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Copper catalyzed Gomberg–Buchmann–Hey reaction using aryldiazonium tosylate

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ABSTRACT

Copper catalyzed modification of Gomberg–Bachmann–Hey reaction to synthesize symmetrical/unsymmetrical biaryls via diazotization of anilines with *p*-TSA and $NaNO_2$ system at 50 °C, in aromatic liquids as solvents and second partners was successfully developed. Aniline and 3-nitronaniline gave biphenyl and 3-nitrobiphenyl, respectively, with moderate yields. All *para*-substituted anilines gave comparatively higher yields while in the other cases including *ortho*-substituted anilines yields were lower. Except anilines with *o*-$NHCOCH_3$ and *o*-$CONH_2$ which gave symmetrical biaryls, all others gave selectively unsymmetrical biaryls.

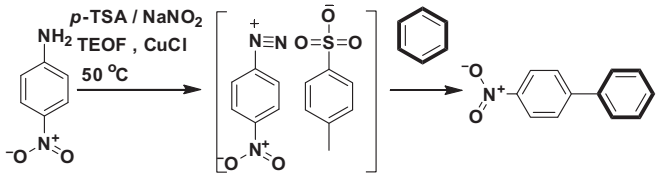
Gomberg–Buchmann–Hey (GBH) reaction[1a,b] is one of the classical methods for aryl C–C coupling wherein generation of aryl radical through degradation of aryldiazonium salt in the presence of a base viz. sodium hydroxide[2a,b] or sodium acetate[3] in aromatic liquids as second partner at 0–5 °C to yield biaryl compounds. This reaction is well studied mechanistically[4] and few improvements have been made. Despite wide applicability of GBH reaction it is least preferred for industrial applications because diazotization in aqueous medium leads to biphasic reaction.

The biaryl scaffold is an important substructure in a number of bioactive and functional molecules. It is found in many categories of pharmaceutically active ingredients such as antibiotics, antiinflammatory, antihypertensive, antifungal, anticancer, antihistaminic, and infertility treatment.[5–7] Clinically used antihypertensive drugs like candesartan, losartan, valsartan, and telmisartan contain this scaffold.

Syntheses of biaryls have been the focus of synthetic activity of chemist for over 100 years.[8] There are several methods for aryl C–C bond formation; the most common one is based on transition metal catalyzed coupling reactions viz. Mizeroki-Heck, Nigishi, Stille, Suzuki-Miyaura.[9–11] Majority of these methods need pre-functionalization of the coupling reactants with halogen, boronic acid, silane, mesylate, and triflate and so on. These methods of aryl C–C bond formation although high yielding with great specificity require precious metals and specially synthesized ligands.

Biaryls are accessible by classical methods as well as Ullmann reaction,[8] Gatterman reaction,[12] GBH reaction and also via decomposition of biaryl peroxides to generate radical followed by coupling with aromatic counterpart.[13] All these methods have several disadvantages such as low yields, harsher conditions, large amount of waste generation, and tedious workup procedures. However, the major advantage is that these reactions require cheaper catalysts with no additional requirement of ligands. These advantages have triggered the reinvestigation of the classical methods and one of these being GBH reaction.

Important modifications in GBH reaction are synthesis of aryldiazonium salts in neutral aprotic, homogenous medium by the use of alkyl nitrites[14] or alkyl thionitrites.[15] The issue of heterogenicity was dealt with by the use of phase-transfer catalysts such as 18-Crown-6 with potassium acetate[16a] as well as with potassium *t*-butoxide as bases[16b] and the methods have also been modified for intra-molecular ring closure.[17] Stable diazonium salts that can be readily prepared, isolable and nonexplosive in solid state are reported and these include aryldiazonium tetrafluoroborate,[18]



Scheme 1. Copper catalyzed GBH reaction of 4-nitroaniline in benzene as solvent/reactant.

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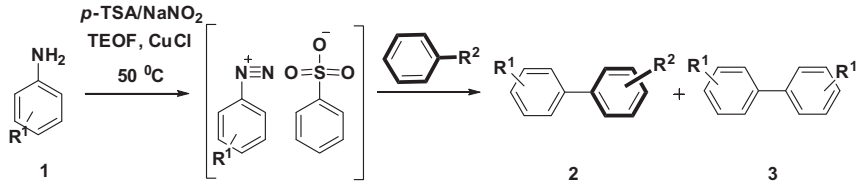
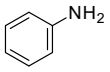
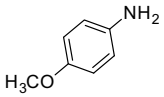
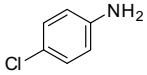
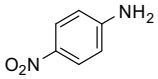
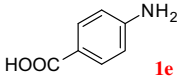
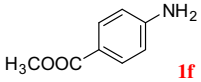
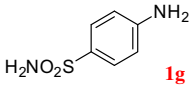
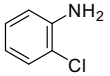
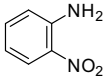
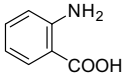
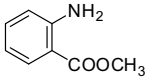
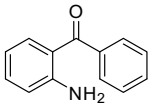
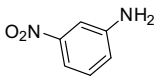
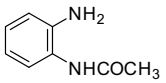
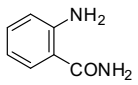
Table 1
Reaction results of aryldiazonium tosylate with benzene aromatic solvent/reactant (Method A)



Entry	Anilines **1**	Product(s) Yield[a](%)		Mp °C	Mp °C, lit. (Ref.)
		2 (Lit.[b])	**3**		
1	 **1a**	**2a**, 55 (47)	**3a**, 0	69–70	70–72[27]
2	 **1b**	**2b**, 60 (26)	**3b**, 0	82–83	84–87[28]
3	 **1c**	**2c**, 75 (60)	**3c**, 0	72–74	75–78[29]
4	 **1d**	**2d**, 70 (67)	**3d**, 0	112–114	114.5–115[30]
5	 **1e**	**2e**, 70	**3e**, 0	215–217	218–219.4[31]
6	 **1f**	**2f**, 67	**3f**, 0	112–114	115–116[32]
7	 **1g**	**2g**, 80	**3g**, 0	224–226	227–228[33]
8	 **1h**	**2h**, 55	**3h**, 0	Oil	34[27]
9	 **1i**	**2i**, 40 (33)	**3i**, 0	Oil	37–38[34]
10	 **1j**	**2j**, 37	**3j**, 0	110–112	113–114[35]
11	 **1k**	**2k**, 45	**3k**, 0	112–113	115[36]
12	 **1l**	**2l**, 43[c]	**1l**, 0	Oil	––
13	 **1m**	**2m**, 60	**3m**, 0	60–61	60–61[37]
14	 **1n**	**2n**, 0	**3n**, 75	160–162	164–165.5[38]

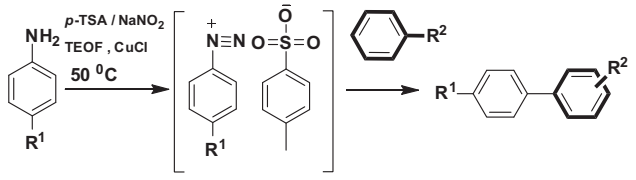
(*continued on next page*)

Table 1 (*continued*)

Entry	Anilines **1**	Product(s) Yield[a](%)		Mp °C	Mp °C, lit. (Ref.)
		2 (Lit.[b])	**3**		
15	 **1o**	**2o**, 0	**3o**, 78	208–210	209–211[39]

[a] Isolated yield.
[b] Yields taken from Ref.15.
[c] 29% of 9-fluorenone was formed, by GC.

Table 2
Reaction results of aryldiazonium tosylate with benzonitrile and chlorobenzene aromatic solvent/reactant (Method B)



Entry	Anilines R_1	Aromatic solvent/reactant R_2	Biaryl isomer ratio[a]		
			o-	*m*-	*p*-
1	CH_3	CN	50	—	50
2	H	Cl	46	31	24

[a] By comparison of retention times with standard and area percent by GC analysis.

hexafluorophosphate,[19] and aryldiazonium *o*-benzenedisulfonamides.[20] Similarly, aryldiazonium tosylates $Ar_1N2^+Ar_2SO_3^-$ are reported about half a century ago[21] and these have been used recently for iodination.[22]

This inspired us to investigate the use of aryldiazonium tosylate for aryl C–C coupling. Herein we report the rapid generation and copper catalyzed coupling of aryldiazonium tosylate in nonaqueous conditions with aromatic liquid as solvent/reactant to yield baryls.

For preliminary experiment 4-nitroaniline was used as a representative substrate which was diazotized with *p*-toluenesulfonic acid (*p*-TSA) and $NaNO_2$ in the presence of triethylorthoformate (TEOF) as water scavenger[23] and CuCl as a catalyst in benzene as aromatic reactant/solvent at 50 °C to yield selectively 4-nitrobiphenyl with no detectable amount of symmetrical biaryl (Scheme 1).

To study the general applicability substrates including anilines with electron-donating as well as electron-withdrawing substituents at different positions were selected.

Anilines reacted with benzene using Method A[24] resulted in corresponding symmetrical/unsymmetrical biaryls. Aniline and 3-nitronaniline gave biphenyl and 3-nitrobiphenyl, respectively, with moderate yields. (Table 1, entries 1 and 13). In general the yields were higher with *para*-substituted anilines and lower in all the other cases.

To explore the effect of substitution and generalize the scope, the present method was applied to a variety of anilines with electron withdrawing and electron releasing groups at different position. In all cases irrespective of the nature and position of the substituents only unsymmetrical biaryls were obtained (Table 1, entries 1–13), Only in two cases symmetrical biaryls arising out of self coupling were isolated (Table 1, entries 14 and 15). Irrespective of the nature of substituents, yields were uniformly higher in all *para*-substituted anilines (Table 1, entries 2–7) whereas lower in *ortho*-substituted cases (Table 1, entries 8–12). The product 2,2′-diacetylaminobiphenyl was subjected to hydrolysis while 2,2′-biphenyl carboxamide to Hoffmann degradation yielded identical product, that is, 2,2′-diaminobiphenyl.[25] As expected in the case of 2-aminobenzophenone, 9-fluorenone was formed as a by product due to intramolecular cyclization (Table 1, entry 12).

Selective formation of unsymmetrical biaryls is attributed to rapid generation of aryl radical in dilute solution where solvent plays a dual role as diluent and reactant. In the two exceptional cases (Table 1, entries 14 and 15) where only symmetrical biaryls are formed due to self coupling, it is difficult to give a convincing explanation. However, it could be postulated that a dimeric Cu-complex by the participation of nitrogen containing neighboring groups prior to generation of free radicals is responsible.

o-Tolylbenzonitrile (OTBN) is an important intermediate in the synthesis of sartan series of drugs such as losartan, candesartan, and valsartan. Synthesis of OTBN was attempted by Method B[26] using *p*-toluidine and benzonitrile as the solvent/reactant. The results indicated that the product was a 1:1 mixture of OTBN and *p*-tolylbenzonitrile (Table 2, entry 1). In the same way reaction of aniline with chlorobenzene resulted in the mixture of *o, m*, and *p*-substituted biaryls in the ratio of 46:31:23 (Table 2, entry 2).

In summary a new modification of GBH reaction that can be conducted in organic solvent at a higher temperature using copper as catalyst has been successfully developed. Present method is applicable for the synthesis of symmetrical/unsymmetrical biaryl with moderate to good yields depending on the substrates.

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24. *General procedure (Method A)*: To a solution of aniline (32.25 mmol) in 30 ml of benzene was added *p*-TSA (12.25 g, 64.5 mmol), TEOF (4.7 g, 32.25 mmol), CuCl (10 mol %) at rt, mixture was heated to 50 °C. Maintaining 50 °C, powdered $NaNO_2$ (2.09 g, 32.25 mmol) was added portion wise over 15 min, frothing was observed during the addition which subsided. The reaction mixture was maintained at the same temperature for 30 min to complete the reaction, monitored by TLC. The reaction mixture was cooled to rt, filtered to remove the solid precipitated, washed with EtOAc and organic layer was evaporated to dryness to get sticky residue, which was extracted with petroleum ether (60–80) followed by evaporation of solvent to yield the crude biaryl. It was purified by recrystallization from methanol/column chromatography ethyl acetate/petroleum ether (0.5:10) as eluent. The products were confirmed by physical constants. The results are summarized in Table 1.
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26. *General procedure (Method B):* Procedure same as Method A except in the place of benzene, chlorobenzene or benzonitrile was used and the reaction mixture was analyzed by GC and peaks were identified by comparison with the retention time of standard compounds and ratio was estimated by area percent. The results are summarized in Table 2.
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