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Efficient copper-catalyzed cross-coupling of 1-Boc-piperazine with aryl iodides and its application in the synthesis of trazodone

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ABSTRACT

A convenient and practical strategy is developed for the cross-coupling of *N*-Boc protected piperazines with aryl iodides using CuBr/1,1′-bi-2-naphthol as the catalyst and K_3PO_4 as the base. The protocol affords N-arylated piperazine products in moderate to good yields under the optimized conditions. The application of this catalytic system to the synthesis of trazodone is also successfully demonstrated using commercially available substrates.

Transition metal catalyzed cross-coupling reactions are important for the formation of carbon and heteroatom bonds in organic synthesis.[1] In particular, N-arylated aliphatic amines have found widespread applications in the preparation of numerous intermediates that are prevalent in bioactive pharmaceuticals and conducting materials.[2] Among the various strategies developed to date, the copper-catalyzed Ullmann-type cross-coupling represents a straightforward manner and convenient method for the assembly of the required core structures. However, the classical versions of this cross-coupling have limited synthetic applications due to the harsh reaction conditions employed, such as high reaction temperatures, stoichiometric amounts of a copper catalyst, long reaction times, and low yields.[3] Significant developments made to the Ullmann-type cross-coupling reaction have been concerned with the addition of assisting ligands to the protocols to enhance the reactivity of the copper catalysts and thereby increasing the reaction rate.[4] Wan reported the N-arylation of aliphatic amines with aryl halides using copper powder or CuI in combination with racemic 1,1′-bi-2-naphthol (*rac*-BINOL) as the catalyst.[5] Fu has demonstrated an efficient CuBr/*rac*-BINOL-catalyzed N-arylation of aliphatic amines with aryl iodides at room temperature.[6] However, the cross-coupling of piperazine-based secondary amines with aryl iodides remains limited. Hence, there is still a need to develop simple protocols for the cross-coupling of this class of cyclic secondary amine.

In this Letter, we disclose our findings on the application of a copper ligand assisted catalytic system for the N-arylation of *N*-Boc-protected piperazines. Thereafter, we validated the protocol by applying the catalytic system to the synthesis of *tert*-butyl 4-(3-chlorophenyl)piperazine-1-carboxylate (**3a**), an important intermediate for the synthesis of trazodone.

In our initial studies, the reaction between 1-Boc-piperazine (1.5 equiv) and 3-chloro-iodobenzene (1.0 mmol) was selected as the model system for optimizing the reaction conditions (Table 1). The reaction carried out using a combination of CuBr (20 mol %), *rac*-BINOL (40 mol %), and K_3PO_4 (2 equiv) in DMF (0.5 mL) at 100 °C led to a significant formation of the desired product. However, the presence of a side product leads to difficulties in the purification step. Based on ^{1}H NMR analysis of the crude material, it was apparent that the side product was probably generated via the N-arylation of the assisting ligand. In order to remove the side product from an economical viewpoint, the catalyst:ligand loading was reduced to 20:15 (mol %) and the catalyst was pre-formed for 10 min prior to the addition of the substrates. To our delight, this modified procedure afforded a good isolated yield (71%) of the product (Table 1, entry 1). Encouraged by this result, we investigated the merits of various copper salts for the N-arylation process (entries 1–4). Among these, CuBr was the best catalyst. Next, we probed the ligand effect using a series of commercially available ligands: *N*,*N*′-dimethylethylenediamine (DMEDA, L2, entry 5), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, L3, entry 6), *trans*-1,2-diaminocyclohexane (L4, entry 7), and 2,2,6,6,-tetramethylheptane-3,5-dione (TMHD, L5, entry 8). The use of *rac*-BINOL was shown to be critical for the success of this protocol as

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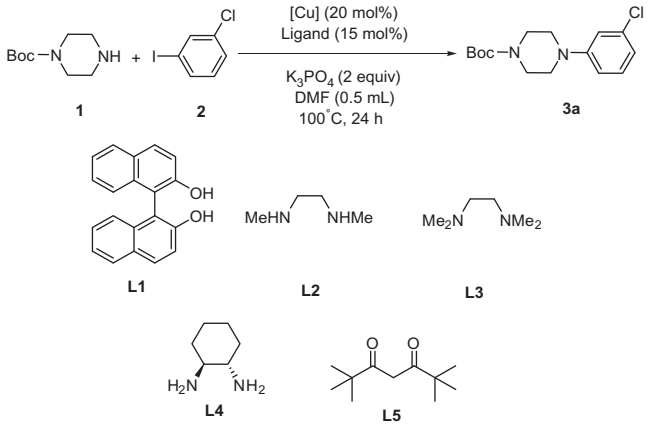
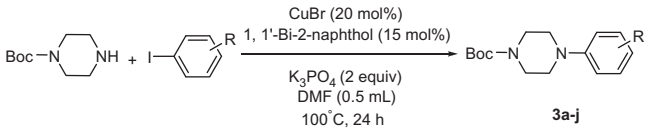
Table 1
Optimization studies on the copper-catalyzed cross-coupling of 1-Boc-piperazine with 3-chloro-iodobenzene[a]

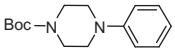
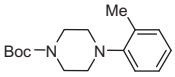
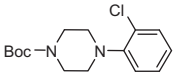
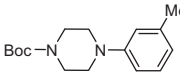
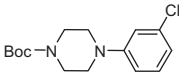
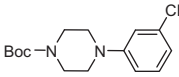
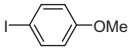
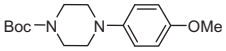
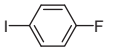
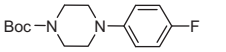
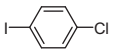
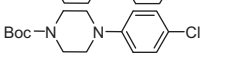
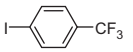
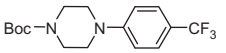


Entry	(Cu) source	Ligand	Yield[b] (%)
1	CuBr	**L1**	71
2	CuCl	**L1**	55
3	CuI	**L1**	68
4	Cu_2O	**L1**	58
5	CuBr	**L2**	0
6	CuBr	**L3**	Trace
7	CuBr	**L4**	0
8	CuBr	**L5**	Trace

[a] Unless otherwise shown, the reaction was carried out with 1-Boc-piperazine (1.5 mmol), 3-chloro-iodobenzene (1.0 mmol), K_3PO_4 (2 equiv), (Cu) source (0.2 mmol), ligand (0.15 mmol), DMF (0.5 mL), 100 °C, 24 h.
[b] Isolated yield after column chromatography.

Table 2
CuBr-catalyzed N-arylation of 1-Boc-piperazine with different aryl iodides[a]



Entry	ArX	Product		Yield[b] (%)
1			**3b**	57
2			**3c**	36
3			**3d**	41
4			**3e**	60
5			**3a**	71
6			**3f**	70
7			**3g**	72
8			**3h**	60
9			**3i**	71
10			**3j**	60

[a] Unless otherwise shown, the reaction was carried out with 1-Boc-piperazine (1.5 mmol), aryl iodide (1.0 mmol), K_3PO_4 (2.0 mmol), CuBr (0.2 mmol), 1,1′-bi-2-naphthol (0.15 mmol), DMF (0.5 mL), 100 °C, 24 h.
[b] Isolated yield after column chromatography.

the other ligands gave either traces of the product or no product formation. The optimal condition for the cross-coupling of 1-Boc-piperazine with the aryl iodide was achieved using a combination of CuBr (20 mol %), 1,1′-bi-2-naphthol (15 mol %), and K_3PO_4 (2 equiv) in DMF (0.5 mL) at 100 °C for 24 h.

The generality of the reaction was next examined under our optimized conditions using different functionalized aryl halides. The results are summarized in Table 2. In general, good yields were obtained for the cross-coupling of sterically unhindered aryl iodides. *ortho*-Substituted aryl iodides gave moderate yields (Table 2, entries 2 and 3) due to steric effects. No significant electronic effects were observed for both *meta*- and *para*-substituted aryl iodides (entries 4–10).

These results prompted us to attempt the synthesis of 1-(3-chlorophenyl)piperazine, a key intermediate in the synthesis of trazodone,[7] which has antidepressant, anxiolytic, and hypnotic properties. It is a widely used antidepressant drug that has medium to high affinity for several serotonin receptors such as $5HT_{2A}$ and the α_1 adrenergic receptor.[8] The synthesis of trazodone could be addressed efficiently by employing an N-arylation and two nucleophilic substitution reactions. Herein, we apply our newly developed copper-catalyzed cross-coupling strategy to synthesize the key intermediate for the preparation of trazodone.

Our synthesis started with the C–N cross-coupling of commercially available 1-Boc-piperazine and 3-chloro-iodobenzene (Scheme 1). As previously discussed the application of our copper-catalyzed system afforded *tert*-butyl 4-(3-chlorophenyl)piperazine-1-carboxylate in 71% yield. This intermediate **3a** was then treated with trifluoroacetic acid to remove the Boc protecting group. Next, mono-alkylation was carried out between intermediate **4** and commercially available 1,3-dibromopropane using sodium hydride to afford **6** in good yield. Subsequent nucleophilic substitution of bromide **6** with commercially available 2*H*-[1,2,4]triazolo[4,3-*a*]pyridin-3-one and purification gave trazodone (**8**) in 65% yield.[9] The incorporation of the cross-coupling strategy to the synthetic route provides a convenient and rapid method for chemical modifications to access a large range of structurally related analogues.

In summary, a straightforward and operationally simple route for the synthesis of N-arylated piperazines promoted by a copper salt in DMF at moderate temperature has been developed. In most cases, the N-arylated piperazine derivatives were obtained in moderate to good yields. The use of cheap and readily available CuBr, and *rac*-BINOL and the practical protocol should render this approach an attractive alternative to access various N-arylated piperazines. In addition, the extension of this system to the synthesis of trazodone increases the synthetic utility of the catalytic system. Overall, we believe that this catalyst system could serve as an important protocol for synthesizing biological and pharmaceutical products that require the formation of N-arylated piperazines.

Acknowledgments

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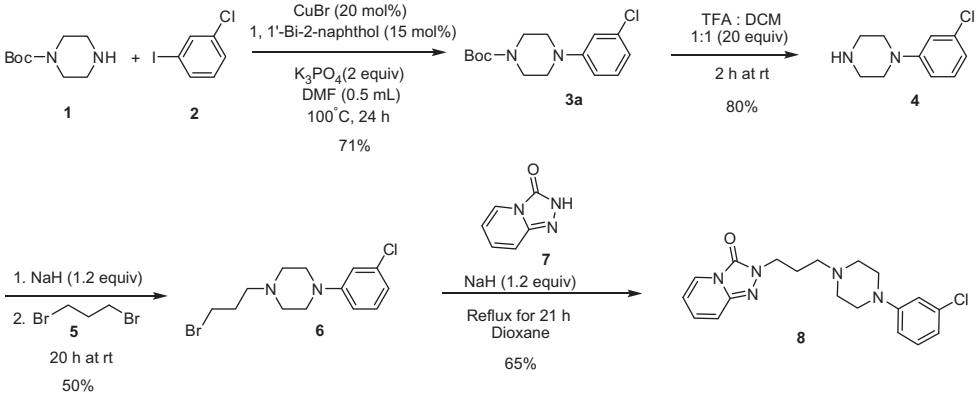
Supplementary data

Supplementary data (experimental procedures and compound characterization data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.104.



Scheme 1. Synthesis of trazodone.

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