to couple aryl iodides with excess of alcohol at 110 °C (or 120 °C for few examples), using 1,10-phenanthroline as the ligand and CuI as the catalyst.[6a] Very soon later, they reported the copper-catalyzed O-arylation of N-substituted β-amino alcohols at 125 °C in butyronitrile.[6b] Hosseinzadeh et al. used the Buchwald group's protocol to accomplish the etherification of aryl iodides, but chose KF–Al_2O_3 as the base instead of Cs_2CO_3.[6c] Recent work in Stockland's group with self-assembled octanuclear copper clusters as catalysts has made it successful to synthesize aryl alkyl ethers in good yields at 110 °C using an oil bath or with microwave heating.[6d]

Our group recently observed that amino acids not only accelerated the coupling of themselves with aryl halides,[7a,b] but also promoted the coupling reactions of amines and phenols with aryl halides.[7c–e] Thus, it was a natural extension for us to investigate the copper-catalyzed coupling of aliphatic alcohols with aryl halides using amino acid as the ligand.

In the first stage of the study, we focused on the coupling between 4-iodoanisole and ethanol. A variety of experimental conditions were examined (see Table 1). The highest yield (93%) was obtained when we used CuI (10 mol%) as the catalyst, *N*,*N*-dimethylglycine (20 mol%) as the ligand, Cs_2CO_3 as the base, alcohol as the solvent, and performed the reaction at 110 °C. Other bases, including K_3PO_4, K_2CO_3 and CsOAc, provided lower yields. Alcohol itself was found to be the best solvent, as DMSO, DMF and dioxane caused much lower yields. Furthermore, using L-proline as the ligand gave an unsatisfying yield. Because *N*-(4-methoxyphenyl)-L-proline was isolated in all cases of L-proline as the ligand, we reasoned that the moderate yield might result from the coupling of L-proline with 4-iodoanisole. Thus, *N*,*N*-dimethylglycine, a much less reactive ligand toward coupling, was chosen.

Using the CuI–*N*,*N*-dimethylglycine–Cs_2CO_3–alcohol procedure, we studied the C–O coupling reactions between a number of alcohols and aryl iodides (see Table 2). It was found that primary alcohols such as methanol, ethanol, benzyl alcohol, 2-phenylethanol, and 3-methylbut-2-en-1-ol can all be successfully transformed to their corresponding ethers under our conditions. The reaction also proceeded well with aryl iodide carrying either electron-donating (e.g. OMe) or electron-withdrawing groups (e.g. CF_3). However, when 4-iodoanisole reacted with *N*-Boc-β-aminoethanol, we obtained *N*-4-methoxyphenyloxazolidinone (entry 17). This is because oxazolidinone, the product of the self-cyclization of alcohol under the basic condition, coupled with 4-iodoanisole to give the N-arylated product. It is notable that a wide range of functional groups such as nitro, keto, aniline, trifluoromethyl and olefin groups are well tolerated under our conditions. Although the conversion of substrates with free NH_2 groups was almost complete after 20 hours, the desired products were isolated in comparatively moderate yield as a result of decomposition of the starting materials.[6a]

For the generation of aryl alkyl ethers from secondary alcohols, it was found that using our protocol, only cyclic alcohols such as cyclopentanol were coupled with aryl iodides to give the moderate to good yields. For open-chain alcohols as isopropanol, just the low yield was

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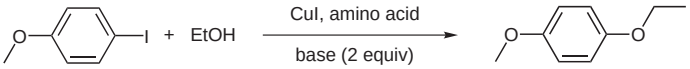
Table 1 CuI-Catalyzed Coupling Reaction of 4-Iodoanisole and Ethanol under Various Conditions



Entry	Solvent	Base	Ligand	Temp (°C)	Time (h)	Yield (%)[b]
1	DMSO	Cs_2CO_3	L-Proline	80	24	20
2	DMF	Cs_2CO_3	L-Proline	80	24	7
3	Dioxane	Cs_2CO_3	L-Proline	80	24	8
4	DMSO	CsOAc	L-Proline	80	24	2
5	DMSO	K_3PO_4	L-Proline	80	24	8
6	DMSO	K_2CO_3	L-Proline	80	24	10
7	EtOH	Cs_2CO_3	L-Proline	80	24	72[c]
8	EtOH	Cs_2CO_3	*N*,*N*-Dimethylglycine	80	40	60[c]
9	EtOH	Cs_2CO_3	L-Proline	80	40	77[c]
10	EtOH	Cs_2CO_3	L-Proline	80	40	54[c,d]
11	EtOH	Cs_2CO_3	*N*,*N*-Dimethylglycine	110	24	93[c]

[a] Reaction conditions: 4-iodoanisole (2.0 mmol), ethanol (8 mmol), base (4.0 mmol), CuI (0.2 mmol), ligand (0.4 mmol), solvent (2 mL).
[b] Isolated yield.
[c] Alcohol itself was used as the solvent.
[d] CuI (0.4 mmol) and L-proline (0.8 mmol) were used.

obtained (compare entries 10, 11, 19 and 12). However, both cyclic and open-chain secondary alcohols can be smoothly arylated under Buchwald's conditions using 1,10-phenanthroline as the ligand.

Still, on comparing our protocol with Buchwald's,[6a] we found that both methods were successfully applied when aryl iodides coupled with primary alcohols, except in the case in which the coupled product of *o*-iodobenzene and methanol was obtained in much higher yield using our catalytic system rather than Buchwald's (entry 6). Thus, our protocol can be considered a complement to Buchwald's.

Table 2 *N*,*N*-Dimethylglycine-Promoted CuI-Catalyzed Coupling Reactions of Aryl Halides with Alcohols[a,8]

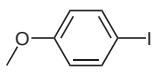
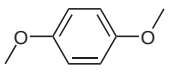
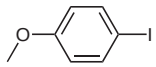
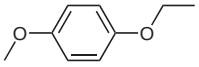
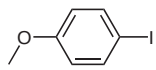
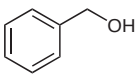
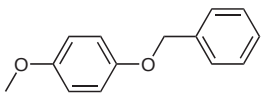
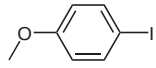
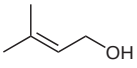
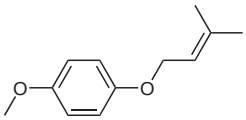
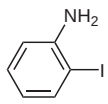
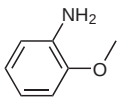
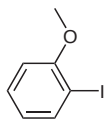
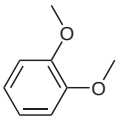
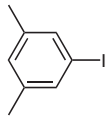
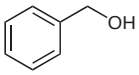
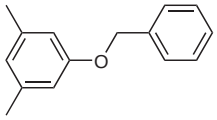
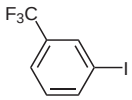
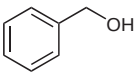
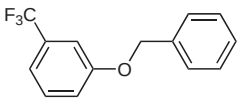
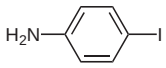
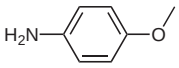
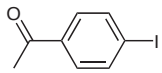
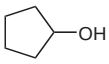
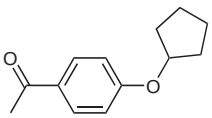
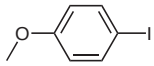
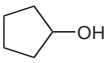
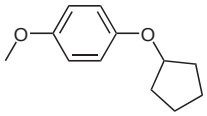
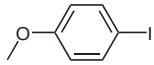
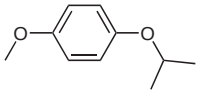
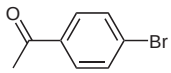
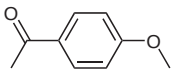
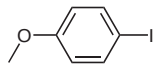
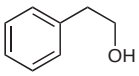
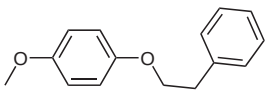
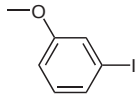
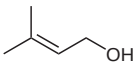
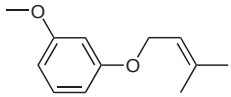
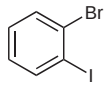
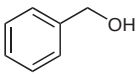
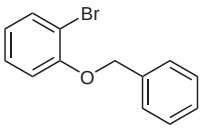
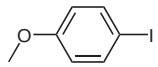
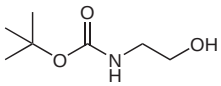
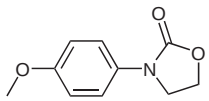
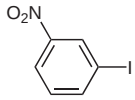
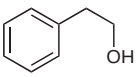
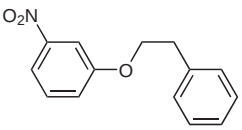
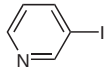
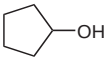
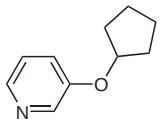
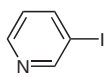
Entry	Aryl iodide	Alcohol	Product	Time (h)	Yield (%)[b]	Yield (%)[c]
1				24	97	88
2				24	93	78
3[9]				24	95	93
4				24	92	88
5				20	50	53
6				24	98	17

Table 2 *N*,*N*-Dimethylglycine-Promoted CuI-Catalyzed Coupling Reactions of Aryl Halides with Alcohols[a,8] (continued)

Entry	Aryl iodide	Alcohol	Product	Time (h)	Yield (%)[b]	Yield (%)[c]
7				24	95	92
8				22	96	90
9				22	67	58
10				22	50	61
11				40	78	75[d]
12				40	25	79
13				24	38	
14				24	96	67
15				24	94	81
16				24	84	71
17				24	88	
18				24	76	70
19				24	77	86
20[10]				24	80	86

[a] Reaction conditions: aryl halide (2.0 mmol), alcohol (2 mL), Cs_2CO_3 (4.0 mmol), CuI (0.2 mmol), *N*,*N*-dimethylglycine·HCl (0.4 mmol), 110 °C.
[b] Isolated yield.
[c] Isolated yield for the coupling reaction of aryl iodide with alcohol using Buchwald's conditions.[6a]
[d] Reaction temperature: 120 °C.

Although the above procedure is clearly successful for the coupling reaction between aryl iodides and alcohols, using the same procedure for aryl bromide provided a low yield of the ether (entry 13). Further studies into the scope and mechanism of this reaction are currently underway in our laboratories.

In conclusion, we have demonstrated that *N*,*N*-dimethylglycine is an excellent ligand for Ullmann-type coupling of aryl iodides and aliphatic alcohols. The present reaction, which worked under our relatively mild conditions using an experimentally simple catalytic system, was applicable for a wide scope of substrates. Given these attributes, it should find applications in organic synthesis.

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(8) ***N*,*N*-Dimethylglycine-Promoted Coupling Reactions of Aryl Halides with Alcohols; General Procedure**: A resealable tube or test tube with a removable cap was charged with CuI (10 mol%), *N*,*N*-dimethylglycine·HCl (20 mol%), Cs_2CO_3 (2 equiv), and aryl halide (if solid, 2 mmol). The tube was evacuated and backfilled with N_2 (3 cycles). Alcohol (2 mL) and aryl halide (if liquid, 2 mmol) were added by syringe at r.t. under nitrogen. The sealed or capped tube was put into the oil bath that was preheated to 110 °C and the reaction mixture was stirred for the time specified. The cooled mixture was partitioned between H_2O (10 mL) and EtOAc or Et_2O (20 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc or Et_2O (10 mL) each time until TLC showed no trace of product left in the aqueous layer. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography on silica gel [2 × 20 cm, PE (30–60 °C)–EtOAc or Et_2O] gave the desired product.

(9) **4-Benzoxyanisole (Table 2, Entry 3)**: white solid; mp 60–62 °C (Lit.[6a] mp 63 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.43 (m, 5 H), 6.91 (d, *J* = 8.9 Hz, 2 H), 6.83 (d, *J* = 8.9 Hz, 2 H), 5.02 (s, 2 H), 3.77 (s, 3 H). MS (EI): *m*/*z* = 214 [M^+], 123, 95, 92, 91, 65, 63, 41.

(10) **3-(3-Methylbut-2-enyloxy)pyridine (Table 2, Entry 20)**: yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.32 (s, 1 H), 8.21 (s, 1 H), 7.20 (s, 2 H), 5.46–5.49 (m, 1 H), 4.56 (d, *J* = 7.0 Hz, 2 H), 1.80 (s, 3 H), 1.75 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.0, 141.9, 139.0, 138.1, 123.8, 121.4, 119.0, 65.1, 25.8, 18.3. MS (EI): *m*/*z* = 163 [M^+], 162, 95, 69, 68, 67, 41. HRMS (EI): *m*/*z* [M^+] calcd for $C_{10}H_{13}NO$: 163.0997; found: 163.1002.