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ARTICLE

# $Fe_3O_4$@$SiO_2$/Schiff base/Cu(II) Complex as an Efficient Recyclable Magnetic Nanocatalyst for Selective Mono N-Arylation of Primary O-Alkyl Thiocarbamates and Primary O-Alkyl Carbamates with Aryl Halides and Arylboronic Acids

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An efficient, convenient and novel method for the selective mono N-arylation of primary O-alkyl thiocarbamates and primary O-alkyl carbamates with aryl halides and arylboronic acids in the presence of recyclable magnetic Cu(II) nanocatalyst is described. A variety of mono N-arylated O-alkyl thiocarbamates and O-alkyl carbamates were prepared in good to excellent yields with a broad range of aryl coupling partners. The magnetic nanocatalyst can be easily recovered with an external magnetic field and reused at least five times without noticeable leaching or loss of its catalytic activity. This cost effective and eco-friendly methodology has some other advantages, such as easy preparation of the catalyst, simple work-up procedure, and easy purification, which makes this protocol interesting for the users in various fields of pharmacology and biotechnology systems.



## Introduction

Because of an important role of *N*-substituted *O*-thiocarbamates and carbamates in many areas of industry and science including biology,[1] agriculture,[2] medicinal chemistry,[3] coatings and materials science,[4] the selective synthesis of these compounds is the subject of an important challenge in organic chemistry.[5]

These N-substituted thioesters and esters of carbamic acid, in addition to widely as insecticides,[6] pesticides[7] and drug design,[8] they show a wide range of biological activity like herbicides,[9] antibacterial agents,[10] antimicrobial agents,[11] antiviral agents,[12] anti-HIV,[13] anticancer[14] and antitumor.[11b, 13f, 15] In particular, mono N-substituted O-alkyl thiocarbamates and *O*-alkyl carbamates are found in numerous the therapeutically relevant compounds, including approved pharmaceuticals such as flupirtine, retigabine, albendazole and NNB (*O*-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl] (4-bromophenyl) thiocarbamate) that are depicted in Figure 1.[16]

These compounds are appearing in organic chemistry, especially as amine protecting groups in peptide synthesis,[17] materials and polymer chemistry,[18] and also as a valuable intermediate for the synthesis of other useful products[19-23] such as thiols *via* Newman–Kwart rearrangement,[20] organocatalysts,[21] dendrimers[22] and supramolecular assemblies.[23]

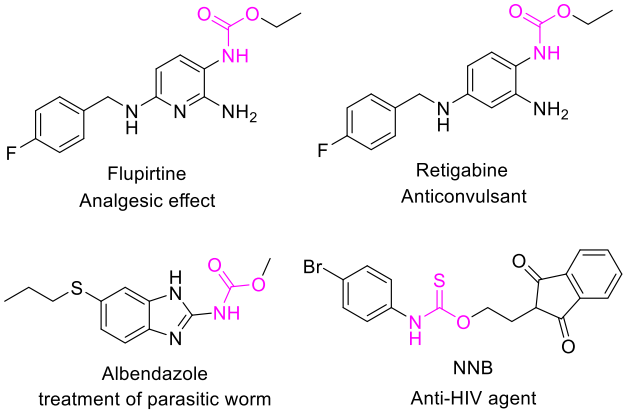


**Figure 1.** Some biologically active mono N-substituted O-alkyl thiocarbamates and O-alkyl carbamates

The most common methods for the synthesis of these compounds have been using toxic and harmful chemicals such as phosgene,[24] thiophosgene,[25] isocyanate[26] and isothiocyanate.[26c, 27] To avoid the use of these hazardous reagents, several methods have also been reported.[28, 29] However, these methodologies may present some disadvantages such as multi-step procedures, high temperature or pressure, high cost and unstable reagents, large excess amounts of carbonyl and thiocarbonyl sources, non-selective reactions and narrowed scope of amines.[29]

After the successful efforts for the synthesis of new compounds with N-arylation reactions in the presence of transition metals catalysts such as Pd, Cu, Ni, Fe, and etc.[30] During the past two decades, trying to synthesize of *N*-aryl carbamates by using transition metals as a catalyst has attracted much interest.[31-33] However, these new protocols

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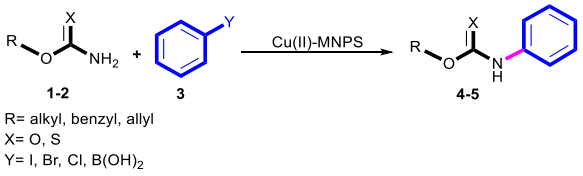
rely heavily on expensive ligands or bases and reactive functional groups, which usually require cumbersome synthetic procedures.[31] Also, inability to recover the transition metals used as the catalyst is one of the main drawbacks of these methods.[32-33] Despite the broad spectrum of coupling partners that have been described, we are unaware of any reports of the transition metal-catalyzed selective *N*-arylation of O-alkyl thiocarbamates even with the versatility of this functional group in synthesis.

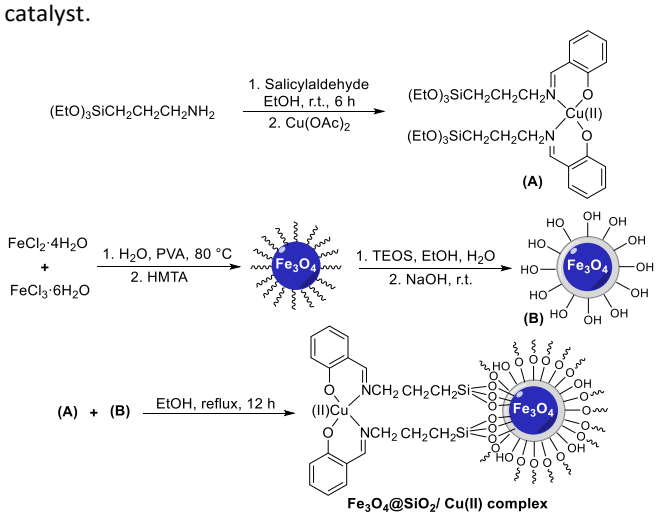
Based on the growing demand for environmental- benign technologies that are operating in accordance with the principles of green chemistry in the last few years, some research groups designed new clean, safe, sustainable and selective methodologies for the synthesis of the different class of organic compounds with silica-based magnetically retrievable core-shell nanocatalysts.[34-35] Following our ongoing studies for designing and employing new reusable magnetic nanocatalysts in synthesis of the important organic chemistry,[35] herein for the first time, we report the utilization of $Fe_3O_4$@$SiO_2$/Schiff Base/Cu(II) Complex as a magnetic nanocatalyst for selective mono N-arylation of *O*-alkyl thiocarbamates and O-alkyl carbamates through coupling reaction with aryl halides and arylboronic acids as coupling partners (Scheme 1).




**Scheme 1.** N-Monoarylation of primary O-alkyl thiocarbamates and O-alkyl carbamates

## Results and discussion

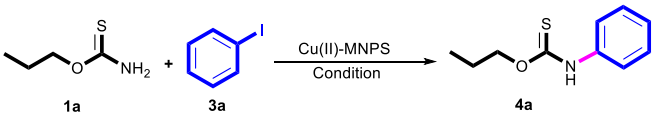
The retrievable magnetite ($Fe_3O_4$) silica-based copper(II) nanocatalyst(Cu(II)-MNPS) was synthesized through the protocol which was reported in 2012 by our research group.[35a] Scheme 2 concisely describes the synthetic procedure of the catalyst.




**Scheme 2.** Synthetic procedure of $Fe_3O_4$@$SiO_2$/Cu(II) complex.

After preparation of Cu(II)-MNPS catalyst, its catalytic activity was tested in N-arylation of primary O-alkyl thiocarbamates reaction. In our first phase of screening experiment, 1 mmol of O-propyl thiocarbamate (**1a**) and 1 mmol of iodobenzene (**3a**) were used as the model substrates to optimize reaction media factors including the amount of catalyst, bases, solvents, and reaction temperatures (Table 1).

**Table 1.** Optimization of the reaction parameters for the preparation of O-propyl phenylthiocarbamate (**4a**).[a]




| Entry | Solvent | Base (mmol) | Catalyst (mol %) | T (°C) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | $H_2O$ | $NaOBu^t$(1) | 0.5 | reflux | 0 |
| 2 | Toluene | $NaOBu^t$(1) | 0.5 | 100 | 75 |
| 3 | DMF | $NaOBu^t$(1) | 0.5 | 100 | Trace |
| 4 | $CH_3CN$ | $NaOBu^t$(1) | 0.5 | reflux | Trace |
| 5 | $CH_2Cl_2$ | $NaOBu^t$(1) | 0.5 | reflux | 0 |
| 6 | Ethanol | $NaOBu^t$(1) | 0.5 | reflux | 0 |
| 7 | Methanol | $NaOBu^t$(1) | 0.5 | reflux | 0 |
| 8 | Dioxane | $NaOBu^t$(1) | 0.5 | 100 | 68 |
| 9 | DMSO | $NaOBu^t$(1) | 0.5 | 100 | 20 |
| 10 | Toluene | KOH(1) | 0.5 | 100 | 0 |
| 11 | Toluene | $KHCO_3$(1) | 0.5 | 100 | 0 |
| 12 | Toluene | KOAc(1) | 0.5 | 100 | 0 |
| 13 | Toluene | CsF(1) | 0.5 | 100 | 12 |
| 14 | Toluene | $K_3PO_4$(1) | 0.5 | 100 | Trace |
| 15 | Toluene | $K_2CO_3$(1) | 0.5 | 100 | 10 |
| 16 | Toluene | $CsCO_3$(1) | 0.5 | 100 | 53 |
| 17 | Toluene | $Et_3N$(1) | 0.5 | 100 | 0 |
| 18 | Toluene | Pyridine(1) | 0.5 | 100 | 0 |
| 19 | Toluene | None | 0.5 | 100 | 0 |
| **20** | **Toluene** | $NaOBu^t$(1.5) | **0.5** | **100** | **85** |
| 21 | Toluene | $NaOBu^t$(2) | 0.5 | 100 | 84 |
| 22 | Toluene | $NaOBu^t$(1.5) | 0.5 | 25 | Trace |
| 23 | Toluene | $NaOBu^t$(1.5) | 0.5 | 50 | 38 |
| 24 | Toluene | $NaOBu^t$(1.5) | 0.5 | 70 | 57 |
| 25 | Toluene | $NaOBu^t$(1.5) | 0.5 | 80 | 61 |
| 26 | Toluene | $NaOBu^t$(1.5) | 0.5 | 90 | 78 |
| 27 | Toluene | $NaOBu^t$(1.5) | 0.5 | 110 | 85 |
| 28 | Toluene | $NaOBu^t$(1.5) | 0.5 | 120 | 84 |
| 29 | Toluene | $NaOBu^t$(1.5) | None | 100 | 0 |
| 30 | Toluene | $NaOBu^t$(1.5) | 0.25 | 100 | 71 |
| 31 | Toluene | $NaOBu^t$(1.5) | 0.75 | 100 | 83 |

[a] Reaction conditions: *O*-propyl thiocarbamate (1 mmol), iodobenzene (1 mmol), base and catalyst in solvent (2 mL), under an atmosphere of air for 3 h.
[b] Isolated yield.

As shown in Table 1, the efficiency of model reaction was explored in with several common solvents, such as $H_2O$, DMF, DMSO, dioxane, toluene, dichloromethane, acetonitrile,

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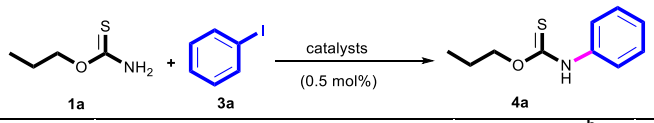
methanol and ethanol, and in the presence of bases, such as KOH, $KHCO_3$, KOAc, CsF, $K_3PO_4$, $CsCO_3$, $K_2CO_3$, $NaOBu^t$, pyridine and triethylamine at different temperatures. According to these data, the presence of catalyst and base are necessary and critical for this reaction (Table 1, entries **19** and **29**) and the best efficiency was provided when the model reaction was run in toluene and in the presence of $NaOBu^t$ (1.5 mmol) and Cu(II)-MNPS (0.5 mol%) at 100 $^{O}$C (Table 1, entry **20**).

The effect of other catalysts, such as $Cu(OAc)_2$, $CuO_2$, CuCl, CuBr, CuI, $NiCl_2$, $Fe_3O_4$, $Fe_3O_4$/$Cu(OAc)_2$ and Schiff Base/Cu(II) Complex were explored on the model reaction instead of Cu(II)-MNPS. On the basis of results exhibited in Table 2, the reaction was led to the desired product in the presence of all of the Cu catalysts checked but in low yields after 3 hours at 100 $^{O}$C. Using the mixture of $Fe_3O_4$ and $Cu(OAc)_2$ as the catalyst was conducted to only 13% yield (Table 2, entry **9**). Even using Schiff base/Cu(II) complex as homogeneous catalyst under the optimized reaction conditions, did not result in a better performance than Cu(II)-MNPS (Table 2, entries **10 and 11**).

**Table 2.** The screening of catalytic reactivity of several catalysts on N-arylation of O-propyl thiocarbamate (**1a**).[a]




1a 3a 4a

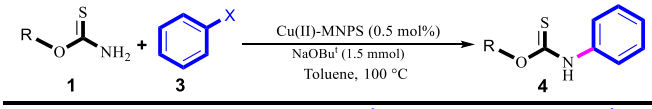
| Entry | Catalyst | Yield (%)[b] |
|---|---|---|
| 1 | $Cu(OAc)_2$ | 12 |
| 2 | $CuO_2$ | Trace |
| 3 | CuCl | Trace |
| 4 | CuBr | 12 |
| 5 | CuI | 15 |
| 6 | $NiCl_2$ | 0 |
| 7 | $Fe_3O_4$ | 0 |
| 8 | $Fe_3O_4$@$SiO_2$ | 0 |
| 9 | $Fe_3O_4$/ $Cu(OAc)_2$ | 13 |
| 10 | Schiff base/Cu(II) Complex | 84 |
| 11 | $Fe_3O_4$@$SiO_2$/Schiff base Cu(II) Complex (Cu(II)-MNPS) | 85 |

[a] Reaction conditions: O-propyl thiocarbamate (1 mmol), iodobenzene (1 mmol), $NaOBu^t$ (1.5 mmol) and catalyst (0.5 mol%) in toluene (2 mL), 100 $^{O}$C under an atmosphere of air for 3 h.
[b] Isolated yield.

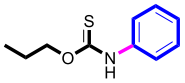
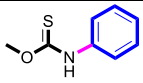
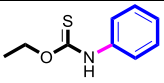
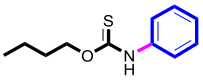
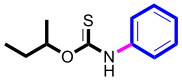
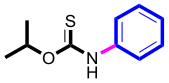
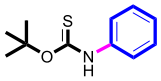
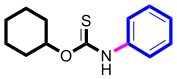
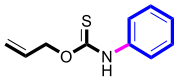
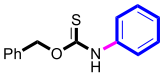
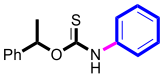
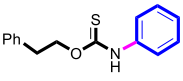
With optimal conditions in hand, further investigations into the substrate scope of this reaction process were performed. A variety of available primary O-alkyl thiocarbamates **1** and primary O-alkyl carbamates **2** were coupled with aryl halides (I, Br, Cl) or arylboronic acid **3** to afford the corresponding *N*-mono substituted O-alkyl thiocarbamates **4** and N-mono substituted O-alkyl carbamates **5**.

As shown in Table 3, most of examined primary O-alkyl thiocarbamate substrates **1** showed a similar performance. This procedure was also effective for secondary O-alkyl thiocarbamates (Table 3, entries **4e**, **4f**, and **4h**), O-*tert*-butyl thiocarbamate, as a sterically hindered O-tertiary alkyl thiocarbamate (Table3, entry **4g**). O-Benzyl thiocarbamates (Table3, entries **4j** and **4k**), which are widely used as the protecting groups in organic synthesis, and O-allyl thiocarbamate were also carried out this reaction effectively (Table3, entry **4i**). Among halobenzenes, iodobenzene exhibited greater reactivity compared to that of bromobenzene and chlorobenzene was the most unreactive one and afforded the cross-coupled products in less than 10% yield even in longer reaction times. Phenylboronic acid was also a suitable substrate for N-arylation of primary O-thiocarbamates. Although primary O-aryl thiocarbamates underwent the N-arylation reaction with halobenzenes (I, Br, Cl) and phenylboronic acid, on the base of TLC monitoring, but, due to the instability of the corresponding products, their purification was not possible by chromatographic procedures, which are in agreement to the report of Buchwald and co-workers.[32a]

**Table 3.** Coupling of primary O-alkyl thiocarbamates **1** with halobenzenes and phenylboronic acid.[a]




1 3 4

| | | |
|---|---|---|
|  **4a** X: I, 85%[b], 3h X: Br, 79%[b], 3h X: Cl, 08%[b], 8h X: $B(OH)_2$,77%[b], 3h |  **4b** X: I, 83%[b], 3h X: Br, 78%[b], 3h X: Cl, 09%[b], 8h X: $B(OH)_2$,78%[b], 3h |  **4c** X: I, 82%[b], 3h X: Br, 75%[b], 3h X: Cl, 07%[b], 8h X: $B(OH)_2$,78%[b], 3h |
|  **4d** X: I, 88%[b], 3h X: Br, 80%[b], 3h X: Cl, 09%[b], 8h X: $B(OH)_2$,79%[b], 3h |  **4e** X: I, 80%[b], 3h X: Br, 74%[b], 3h X: Cl, 06%[b], 8h X: $B(OH)_2$,73%[b], 3h |  **4f** X: I, 79%[b], 3h X: Br, 74%[b], 3h X: Cl, 05%[b], 8h X: $B(OH)_2$,72%[b], 3h |
|  **4g** X: I, 80%[b], 3h X: Br, 74%[b], 3h X: Cl, 06%[b], 8h X: $B(OH)_2$,75%[b], 3h |  **4h** X: I, 81%[b], 3h X: Br, 79%[b], 3h X: Cl, 09%[b], 8h X: $B(OH)_2$, 80%[b], 3h |  **4i** X: I, 86%[b], 3h X: Br, 80%[b], 3h X: Cl, 09%[b], 8h X: $B(OH)_2$, 81%[b], 3h |
|  **4j** X: I, 82%[b], 3h X: Br, 79%[b], 3h X: Cl, 08%[b], 8h X: $B(OH)_2$,80%[b], 3h |  **4k** X: I, 75%[b], 3h X: Br, 74%[b], 3h X: Cl, 06%[b], 8h X: $B(OH)_2$,70%[b], 3h |  **4l** X: I, 83%[b], 3h X: Br, 78%[b], 3h X: Cl, 08%[b], 8h X: $B(OH)_2$,79%[b], 3h |

[a] Reaction conditions: *O*-alkyl thiocarbamates (1 mmol), halobenzenes or phenylboronic acid (1 mmol), $NaOBu^t$ (1.5 mmol) and catalyst (0.0250 g, 0.5 mol%) in toluene (2 mL), 100 $^{O}$C under an atmosphere of air.
[b] Isolated yield.

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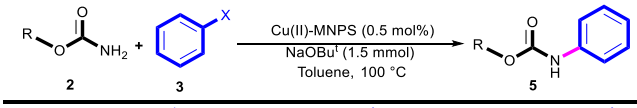
Because of the results achieved in N-arylation of primary O-alkyl thiocarbamates **1** for determination the scope of this protocol, the catalytic activity of $Fe_3O_4$@$SiO_2$/Schiff base/Cu(II) complex was studied in N-arylation of primary O-alkyl carbamates **2** by halobenzenes and phenylboronic acid under the optimized conditions achieved in N-arylation of O-alkyl thiocarbamates **1** (Table 4). The data exhibited in Table 4 confirmed the efficient activity of the catalyst and the order of activity of halobenzenes and phenylboronic acid was appeared to be I>Br≈ $B(OH)_2$>> Cl, which is the same as their activity in *N*-arylation of primary O-alkyl thiocarbamates **1**. In addition, a wide array of primary O-alkyl carbamates **2** was subjected to this reaction and the corresponding products were obtained in good to excellent yields.

**Table 4.** Coupling of primary O-alkyl carbamates **2** with halobenzenes and phenylboronic acid[a]

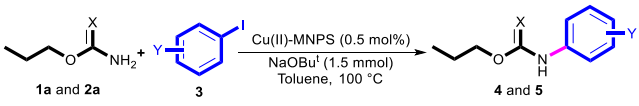



| | | |
|---|---|---|
| **5a**<br>X: I,94%[b], 3h<br>X: Br, 88%[b], 3h<br>X: Cl,08%[b], 8h<br>X: $B(OH)_2$,89%[b], 3h | **5b**<br>X: I,93%[b], 3h<br>X: Br, 82%[b], 3h<br>X: Cl,09%[b], 8h<br>X: $B(OH)_2$, 88%[b], 3h | **5c**<br>X: I,92%[b], 3h<br>X: Br, 87%[b], 3h<br>X: Cl,07%[b], 8h<br>X: $B(OH)_2$, 88%[b], 3h |
| **5d**<br>X: I,95%[b], 3h<br>X: Br,90%[b], 3h<br>X: Cl,09%[b], 8h<br>X: $B(OH)_2$,89%[b], 3h | **5e**<br>X: I,88%[b], 3h<br>X: Br,79%[b], 3h<br>X: Cl,08%[b], 8h<br>X: $B(OH)_2$, 85%[b], 3h | **5f**<br>X: I, 87%[b], 3h<br>X: Br, 84%[b], 3h<br>X: Cl,08%[b], 8h<br>X: $B(OH)_2$, 85%[b], 3h |
| **5g**<br>X: I, 88%[b], 3h<br>X: Br,79%[b], 3h<br>X: Cl,06%[b], 8h<br>X: $B(OH)_2$,80%[b], 3h | **5h**<br>X: I,90%[b], 3h<br>X: Br, 88%[b], 3h<br>X: Cl,08%[b], 8h<br>X: $B(OH)_2$, 89%[b], 3h | **5i**<br>X: I,94%[b], 3h<br>X: Br, 82%[b], 3h<br>X: Cl,09%[b], 8h<br>X: $B(OH)_2$, 88%[b], 3h |
| **5j**<br>X: I,90%[b], 3h<br>X: Br, 81%[b], 3h<br>X: Cl,09%[b], 8h<br>X: $B(OH)_2$,89%[b], 3h | **5k**<br>X: I, 89%[b], 3h<br>X: Br, 82%[b], 3h<br>X: Cl,05%[b], 8h<br>X: $B(OH)_2$, 88%[b], 3h | **5l**<br>X: I,93%[b], 3h<br>X: Br, 86%[b], 3h<br>X: Cl,08%[b], 8h<br>X: $B(OH)_2$,91%[b], 3h |

[a] Reaction conditions: primary *O*-alkyl carbamates (1 mmol), halobenzenes or phenylboronic acid (1 mmol), NaOBu$^t$ (1.5 mmol) and catalyst (0.0250 g, 0.5 mol%) in toluene (2 mL), 100 $^O$C under an atmosphere of air.
[b] Isolated yield.

For determination of generality of the methodology, the variety of aryl iodides with electron-releasing and electron-withdrawing substitutions were utilized for *N*-arylation of primary O-propyl thiocarbamate (**1a**) and primary O-propyl carbamate (**2a**) that the related results were collected in Table 5. The reaction was equally effective for both electron donating and electron withdrawing groups in aryl iodides. Among *ortho*-, *meta*- and *para*- iodo toluene, it was *ortho*-isomer that carried out the N-arylation reaction in low yield (Table 5, entries **4o** and **5o**) because of probably the steric effect of the methyl group. Fortunately, 3-iodothiophene, as a heteroaryl iodide, underwent the N-arylation reaction efficiently and provided the corresponding products in good yields (Table 5, entries **4t** and **5t**).

**Table5.** Copper-catalyzed C-N cross-coupling of O-propyl thiocarbamate (**1a**) and O-propyl carbamate (**2a**) with aryl iodides [a]




| | | |
|---|---|---|
| **4a** (X: S), 85%[b], 3h<br>**5a** (X: O), 94%[b], 3h | **4m** (X: S), 82%[b], 3h<br>**5m** (X: O), 89%[b], 3h | **4n** (X: S), 80%[b], 3h<br>**5n** (X: O), 87%[b], 3h |
| **4o** (X: S), 46%[b], 3h<br>**5o** (X: O), 51%[b], 3h | **4p** (X: S), 84%[b], 3h<br>**5p** (X: O), 88%[b], 3h | **4q** (X: S), 85%[b], 3h<br>**5q** (X: O), 93%[b], 3h |
| **4r** (X: S), 83%[b], 3h<br>**5r** (X: O), 93%[b], 3h | **4s** (X: S), 81%[b], 3h<br>**5s** (X: O), 94%[b], 3h | **4t** (X: S), 80%[b], 3h<br>**5t** (X:O), 89%[b], 3h |
| **4u** (X: S), 86%[b], 3h<br>**5u** (X: O), 92%[b], 3h | | **4v** (X: S), 84%[b], 3h<br>**5v** (X: O), 90%[b], 3h |

[a] Reaction conditions: *O*-propyl thiocarbamate or *O*-propyl carbamate (1 mmol), aryl iodides (1 mmol), NaOBu$^t$ (1.5 mmol) and catalyst (0.0250 g, 0.5 mol%) in toluene (2 mL), 100 $^O$C under an atmosphere of air.
[b] Isolated yield.

Furthermore, to check chemoselectivity of the protocol, the reaction between 1-bromo-4-iodobenzene with O-propyl thiocarbamate (**1a**) and O-propyl carbamate (**2a**) were investigated under optimized condition. The result of this study indicated that the C-N coupling reaction has been taken place only on the carbon atom bearing iodine and only O-propyl (4-bromophenyl)thiocarbamate and O-propyl (4-bromophenyl)carbamate were prepared respectively (Table 6, entry **1A**). Then the same reaction was performed between 1-chloro-4-iodobenzene with O-propyl thiocarbamate (**1a**) and O-propyl carbamate (**2a**). In these cases, only the corresponding O-propyl (4-chlorophenyl)thiocarbamate and O-propyl (4-chlorophenyl)carbamate were obtained (Table 6, entry **2B**). Finally, the reaction of O-propyl thiocarbamate (**1a**)

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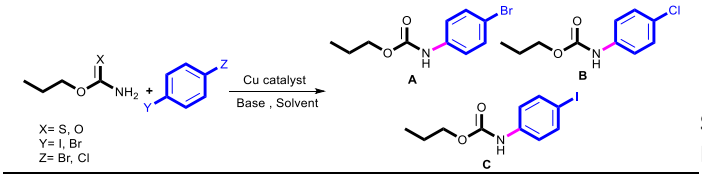
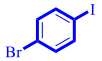
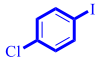
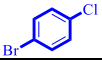
and O-propyl carbamate (**2a**) with 1-bromo -4-chlorobenzene were examined and as it is exhibited in Table 6 only the O-propyl (4-chlorophenyl)thiocarbamate and O-propyl (4-chlorophenyl)carbamate were obtained (Table 6, entry **3B**). These results indicate excellent chemoselectivity and the C-N coupling reaction have occurred only on the carbon atom bears less electronegative halogen atom.

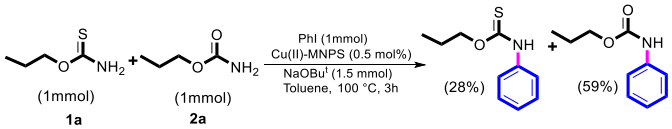
**Table 6.** Chemoselectivity of the C-N coupling reaction of aryl halides [a]




| Entry | Substrate | X | Product A (Yield %)[b] | Product B (Yield %)[b] | Product C (Yield %)[b] |
|---|---|---|---|---|---|
| 1 |  | S | 84% | - | 0% |
| | | O | 93% | - | 0% |
| 2 |  | S | - | 86% | 0% |
| | | O | - | 92% | 0% |
| 3 |  | S | 0% | 79% | - |
| | | O | 0% | 83% | - |

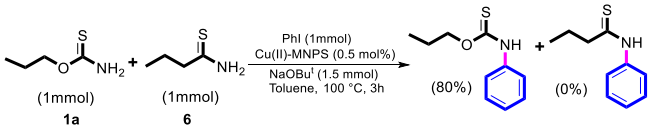
[a] Reaction conditions: *O*-propyl carbamate or *O*-propyl thiocarbamate (1 mmol), dihalobenzenes (1 mmol), $NaOBu^t$ (1.5 mmol) and catalyst (0.0250 g, 0.5 mol%) in toluene (2 mL), 100 $^{O}$C under an atmosphere of air for 3 h.
[b] Isolated yield.

Through a careful investigation to compare the reactivity among primary O-alkyl thiocarbamate **1** and primary O-alkyl carbamate **2**, the C-N coupling reaction between O-propyl thiocarbamate (**1a**) and O-propyl carbamate (**2a**) with iodobenzene was examined. For this purpose, 1mmol of iodobenzene was reacted with 1mmol of O-propyl thiocarbamate (**1a**) and 1mmol of O-propyl carbamate (**2a**) in the presence of the catalyst under the optimized conditions. As it is depicted in scheme 2, analysis of the reaction mixture disclosed appeared that O-propyl carbamate (**2a**) underwent the C-N coupling more than O-propyl thiocarbamate (**1a**). This could be due to the stronger nucleophilicity of the nitrogen atom in O-alkyl carbamate **2** in comparison to O-alkyl thiocarbamate **1**, which is important in Cu catalyzed C-N coupling reactions.



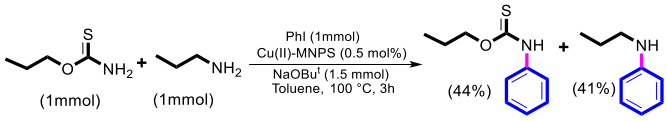

**Scheme 3.** Reactivity of *O*-propyl thiocarbamate (**1a**) and *O*-propyl carbamate (**2a**) toward N-arylation reaction.

In order to compare the reactivity among O-alkyl thiocarbamates **1**, thioamides and aliphatic amines toward the C-N coupling reaction, the reaction of O-propyl thiocarbamate (**1a**), butyrthioamide (**6**) and propylamine (**7**) with iodobenzene in the presence of the catalyst under optimized condition was chosen as a model reaction. Therefore, initially, equimolar of O-propyl thiocarbamate (**1a**) (1mmol) and butyrthioamide (**6**) (1mmol) reacted with iodobenzene (1mmol) in the presence of the catalyst. As it is depicted in scheme 4, analysis of the reaction mixture revealed that butyrthioamide (**6**) has remained unchanged and only O-propyl thiocarbamate (**1a**) underwent selectively the C-N coupling. This might be again due to the stronger nitrogen nucleophilicity in O-alkyl thiocarbamates **1** than alkyl thioamides **6**.



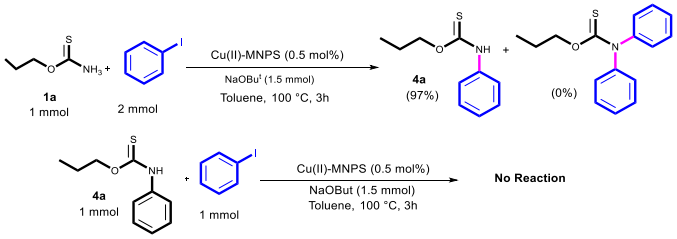

**Scheme 4.** Reactivity of *O*-propyl thiocarbamate (**1a**) and butyrthioamide (**6**) toward *N*-arylation reaction

However, in the reaction between O-propyl thiocarbamate (**1a**) (1mmol) and iodobenzene (1mmol) in the presence of propylamine (**7a**) as a competitive partner, no selectivity was observed. More specifically, they underwent the coupling reaction and gave similar yields (Scheme 5). So it can be concluded that *O*-alkyl thiocarbamates **1** are more reactive than thioamides in this procedure but they have no superiority over aliphatic amines.




**Scheme 5.** Chemoselectivity study of the C-N coupling reaction between *O*-propyl thiocarbamate (**1a**) and n-propylamine (**7**)

In the next step, a set of two reactions were designed to confirm selectivity of the present method toward mono N-arylation of primary O-alkyl thiocarbamate **1**. For this purpose, 1 mmol of O-propyl thiocarbamate (**1a**) was reacted with 2 mmol iodobenzene under the optimized reaction conditions. It was observed that in spite of using the excess amount of iodobenzene, only mono N-arylation took place and the product of N, N-diarylation was not detected in the reaction mixture by TLC monitoring. In the second experiment, 1 mmol of O-propyl phenylthiocarbamate (**4a**) was treated with 1 mmol of iodobenzene under the optimized reaction condition. As shown in scheme 6, this reaction was not preceded at all and O-propyl phenylthiocarbamate (**4a**) remained intact. This might be due to stronger nitrogen nucleophilicity and the less steric hindrance in O-propyl thiocarbamate (**1a**) than O-propyl phenylthiocarbamate (**4a**).




**Scheme 6.** Study of selective mono *N*-arylation of *O*-propyl thiocarbamate

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The magnetic property of the catalyst is demonstrated in Figure 2. According to this scheme, the catalyst has good dispersity in the reaction media and it can be easily removed from the mixture by an external magnetic field.

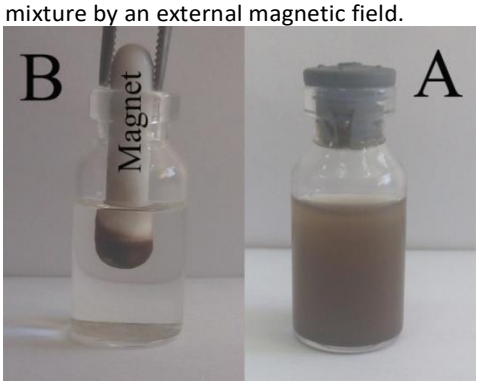



**Figure 2.** Photo images of magnetic field-responsive of the $Fe_3O_4$@$SiO_2$/Schiff base of Cu (II) nanoparticles before magnetic field (**A**) and under magnetic field (**B**)

To determine the recyclability of the catalyst, after completion of C-N coupling of O-propyl thiocarbamates (**1a**) and phenyl iodide, the catalyst was removed from the mixture by an external magnetic field because of the magnetic property of the catalyst, which its magnetic field responsivity has exhibited in Figure 3, and reused in another same reaction. This process was repeated again and as it is depicted in Figure 4, the catalyst remains its catalytic activity over five runs. This result is an evidence for the stability and efficiency of the catalyst.

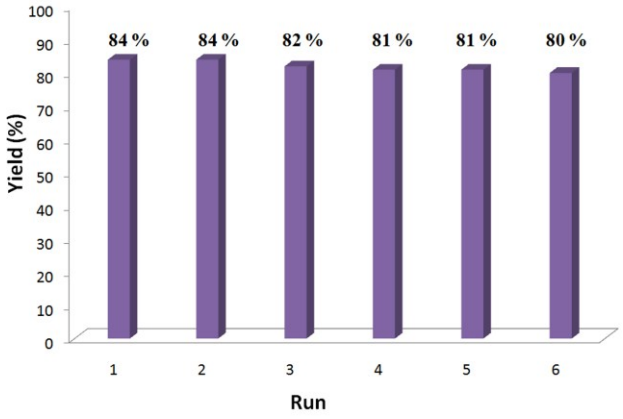



**Figure 3.** Reuse of the catalyst for C-N coupling of *O*-propyl thiocarbamate (**1a**) and iodobenzene.

Moreover, to determine responsible Cu species for carrying out N-arylation of thiocarbamates, the hot filtration test was performed. When the reaction time reached half done, the catalyst nanoparticles were taken out from the reaction mixture by an external magnetic field, the residue was allowed to stir under the reaction conditions. The analysis of the reaction mixture by TLC monitoring did not show any considerable progress. These results showed that only a few species of Cu may exist in the solution phase and the main responsible species that catalyzes the N-arylation reaction is the magnetic heterogeneous Cu (II) complex.

Figure 4 represents the XRD pattern and FE-SEM image of the recycled catalyst after the sixth run. This figure shows that characteristic peaks of $Fe_3O_4$ are present. Also, Comparison of the FE-SEM images between the fresh catalyst and recovered catalyst after the sixth run demonstrates that Cu nanocatalyst keeps its spherical shape with little agglomeration, which might be the another important cause of yield decreasing.

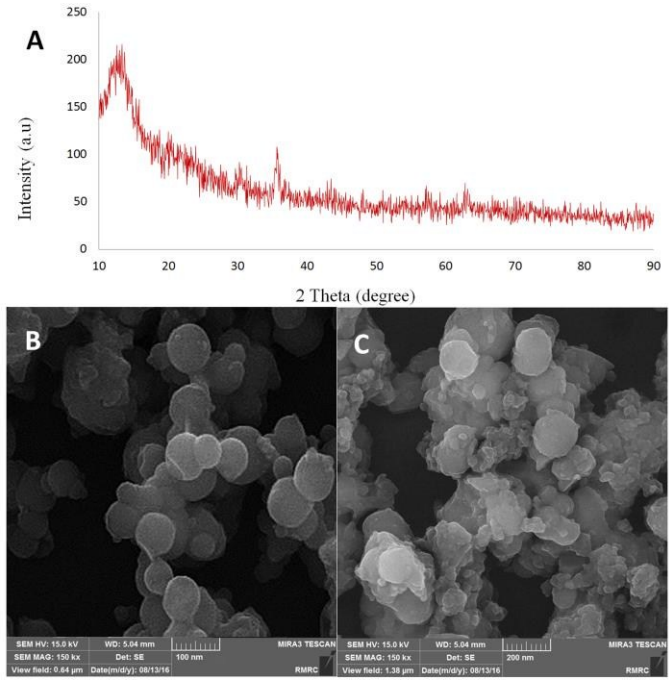



**Figure 4.** (a) XRD patterns of the recovered catalyst after the sixth run; (b) and (c) TEM images of the catalyst before reaction and after six cycles of reactions.

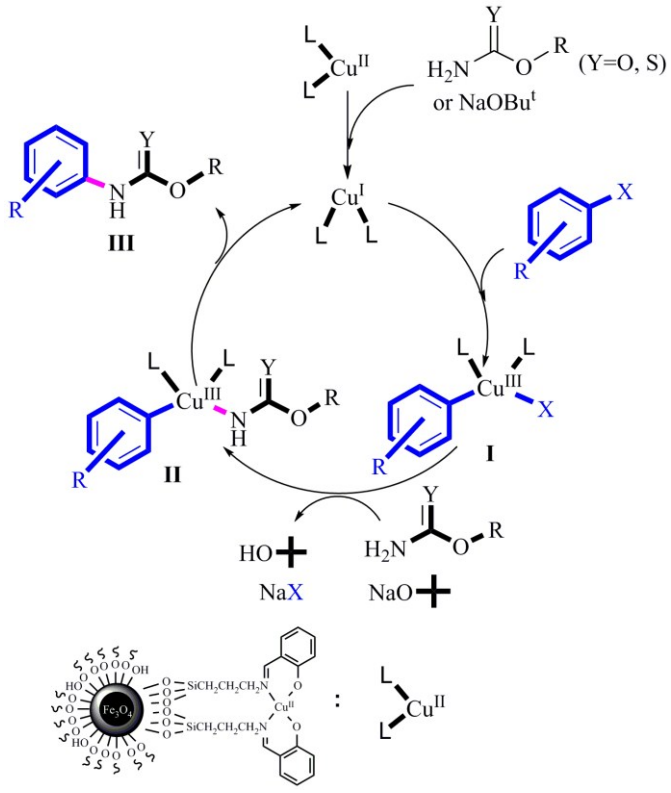
Inductively Coupled Plasma (ICP) analysis was also performed for the fresh catalyst and the catalyst after first and the sixth runs to determine the amount of copper leaching. According to this test, the amount of copper on the fresh catalyst was measured to be 0.21 mmol/g. ICP analysis showed only 0.2% and 3.2 % copper leaching after the first and the sixth runs respectively. These data along with the results retrieved from the hot filtration test confirm the high heterogeneity and stability of the catalyst.

Furthermore, for determine the stability of catalyst under the reaction conditions, the recovered catalyst of model reaction was weighed. After the first and the sixth runs, respectively 0.0248 gr and 0.0245 gr of catalyst was recycled that these results indicate the high stability and also the high recovered ability of the catalyst with using an external magnetic field.

The active form of copper is generally believed to be Cu(I) in C–N cross-coupling reactions. Copper catalysts in 0, +1, and +2 oxidation states can be used to catalyze *N*-arylation reactions. However, when Cu(0) or Cu(II) sources are used; the active Cu(I) species is formed by in situ reduction or oxidation of the copper source. In kinetic studies of the Ullmann

coupling of phenyl halides with diphenylamine, Cu(I) halides give reaction rates that are significantly higher than when Cu(II) salts are used.[36] When Cu(II) precursors are used, reduction to Cu(I) by alkoxide or amide reagents is observed.[36, 37] Reduction of Cu(II) can be accelerated by ligands that stabilize the Cu(I) oxidation state, such as neocuproine.[38] Reduction of Cu(II) ions by amide or alkoxide ligands has been confirmed by electron paramagnetic resonance (EPR) spectroscopy of catalyst systems.[39, 40] Amino acid complexes of Cu(I) ions are observed under catalytic conditions by electrospray–mass spectrometry (ESI–MS) analysis of reaction mixtures.[41]

According to the literature reports on the reduction of Cu(II) to Cu(I) by alkoxide and amide reagents[36, 37, 39, 40] and acceleration this process by ligands that are able to stabilize the Cu(I) oxidation state,[38, 41] the following plausible mechanism might be proposed for N-arylation of primary O-alkyl thiocarbamates and primary alkyl carbamates (Scheme 7). Initially, the copper (II) complex reduction is initiated by t-butyl oxide or/and the primary thiocarbamate or the primary carbamate, and then copper (I) complex is converted to copper (III) intermediate **I** by oxidative addition of the aryl halide. Finally, substitution of halide on the intermediate **I** by the nucleophile (thiocarbamates or carbamates) produces **III** and regenerates the active Cu (I) catalyst after occurring reductive elimination reaction on the intermediate **II**.




**Scheme 7.** The plausible mechanism for the copper-catalysed *N*-arylation of primary *O*-alkyl thiocarbamates 1 and primary *O*-alkyl carbamates 2

## Conclusions

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In summary, we have described an efficient, mild and selective mono N-arylation of primary O-alkyl thiocarbamates **1** and primary O-alkyl carbamates **2** derivatives with aryl halides or arylboronic acids **3** in the presence of magnetic copper (II) nanocatalyst. The method is tolerant of a variety of functional groups in both primary *O*-alkyl thiocarbamates **1** or carbamates **2** coupling partners allowing for further synthetic manipulation. This recyclable catalyst offers advantages like simple work-up and high yields. In addition, exploitation of this work in the preparation of arrays of drug-like molecules is currently underway.

## Experimental

**General experimental:**

Chemicals were purchased from the Merck, Flucka and Aldrich Chemical Companies in high purity. The Cu(II) complex supported on superparamagnetic $Fe_3O_4$@$SiO_2$ nanoparticles,[35a] primary O-alkyl thiocarbamates[42] and primary O-alkyl carbamates[43] skeletons were accessed following literature protocols. The products were characterized by comparison of their spectral and physical data such as NMR, FT-IR, CHNS and melting point with available literature data. $^1$H and $^{13}$C NMR spectra were recorded with Bruker Avance DPX 250MHz instruments with $Me_4Si$ or solvent resonance as the internal standard. $^1$H NMR spectroscopic data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q= quartet, quint = quintet, sext = sextet, sept = septet, br. = broad, m = multiplet), coupling constants (Hz), and integration. Fourier transform infrared (FTIR) spectra were obtained using a Shimadzu FT-IR 8300 spectrophotometer. The hydrodynamic size of the particles was measured by dynamic light scattering (DLS) techniques, using a HORIBA-LB550 particle size analyzer. Cu loading and leaching test were carried out with an Inductively Coupled Plasma (ICP) analyzer (Varian, vista-pro). Determination of the purity of the substrate and monitoring of the reactions were accomplished by thin-layer chromatography (TLC) on a silica-gel polygram SILG/UV 254 plates.

**General procedure for the preparation of $Fe_3O_4$ nanoparticles:** [35a] To the solution of $FeCl_3{\cdot}6H_2O$ (4.8 mmol) in deionized water (15 mL), added a mixture of polyvinyl alcohol (PVA 15000) (1.0 g), as the surfactant, and $FeCl_2{\cdot}4H_2O$ (4.5 mmol) in deionized water (15 mL). The resultant solution was stirred for 30 min at 80 °C. In the next step, hexamethylenetetramine (HMTA) (1.0 mol/L) was added dropwise with vigorous stirring to reach pH 10 and the resultant mixture was heated for 2 hours at 60 °C. The black magnetite solid produced was separated by an external magnet and washed with hot ethanol three times and dried at 80 °C for 10 hours.

**General procedure for the preparation of $Fe_3O_4$@$SiO_2$ core-shell:** [35a] Initially, in the first step, $Fe_3O_4$ (0.5 g, 2.1 mmol) was dispersed in a solution of ethanol (50 mL), deionized water (5.0 mL) and tetraethoxysilane (TEOS) (0.2 mL). Then 5.0 mL of

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NaOH (10 wt%) was added and this mixture was left to be stirred for 30 min at room temperature. The superparamagnetic core shall ($Fe_3O_4$@$SiO_2$) was separated by an external magnet, washed with a solution of deionized water and hot ethanol three times and dried at 80 $^{o}$C for 10 hours.

**General procedure for preparation of the ligand:** [35a] A solution of the stoichiometric amount of salicylaldehyde (1.0 mmol, 0.122 g) in dry ethanol (25 mL) was added dropwise to the 3-aminopropyl (triethoxy) silane (1.0 mmol, 0.176 g) in 25 mL dry ethanol then the mixture was stirred at room temperature for 6 hours. The resulting salen ligand, as the bright yellow precipitate, was separated by filtration and washed with hot dry ethanol (5.0 mL) and then dried in vacuum. The crude product was recrystallized from dry ethanol to obtain the pure product in 98% yield (0.271 g).

**General procedure for preparation of the Cu(II) complex:** [35a] Anhydrous $Cu(OAc)_2$ (0.186 g, 1.0 mmol) was added to the solution of the synthesized ligand (0.651 g, 2.0 mmol) in ethanol (25 mL) and then the mixture was allowed to be refluxed for 12 hr. After the completion of complex formation, which is determined by TLC monitoring, the resulting product, as a green colour precipitate, was filtered and washed with ethanol. Then the Cu(II) complex was purified by recrystallization from ethanol in 95 yields (0.689 gr).

**General procedure for preparation of the Cu(II) complex supported on superparamagnetic $Fe_3O_4$@$SiO_2$ nanoparticles:** [35a] $Fe_3O_4$@$SiO_2$ (2.0 g) was added to the solution of Cu(II) complex (1.0 mmol) in ethanol (10 mL) and the resultant mixture was refluxed for 12 hours. Then, the produced superparamagnetic nanoparticles ($Fe_3O_4$@$SiO_2$/Cu(II) complex), was separated by an external magnet and dried at 80 $^{o}$C overnight. The product was washed with hot ethanol and water to remove unreacted species and dried at 80 $^{o}$C for 6 h.

**General procedure for the synthesis of primary O-alkyl thiocarbamates:** According to our reported procedure,:[42] DBSA (1.5 mmol, 0.489 g) was added to a mixture of potassium thiocyanate (1.0 mmol, 0.097) and alcohol or phenol (1.0 mmol). Then, the mixture was heated and stirred at 60 $^{o}$C in an oil bath for 12 h. The reaction was monitored by TLC. After completion of the reaction, $CH_2Cl_2$ (10 mL), and saturated $NaHCO_3$ (10 mL) were added. The organic layer was separated from the aqueous layer and washed twice with water (2×10mL). The organic layer was concentrated under reduced pressure and the crude product was purified on a column of silica gel by a mixture of petroleum ether and ethyl acetate (9:1) as the solvent, to provide the desired pure products in high yields.

**General procedure for the selective mono N-arylation of primary O-alkyl thiocarbamates:** The catalyst (0.025 g, 0.5 mol%) was poured in a mixture of primary *O*-thiocarbamates (1.0 mmol), aryl halide (1.0 mmol) and sodium *tert*-butoxide (1.5 mmol) in toluene. The mixture was stirred at 100 °C for the appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction (Monitored by TLC) and separation of the catalyst by a magnetic field, 20 mL of $H_2O$ was added and the mixture was extracted with $CHCl_3$. The organic phase was washed with water (2 × 10 mL) and dried over anhydrous $Na_2SO_4$. Then the solvent was removed under reduced pressure. The resulting crude product was purified by flash chromatography to give the desired cross-coupling products in good to excellent isolated yields.

**General procedure for the synthesis of primary O-alkyl carbamates:** According to our reported procedure, [43] to a mixture of alcohol (1.0 mmol) and potassium cyanate (1.5 mmol) in a mortar, DBSA (1.5 mmol) was added and the mixture was pulverized until a uniform mixture was formed. Then the mixture was kept in an oven at 60 $^{o}$C for 1 hour. After completion of the reaction, $CH_2Cl_2$ (15 mL) and the saturated aqueous solution of NaHCO3 (15 mL) were added to the resulting powder and organic layer was extracted, washed with water (3×15 mL), dried over anhydrous $Na_2SO_4$ and concentrated under vacuum to afford the title crude products. Finally, the pure products were obtained by recrystallization from diethyl ether in high yields.

**General procedure for the selective mono N-arylation of primary O-alkyl carbamates 5:** The catalyst (0.025 g, 0.5 mol %) was added to a mixture of primary O-alkyl carbamates (1.0 mmol), aryl halide (1.0 mmol) and sodium *tert*-butoxide (1.5 mmol) in toluene. The mixture was mixed by heater stirrer at 100 $^{o}$C for the appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction and separation of the catalyst by a magnetic field, 20 ml $H_2O$ was added and the mixture was extracted with $CHCl_3$. The organic phase was washed with water (2 × 10 mL) and dried over anhydrous $Na_2SO_4$. Then the solvent was removed under reduced pressure. The resulting crude product was purified by flash chromatography to give the desired cross-coupling products in good to excellent isolated yields.

## Acknowledgments

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## Notes and references

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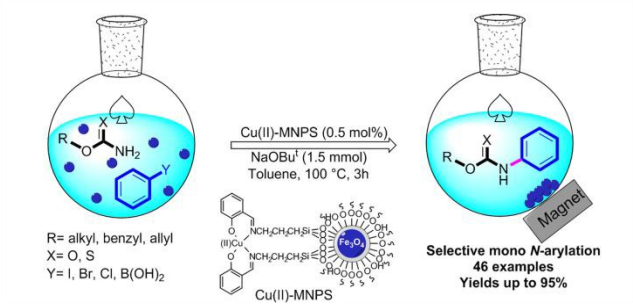


A convenient and efficient selective mono *N*-arylation of primary *O*-alkyl thiocarbamates and carbamates is reported by recyclable magnetic Cu(II) nanocatalyst.