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# Copper-catalyzed arenes amination with saccharins

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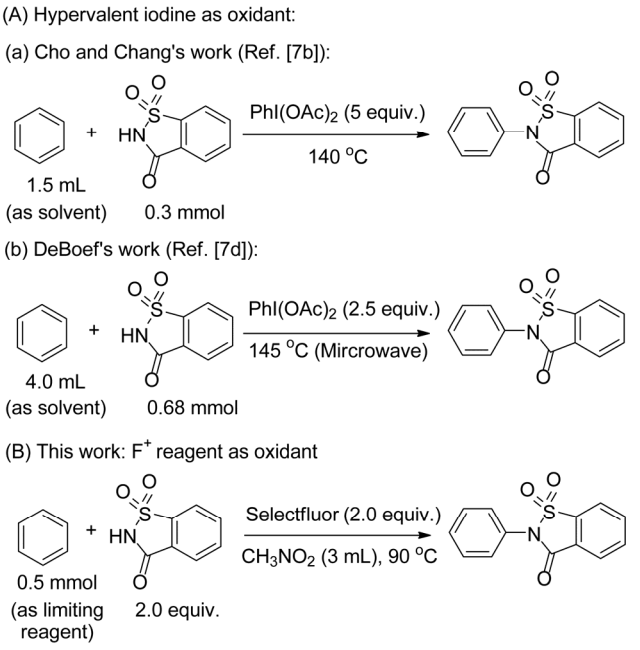
A novel copper-catalyzed direct C–N formation reaction of simple arenes with cheap and pharmacological saccharin derivatives under relatively mild conditions was developed with arenes as limiting reagents. This work provided a new method for oxidative coupling of aromatic C($sp^2$)–H bonds and N–H bonds.

**aromatic amines, C–N bond formation, arenes, saccharins, arenes as limiting reagents**

## 1 Introduction

Aromatic amines widely exist in both naturally occurring and synthetic compounds which demonstrate high levels of biological activity [1]. Accordingly, various methods for the construction of C–N bonds were developed and successfully used in academia [2] and industry [3]. For example, cross coupling reactions of aromatic halides/pseudohalides with amines, as well as arenes with various aminating reagents (e.g., N–Cl, N–Br, N–F, N–O), were commonly applied to form C–N bonds [4–6]. In both cases, prefunctionalization of arenes or amines was required. Recently, the direct C–N formation reaction between C–H and N–H bond [7] became an additional powerful methodology for the construction of C–N bonds, which could avoid prefunctionalization of the substrates and minimize environmental impact. Cho *et al*. [7b] (Scheme 1(A-a)) and DeBoef *et al*. [7d] (Scheme 1(A-b)) reported intermolecular imidation reactions between C–H bonds of arenes and N–H bonds of nitrogen sources with hypervalent iodine(III) as oxidant based on Togo's work [7c]. Under their conditions, arenes were usually used as solvents to ensure efficient amination. As part of our interest in utilizing $F^+$ oxidants to perform benzylic C($sp^3$)–H amination reaction [8], directed aromatic C($sp^2$)–H amination [9], allylic C–H amintion [10], annulation of amidines [11], diamination, aminocynation [12] and aminofluorination [13] of alkenes, herein, in the presence of




**Scheme 1** Synthesis of aromatic amines.

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Selectfluor, copper-catalyzed facile construction of C–N bond between simple arenes (used as limiting reagents) and saccharin derivatives via oxidative coupling of C–H and N–H bonds was realized (Scheme 1(B)). The saccharin moiety has been identified as an important molecular component in various classes of 5HT1a antagonists [14], human leukocyte elastase (HLE) inhibitors [15], analgesics [16], human mast cell tryptase inhibitors [17], α1-a adrenergic receptor antagonists [18] and aldehyde dehydrogenase inhibitors [19]. Therefore, various saccharin derivatives, which were generally synthesized starting from *ortho*-difunctional arenes [20], were chosen as the nitrogen sources in this study. Our new methodology based on the formation of C–N bond directly from C($sp^2$)–H bond of arenes and N–H bond of saccharins will provide an attracting alternative approach for saccharin derivatives.

## 2 Experimental

### 2.1 General experimental section

All reagents were used as received from commercial sources, unless otherwise specified or prepared as described in the literature. All reagents were weighed and handled in air.

$^1$H NMR and $^{13}$C NMR spectra were respectively recorded at 500 and 125 MHz, using tetramethylsilane as an internal reference. Chemical shifts ($\delta$) and coupling constants ($J$) were expressed in parts per million and hertz, respectively.

### 2.2 General procedure for the copper-catalyzed C–N formation of saccharins with arenes

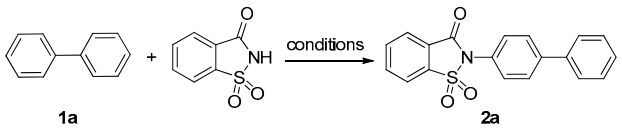
To a 5 mL screw-capped vial equipped with a 15×10 mm spinvane triangular-shaped Teflon stirbar, simple arene **1** (0.5 mmol), saccharin (1.0 mmol), Selectfluor (1.0 mmol), $K_2CO_3$ (1.0 mmol) and CuCl (0.1 mmol) were added in nitromethane (3.0 mL). The mixture was sealed with a Teflon-lined cap and stirred at 90 °C for 6.0 h (monitored by TLC), extracted with dichloromethane (5×3 mL), and dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography to give aromatic amine **2**. The characterizations of aromatic amines **2** and **4** were listed in the Supporting Information online.

## 3 Results and discussion

Initially, biphenyl **1a** (0.5 mmol) was tested in the presence of 10 mol% CuCl, 1,10-phenanthroline (0.1 equiv.), *N*-fluorobenzenesulfonimide (NFSI, 2.0 equiv.) and saccharin (2.0 equiv.) at 90 °C with $CH_3NO_2$ as the solvent. After 6 h, the desired amination product **2a** was obtained in 75% yield (Table 1, Entry 1). The yield of **2a** could be increased to 94% when Selectfluor was employed as the oxidant (Entry 2). Even in the absence of 1,10-phenanthroline, **2a** could also be obtained in 83% yield (Entry 3). However, $F^+$ oxidant 1-fluoro-2,4,6-trimethylpyridinium triflate (NFTMPT) was ineffective (Entry 4), neither were other oxidants such as $Ce(SO_4)_2$, $K_2S_2O_8$ and $PhI(OCOCF_3)_2$ (Entries 5–7). Different copper catalysts like CuBr, $CuCl_2$, $CuF_2$, $CuBr_2$ and $Cu(OTf)_2$ could also promote this amination to provide **2a** in 79%, 54%, 59%, 23% and 37% yields, respectively (Entries 8–11) and no reaction was observed in the absence of copper salt (Entry 12). Solvents such as acetonitrile ($CH_3CN$) and 1,2-dichloroethane (DCE) could afford the desired aminative product but in relatively low yields (Entries 13 and 14). Other solvents, such as tetrahydrofuran (THF), nitrobenzene ($PhNO_2$) and *N,N*-dimethylformamide (DMF) were ineffective (Entries 15–17). It should be noted that only stoichiometric arene substrates were used in all these cases [7b–7d].

With the optimized conditions in hand (Table 1, Entry 2), we next examined the generality of this amination reaction with respect to substitutions at aromatic rings. As described in Table 2, benzene (**1b**) and naphthalene (**1c**) could smoothly react with saccharin to afford **2b** and **2c** in 57%

**Table 1** Optimization of reaction conditions [a]




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

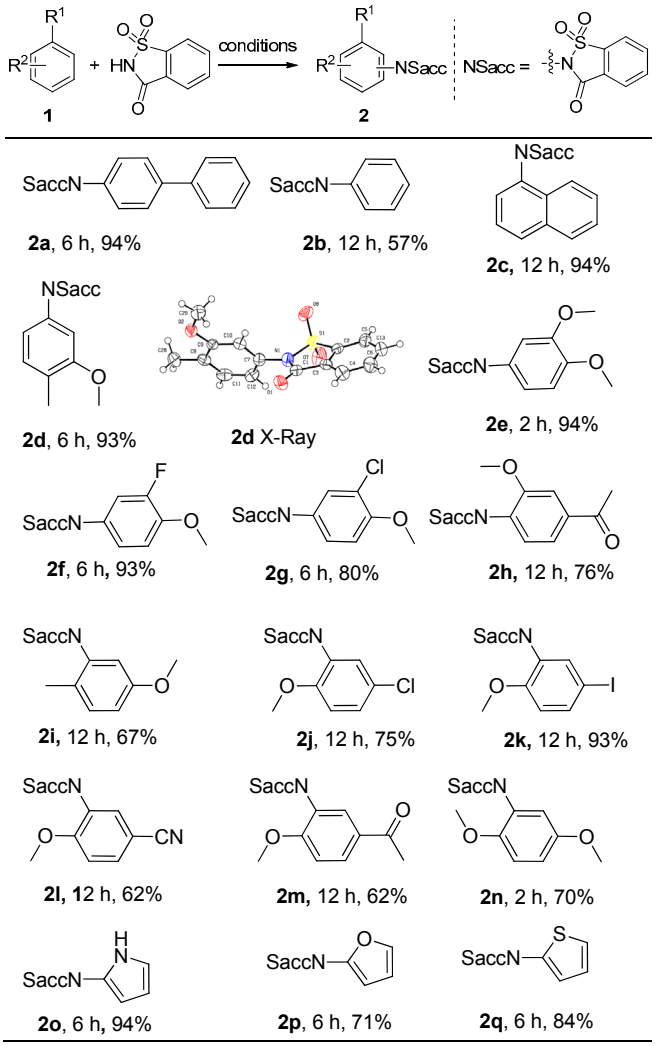
| Entry | Catalyst | Oxidant | Solvent | Yield (%) [b] |
|---|---|---|---|---|
| 1 | CuCl | NFSI | $CH_3NO_2$ | 75 |
| **2** | **CuCl** | **Selectfluor** | **$CH_3NO_2$** | **94** |
| 3 | CuCl | Selectfluor | $CH_3NO_2$ | 83 [c] |
| 4 | CuCl | NFTMPT [d] | $CH_3NO_2$ | 0 |
| 5 | CuCl | $Ce(SO_4)_2$ | $CH_3NO_2$ | 0 |
| 6 | CuCl | $K_2S_2O_8$ | $CH_3NO_2$ | 0 |
| 7 | CuCl | $PhI(OCOCF_3)_2$ | $CH_3NO_2$ | 0 |
| 8 | CuBr | Selectfluor | $CH_3NO_2$ | 79 |
| 9 | $CuCl_2$ | Selectfluor | $CH_3NO_2$ | 54 |
| 9 | $CuF_2$ | Selectfluor | $CH_3NO_2$ | 59 |
| 10 | $CuBr_2$ | Selectfluor | $CH_3NO_2$ | 23 |
| 11 | $Cu(OTf)_2$ | Selectfluor | $CH_3NO_2$ | 37 |
| 12 | none | Selectfluor | $CH_3NO_2$ | 0 |
| 13 | CuCl | Selectfluor | $CH_3CN$ | 65 |
| 14 | CuCl | Selectfluor | DCE | 84 |
| 15 | CuCl | Selectfluor | THF | 5 |
| 16 | CuCl | Selectfluor | $PhNO_2$ | 0 |
| 17 | CuCl | Selectfluor | DMF | 0 |

a) Reactions were carried out with **1a** (0.5 mmol), copper catalyst (10 mol%), 1,10-phenanthroline (0.1 equiv.), Selectfluor (2.0 equiv.), saccharin (2.0 equiv.) and $K_2CO_3$ (2.0 equiv.) in $CH_3NO_2$ (3 mL) at 90 °C for 6 h; b) yield of the isolated product; c) without 1,10-phenanthroline; d) NFTMPT= 1-fluoro-2,4,6-trimethylpyridinium triflate.

and 94% yields, respectively. For substrates **1d–1n** with various electron-withdrawing or electron-donating groups at aromatic rings, the amination reactions proceeded with high site-selectivity, forming **2d–2n** in 62%–94% yields. The structure of **2d** was further confirmed by X-ray crystallography [21]. It should be noted that halogen substituents such as –Cl (**2g** and **2j**) and –I (**2k**) were well tolerated, which provides the possibility for further transformation. In addition, hetero-aromatic compounds such as pyrrole (**1o**), furan (**1p**) and thiophene (**1q**) proved to be suitable substrates for this amination reaction, affording the 2-aminative products **2o**, **2p** and **2q** in 94%, 71% and 84% yields, respectively.

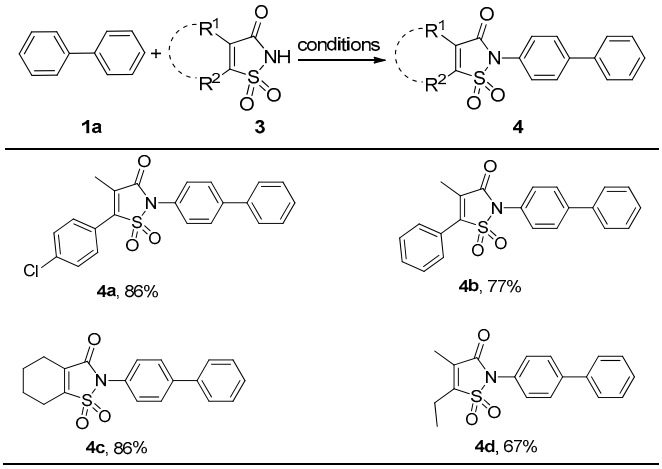
Next, other imide derivatives with substituents at the isothiazol-3(2*H*)-one 1,1-dioxide were examined (Table 3). Both 5-(4-chlorophenyl)-4-methylisothiazol-3(2*H*)-one 1,1-dioxide (**3a**) and 4-methyl-5-phenylisothiazol-3(2*H*)-one

**Table 2** Direct amination with various arenes [a, b]




a) Reactions were carried out with **1** (0.5 mmol), CuCl catalyst (10 mol%), 1,10-phenanthroline (0.1 equiv.), Selectfluor (2.0 equiv.), saccharin (2.0 equiv.) and $K_2CO_3$ (2.0 equiv.) in $CH_3NO_2$ (3 mL) at 90 °C; b) yield of the isolated product.

**Table 3** Direct amination with various nitrogen sources [a, b]

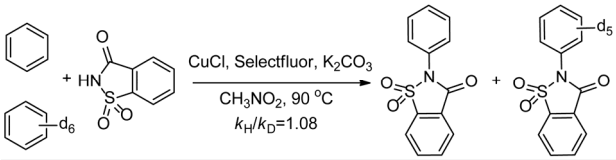



a) Reactions were carried out with **1a** (0.5 mmol), CuCl catalyst (10 mol%), 1,10-phenanthroline (0.1 equiv.), Selectfluor (2.0 equiv.), **3** (2.0 equiv.) and $K_2CO_3$ (2.0 equiv.) in $CH_3NO_2$ (3 mL) at 90 °C for 12 h; b) yield of the isolated product.

1,1-dioxide (**3b**) could undergo direct amination with biphenyl (**1a**), providing **4a** and **4b** in 86% and 77% yields, respectively. Aliphatic disubstituted imides **3c** and **3d** could also give the desired products **4c** and **4d**.

In order to understand the mechanism of these aromatic C($sp^2$)–H amination reactions, we carried out some control experiments. In the presence of 1.0 equiv. of 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO) under standard reaction conditions, the yield of **2a** drastically decreased from 94% to 5%. Moreover, when 1.0 equiv. of 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added, the reaction was completely suppressed and no **2a** was detected. These experimental results suggested a possible radical mechanism. In addition, no isotope effect ($k_H/k_D$=1.08, Scheme 2, the reaction was performed under the optimal reaction conditions) was observed, implying the C–H bond cleavage of benzene was not involved in the rate-limiting step.

Although the detailed mechanism of this amination was unclear at this moment, based on the experimental results and the previous research work [5c,6a,7c,8a,12,13], we presently favor a radical pathway. Initially, in the presence of copper-catalyst, the oxidation of saccharin with Selectfluor provides imidyl radical, which performs addition reaction to the aromatic ring to provide a carbon radical intermediate. The subsequent oxidative aromatization affords the




**Scheme 2** The kinetic deuterium isotope effect of the reaction between benzene and saccharin.

final amination product. The regioselectivities of these amination reactions appear to be controlled by electronic effect of substituent, as shown in Tables 2 and 3. Such amination occurred at the electron-rich position of aromatic rings, which might be attributed to the electrophilic property of imidyl radical species. Interestingly, the amination of 1-methoxy-4-methylbenzene (**1i**) generated a single product **2i** (at *ortho*-position to methyl group) under our reaction conditions, while in DeBoef's work, a mixture of two regioisomers was obtained in a ratio of 2:3 (*o*-methyl:*o*-methoxyl) [7d]. In their work, a nucleophilic amination mechanism was proposed.

## 4 Conclusions

In summary, we have developed a copper-catalyzed intermolecular oxidative C–N formation reaction of simple arenes with cheap and pharmacological saccharins under relatively mild conditions, in which arene substrates served as limiting reagents. High yields, wide arene substrate scope and the useful saccharin moiety made this direct C–H amination strategy very attractive. Further investigation of detailed mechanism and application of this protocol is currently underway in our lab.

### Supporting information

The supporting information is available online at chem.scichina.com and link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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