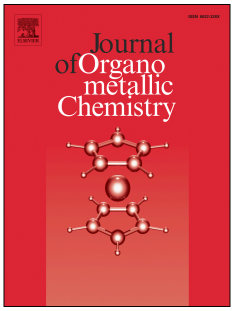

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Sulochana S. Mudaliar, Shailesh N. Zala, Kishor H. Chikhalia

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Copper Catalysed Alkylation of Heteroaryl Chloride via Migratory Insertion of Carbenes.

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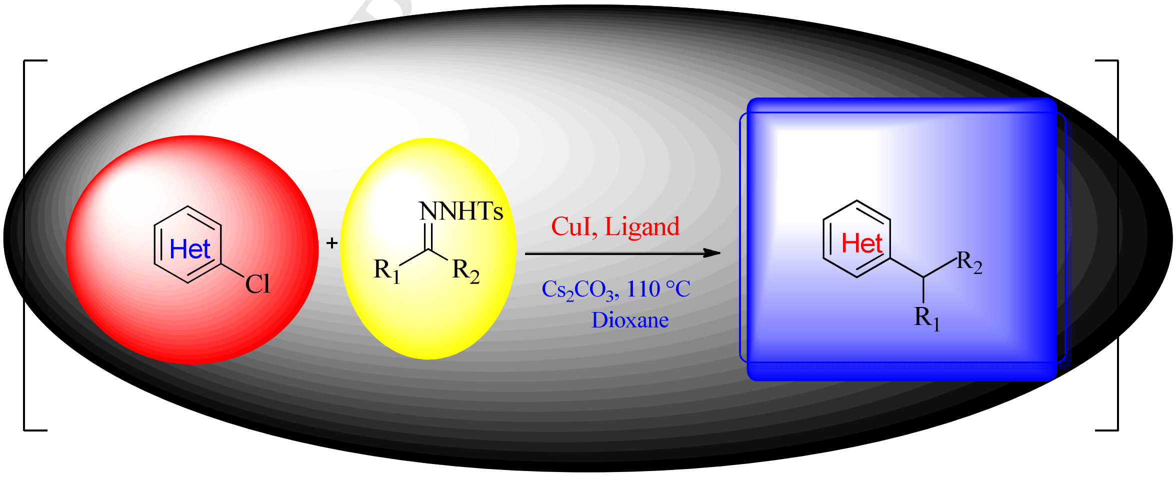
Abstract.

Cross-coupling reaction involving Cu catalysed carbene migratory insertion with N-tosylhydrazones as the reaction partner with various substituted cyanuric chloride were studied, which has been recognized as a new type of cross-coupling reaction. Cu-carbene migratory insertion is proposed to play the key role in this transformation to form C-C bond from heterohalides with various tosylhydrazones. Salient features of this reactions are (i) no stoichiometric organometallic reagents are required (ii) less toxic and step economical reaction (iii) easy to handle, to get moderate to excellent yields. Outcome of this reaction produces 1,1-heterodiaryl alkanes.

Key Words.

Cross-coupling reaction, Cu-catalyst, Migratory insertion, N-tosylhydrazone, Cyanuric chloride.

Graphical abstract.



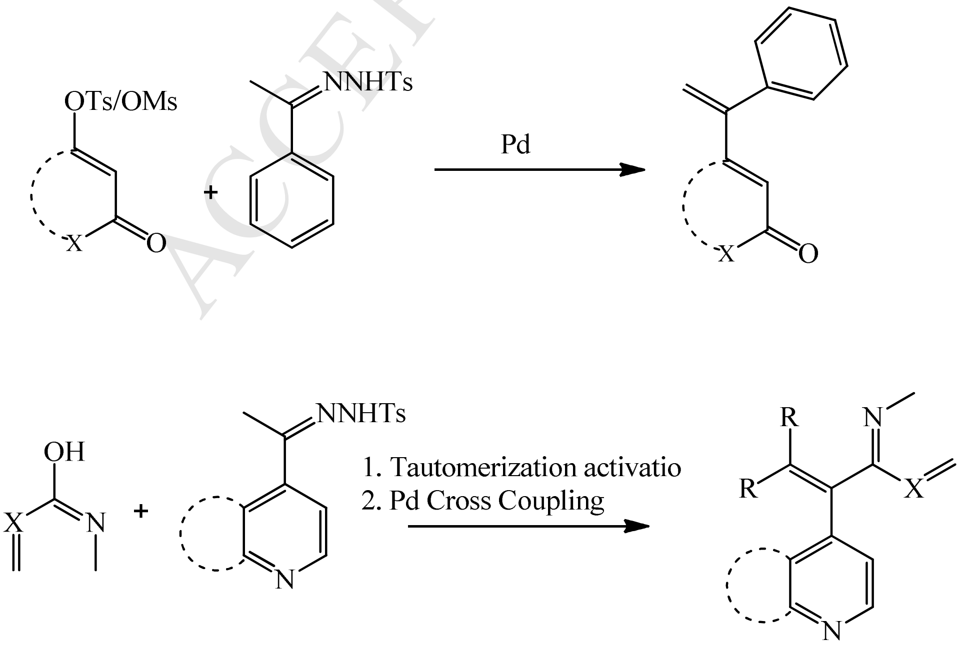
Introduction.

Tranisition metal catalyzed cross-coupling reactions of hydrazenes have been established as new tool for the formation of C-C and Carbon-heteroatom bonds.[1,2] Diazo compounds generates (Pd, Cu, Rh, Ni and Co) metal carbene species under basic conditions and undergoes diverse chemical reactions.[3] Extensive study has been carried out on transition metal catalysed reaction of diazo compounds which leads to the development of new synthetic route in organic synthesis. Diazo compounds are subjected to generate carbene in situ from the corresponding N-tosylhydrazones, which have been used as coupling partner in the cross-coupling reactions.[4-6] Here in we report a Cu-catalyzed carbene migratory insertion of N-tosylhydrazones with substituted heteroaryl chlorides, which resulted 1,1-heterodiaryl alkane compounds as the final product.

It has been widely studied that Pd catalysed cross-coupling reaction can be appropriately incorporated with the carbene insertion reaction.[7] With this combinations, novel transformations that are distinct from both classical cross-coupling and carbene insertion. Recent studies revealed that this chemistry is not only limited to palladium, but Cu proved to be the best catalyst in the carbene migratory insertion via cross-coupling reaction, which gained a great interest in frontiers of synthetic chemistry.[8] Cu-salts possess less toxicity and also inexpensive, easily available transition metal, which is used as catalyst in various cross-coupling reactions. Detail study on Cu carbene migratory insertion were given by Jianbo Wang & co-workers in their catalytic cascade reactions involving metal carbene migratory insertion [9], also they have premeditated a work on direct benzylation of 1,3-azoles with N-tosyl hydrazine, by considering Cu as catalyst.[10] Kozlowski and co-workers have given a detailed overview of cu-catalyzed aerobic organic reactions.[11] Successful migratory insertion carbene reactants contemplated our interest to get new dimension in paradigm of various heterocycles and herein an effort has been made to generate 1,1-heterodiaryl alkane compounds through Cu catalysed carbene insertion reaction.

Basic approach for the synthesis of 1,1-heterodiaryl alkane follows the Heck reaction[12], Grignard reaction[13], or by way of utilizing organometallic reagents such as organotin, organomagnesium, organozinc and organolithium etc.[14-17] Use of this organometallic reagents are toxic, air/moisture sensitive, expensive and also organometallic compounds were synthesised in harsh condition, which is very challenging in an industrial scale.[18] So for the advancement of feasible and environmentally compatible chemical methodologies, we diverged our attention from the general approach of synthesis of heterodiaryl, alkane compounds to the novel type of transition metal catalysed cross coupling reaction. Having wide range applications in the synthetic chemistry N-tosylhydrazones had been proved to be the exceptional coupling partners in the C-H activation reaction. N-tosylhydrazone can be promptly synthesized from the corresponding ketones and also used as a precursors for the generation of the metal-carbene complex through the preparation of diazo compounds without allowing the use of other organometallic reagents.[19-22]

(A). Our Previous work.[23-24]



(B). Our recent work.

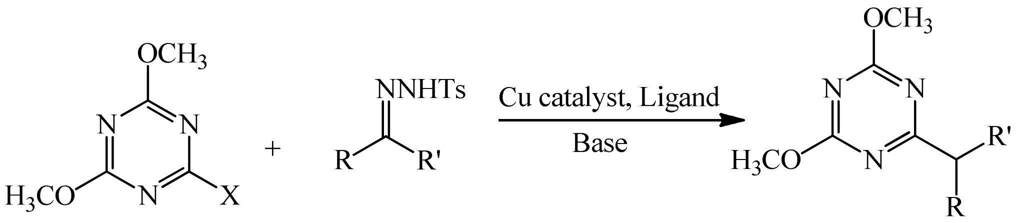


Figure 1. Previous and Recent work of our Group

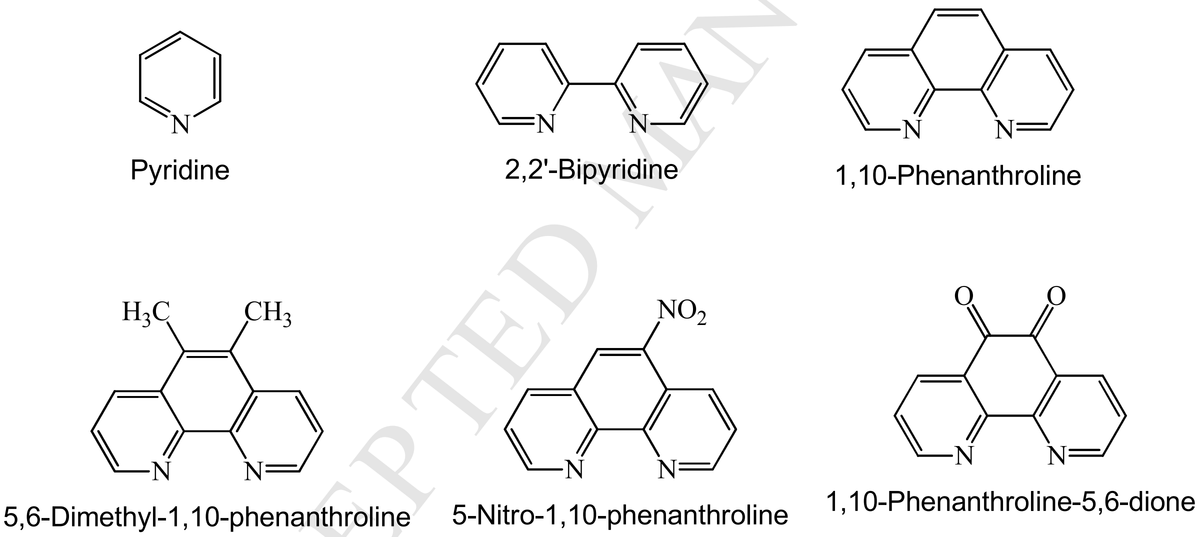
In our previous work, we have reported palladium catalysed cross coupling reaction of tautomerizable heterocycles with coupling partners N-tosylhydrazone via C-OH activation (Fig.1). Palladium catalysed carbene insertion reaction was carried out with tautomeriazbale heterocycles. β-H elimination was carried out in the process to produce a final prouct, which resulted with the C=C in the final step of the reaction.

As an advancement from our previous work, here in we are reporting a Cu catalysed carben migratory insertion for the synthesis of 1,1-heterodiaryl alkane derivatives, which is found more efficient than the previously existing reports. In our previous work Pd-catalysed carbene insertion reaction was employed for the synthesis of 1,1, heterodiaryl alkenes, which was followed through β-H elimination reaction with N-tosylhydrazones and hetero arenol. Previous works on Cu carbene migratory insertion reactions had been studied extensively with activation of acidic proton.[25] Our work is distinctive from the earlier studied work in which C-Cl bond is being activated by employing Cu with Cs_2CO_3 and NaH. This new system of alkylation follows Cu-catalyzed cabene migratory insertion involving protonation under mild condition, use of less toxic transition metal Cu and 1,10-phenanthroline as a ligand. So we imitated our work by employing Cu to the di-substituted chloro heterocycles s-triazine. The synthetic strategy is given in the plausible mechanism. The resulted products were found in the agreement with the desired product.

Result and Discussion.

To investigate the feasibility of preferred reaction, we strived with cyanuric chloride(1a) as a basic material and tosylhydrazone(2a) as a model substrate. Our preliminary inspection was carried out using CuI as catalyst, 1,10pehananthroline as ligand and Cs_2CO_3&NaH as base, refluxing temperature condition utilising 1,4-dioxane as solvent and underneath air. The result which we obtained was formation of aimed product with good yield as it used to be in blend of alternative unintended spinoff in considerable yield. We also investigated the formation of product 3a, with different ligands, catalysts, base as well as solvents. Optimization experiences is recounted in table 1. During the optimization it is observed that utilization of CuI as catalyst yielded the preferred product 9in acceptable to high yield.

Figure. 2 List of lignds used in the reaction



As an alternative of CuI, different copper catalyst like CuCl and CuBr have been additionally employed as effective catalyst but no significant deviation has been observed to CuI. Employment of $Cu(OAc)_2$ proved to be an in appropriate catalyst for this reaction. Ligands have been determined to demonstrate a valuable role in the targeted reaction and screening effect of ligand lead us to conclude that 1,10-phenanthroline proved to be the most productive amongst other verified ligands equivalent to 2,2’-bipyridine, pyridine, 5,6-dimethyl-1,10-

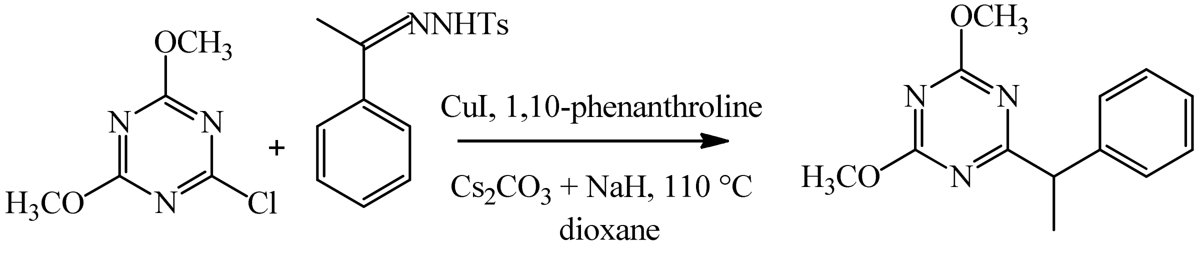
phenanthroline, 5-nitro-1,10-phenanthroline. Furthermore, trace amount of yield was observed in the case of ligand free test.

After the effective optimization of catalyst and ligand we then shifted our attention towards influence of base and solvents on proposed alkylation reaction. Screening experiences divulge that Cs_2CO_3 was once located as most inclined base compared to different viz. KOtBu, K_2CO_3 and LiOtBu. Further study reveals that KOtBu, K_2CO_3 and LiOtBu was found better for other heterocyclic/non-heterocyclic motif motif but in the present study no significant result has been observed, even their combination with other base also did not proved their effectiveness. As it can be observed from table-2.

One more strong base NaH was employed as a part of the following reaction process in which the base has an significant role. It is understood that NaH being a strong base can easily replace the Cl atom. Also reaction was carried out without using NaH, which resulted in trace amount of yield. It is therefore understood that addition of NaH with Cs_2CO_3 afforded better to moderate yield.

After the assessment of bases, the solvent effect for1,4-dioxane, THF, DMF and toluene were consequently examined. Among which 1,4-dioxane resulted better amount yield in comparison to the other solvents. Our study reveals that on increasing polarity of the solvents like DMF and THF resulted in poor yield, where as non-polar solvent like toluene resulted with moderate amount of yield.

Table 1: Reaction Optimization[a]



1a **2a** **3a**

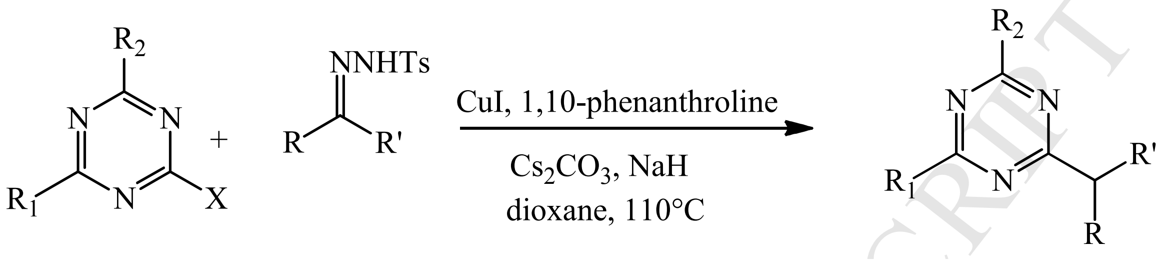
Entry	**Catalyst**	**Ligand**	**Base**	**Solvent**	**Yield**[b]
1	CuI	1,10-Phenanthroline	Cs_2CO_3	1,4-Dioxane	20%
2	CuI	1,10-Phenanthroline	Cs_2CO_3+NaH	1,4-Dioxane	79%
3	CuBr	1,10-Phenanthroline	Cs_2CO_3+NaH	1,4-Dioxane	37%
4	CuCl	1,10-Phenanthroline	Cs_2CO_3+NaH	1,4-Dioxane	12%
5	$Cu(OAC)_2$	1,10-Phenathroline	Cs_2CO_3+NaH	1,4-Dioxane	Trace
6	CuI	Pyridine	Cs_2CO_3+NaH	1,4-Dioxane	49%
7	CuI	2,2'Bipyridine	Cs_2CO_3+NaH	1,4-Dioxane	58%
8	CuI	1,10-Phenanthroline-5,6-dimethyl	Cs_2CO_3+NaH	1,4-Dioxane	63%
9	CuI	1,10-Phenanthroline-5,6-dione	Cs_2CO_3+NaH	1,4-Dioxane	55%
10	CuI	5-Nitro-1,10-phenanthroline	Cs_2CO_3+NaH	1,4-Dioxane	43%
11	CuI	1,10-Phenanthroline	KO^tBu+NaH	1,4-Dioxane	Trace
12	CuI	1,10-Phenanthroline	LiO^tBu+NaH	1,4-Dioxane	Trace
13	CuI	1,10-Phenanthroline	K_2CO_3+NaH	1,4-Dioxane	30%
14	CuI	1,10-Phenanthroline	Cs_2CO_3+NaH	THF	70%
15	CuI	1,10-Phenanthroline	Cs_2CO_3+NaH	Toluene	59%
16	CuI	1,10-Phenanthroline	Cs_2CO_3+NaH	DMF	61%

[a]Reaction condition:Catalyst: 25mol%, ligand: 20 mol%, 1a: 1.0 mmol (0.50 g), 2a: 0.5mmol (0.41g), base:Cs_2CO_3 + NaH 2.5 equivalent, solvent: 5 ml per mmol. Under air for 12 hours. [b]Isolated Yield.

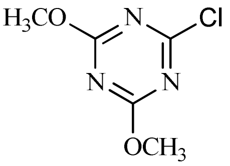
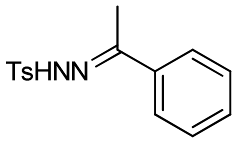
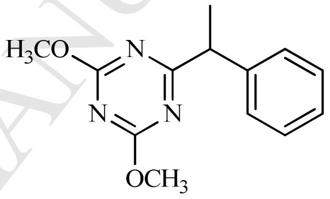
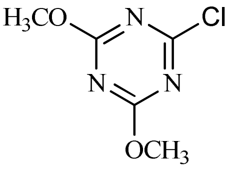
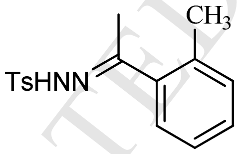
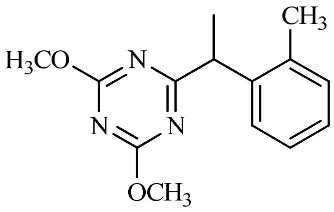
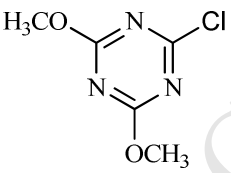
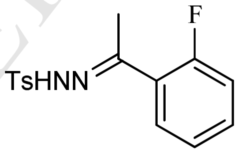
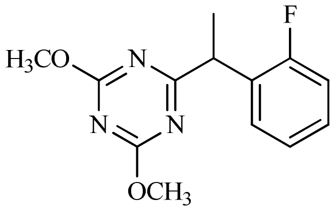
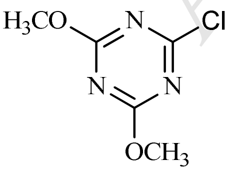
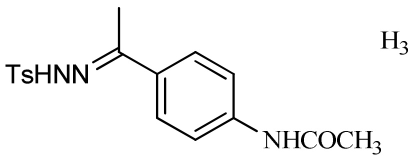
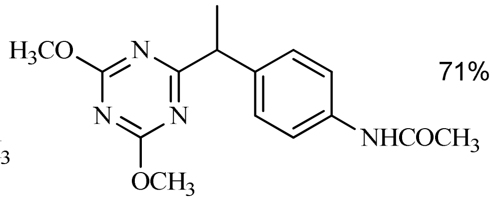
Investigated substrate scope of the reaction with different derivatives of sterically hindered tosylhydrazones and diverse cyanuric chloride derivatives engaging a feasible catalytic system, the obtained results are shown in table 2 and 3. Results of the reaction outcomes were shown in table 2 & 3 suggests that the catalytic system developed in the reaction are suitable for a wide range of coupling partners, such as different hetero halides with substituted N-tosylhydrazones. Based on the results obtained it is being concluded that N-tosylhydrazones containing both electron withdrawing groups and electron donating groups resulted moderate to good amount of yields, but more significantly tosylhydrazones with electron with drawing group appeared with less yield to the others.

In order to enhance the substrate scope, we checked the feasibility of the reaction with structurally altered hetero halides like quinoline, quinazoline,thiophenes, quinaoxaline, pyridazines and N-tosylhydrazones. The acquired resulted are summarized in the table 3.

Table 2: Scope of the reaction with variety of Cyanuric chloride and N-tosylhydrazone[a]



1a **2a** **3a**

1 (a-g)	**2(a-g)**	**3(a-g)**	**Yield**[b]
			79%
			87%
			71%
			71%

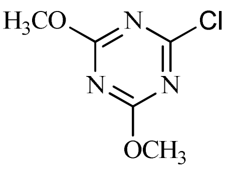
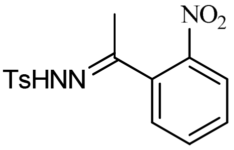
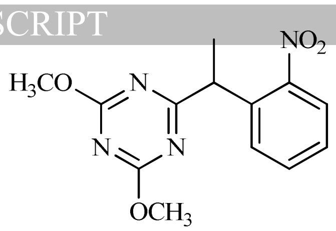
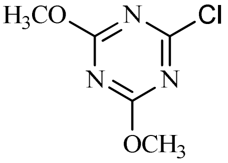
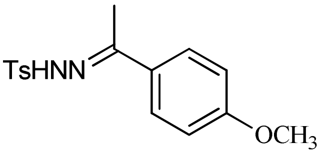
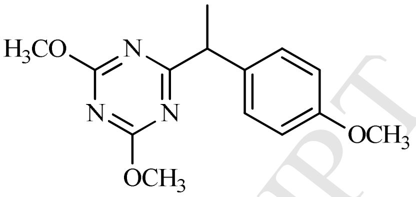
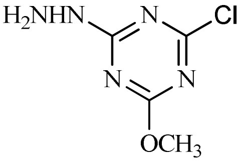
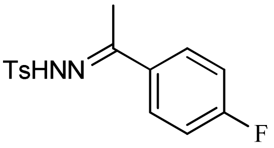
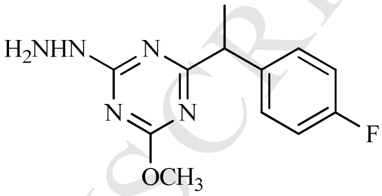
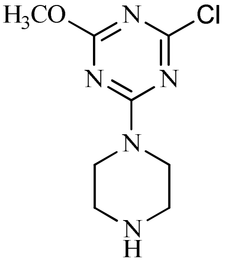
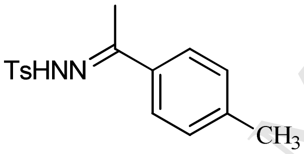
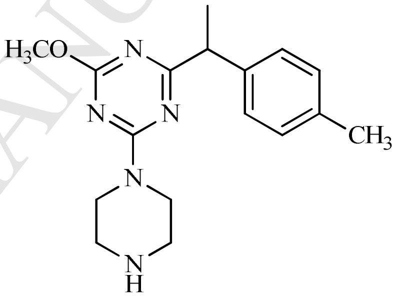
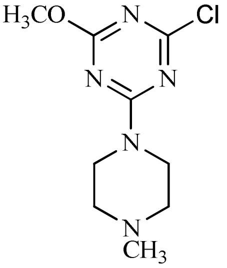
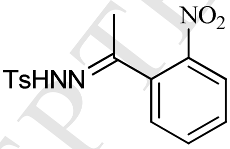
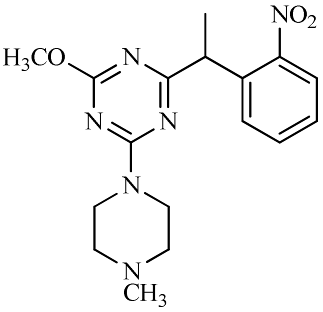
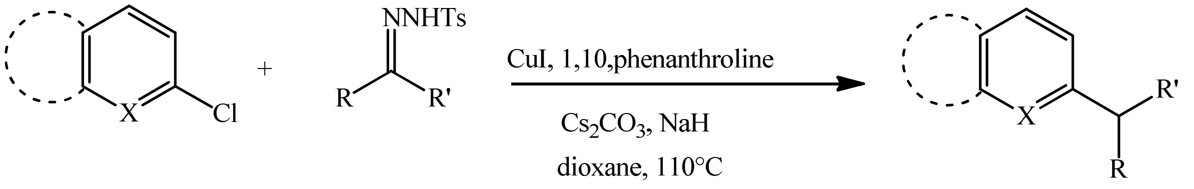
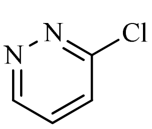
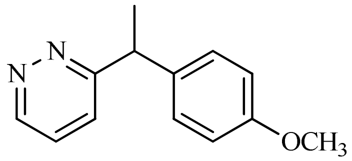
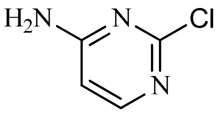
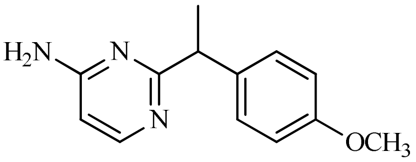
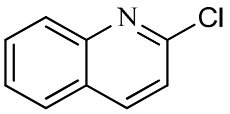
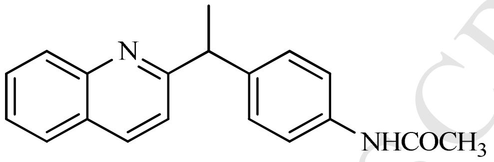
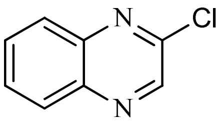
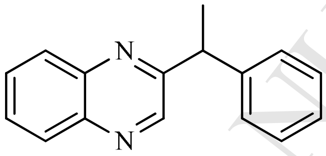
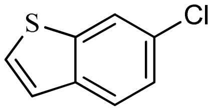
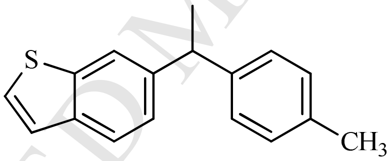
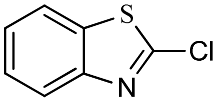
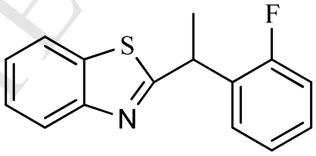
			67%
			89%
			72%
			88%
			75%

Table 3: Scope of the reaction with variety ofheteroaryl amines and N-tosylhydrazones.

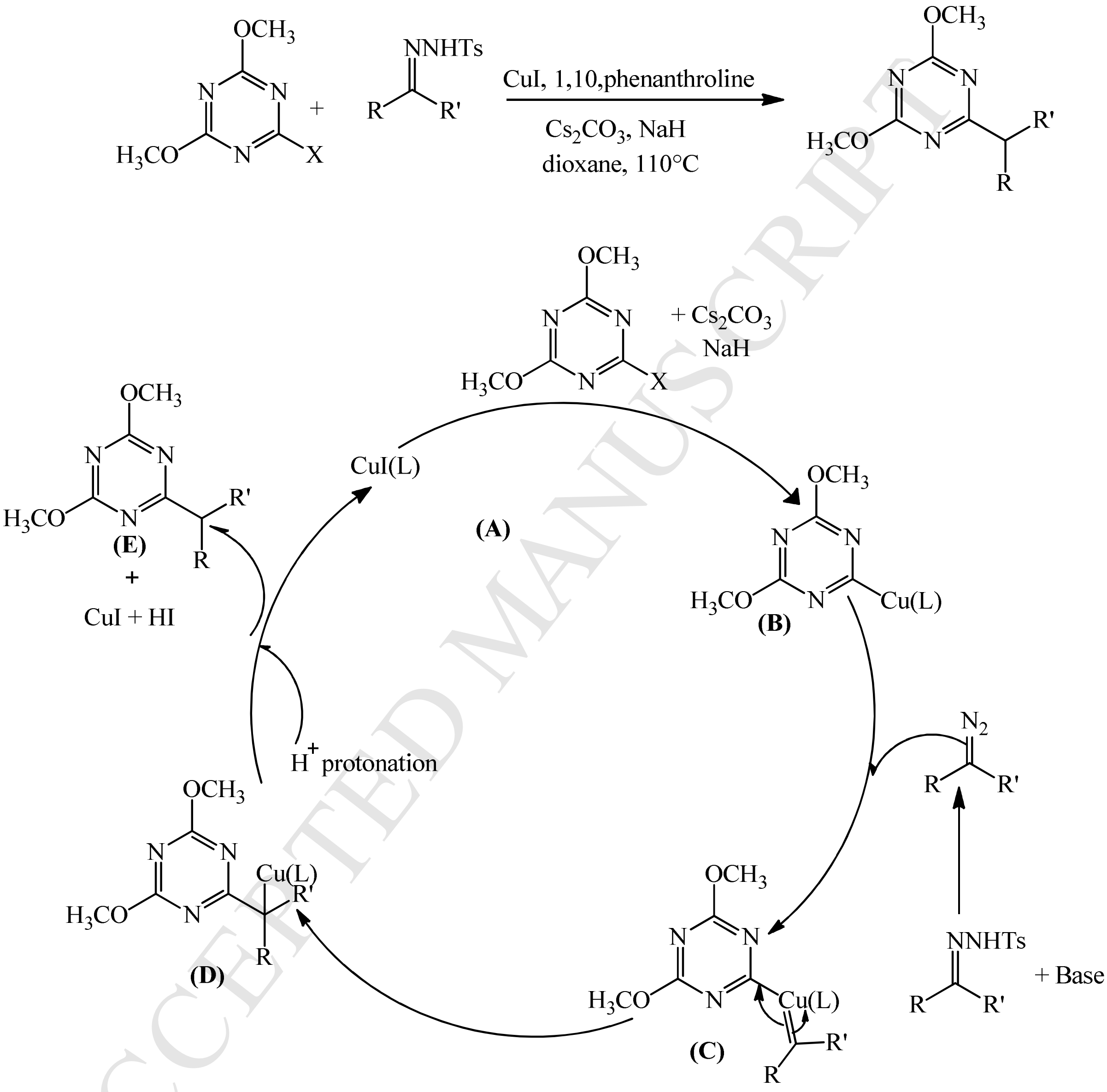


2(b-k)	**3(f-o)**	**Yield^b**
		81%
		89%
		71%
		61%
		79%
		67%

^{a}Reaction condition:Catalyst: 25 mol%, ligand: 20 mol%, 1a: 1.0 mmol (0.50 g), 2a: 0.5 mmol (0.41 g), base:Cs_2CO_3 + NaH 2.5 equivalent, solvent: 5 ml per mmol. Under air for 12 hours. ^{b}Isolated Yield.

On the premise of accomplished outcome and also the literature survey[26-30], of related reaction, a tentative reaction mechanism of copper catalysed carbene migratory insertion reaction of 2,4-dimethoxy-6-chloro s-triazine with N-tosylhydrazone is drafted out as under in Figure 3. Initial coupling reaction between Cu catalyst (**A**) and the primary compound of 2,4 dimethoxy-6-chloro s-triazine carried out in the presnence of base and ligand, by which aryl copper complex was generated(**B**) Diazo compounds were generated form N-tosylhydrazone in the presence of base by in situ formation(**C**). The generated diazo compound is inserted in the aryl copper complex (**B**) to afford the intermediate C, which than undergoes a carbene migration producing alkane complex (**E**). Protonation was carried out in the final step to form the desired product regenerating the CuI catalyst.

Fig. 3: Plausible Mechanism



Conclusion:

In conclusion, we have developed new and feasible method from the commercially available compound s-triazine for the synthesis of 1,1-heterodiaryl alkane compounds by Cu catalyzed carbene migratory insertion, which is environmentally benign, less toxic, cost effective. The significant feature of this reaction is that C-Cl bond was activated using Cu-catalyst has hitherto unreported on this motif. Nevertheless some reports are available only on C-H activation using Cu catalyst for carbene migratory insertion. The method was applied on different heterohalide compounds with diverse N-tosylhydrazone derived from ketones. The said method is proved very effective in the preparation of 1,1-heterodiaryl alkanes than the other traditional method.

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