Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This Accepted Manuscript will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
A direct de-tetra-hydrogenative cross-coupling reaction between C$_{sp3}$–H bond and sulfamide under transition-metal-free condition is reported to give corresponding amidines.
Unexpected C=N bond formation via NaI-catalyzed oxidative de-tetra-hydrogenative cross-couplings between N, N-dimethyl aniline and sulfamides

Yang Zheng, Jincheng Mao, Jie Chen, Guangwei Rong, Defu Liu, Hong Yan, Yongjian Chi and Xinfang Xu*

A direct and convenient C=N bonds formation reaction was reported, which was a de-tetra-hydrogenative cross-coupling (DTCC) reaction between N, N-dimethyl aniline and sulfamide under transition-metal-free condition, and to give sulfonyl amidine derivatives in moderate to high yield.

The cross-dehydrogenative coupling (CDC) has been proved a powerful strategy in organic synthesis to form the C-C and C-X bonds in recent years (Scheme 1, eq 1). However, formation of double bond by removing four hydrogen atoms via twice CDCs is still a great challenge because it is difficult to further remove additional two hydrogen atoms after the single bond was formed through the first CDC reaction. Recently, Jiao and Shi have independently reported the pioneering works in constructing N=N bond to synthesize aromatic azo compounds with copper catalyst (Scheme 1, eq 2). Then, You and co-workers reported another example of formation the C=C bond by palladium catalyzed de-tetra-hydrogenative cross coupling (Scheme 1, eq 3). These reports illuminate a new strategy to construct double bonds via CDC reactions. Inspired by these works, here, we wish to report our recent result on C=N bond formation between C=N-H bond and sulfamide by one-step DTCC reaction under transition-metal-free conditions (Scheme 1, eq 4).

Sulfonyl amidines are very unique motifs, which are important in medicinal and synthetic chemistry. In recent years, many synthetic methods have been developed (Scheme 2), including Li (Method A), Chang (Method B), and others’ work. However, sulfonyl azide was employed in the first two reports, which was expensive and potentially explosive. In addition, the metal catalyst was essential in these transformations. In method C, product A could be achieved in the absence of transition-metal catalyst via the reaction between sulfonamide and formamide. However, formamide is also used as the solvent to insure good conversion. In addition, aromatic formamides could not be involved into the substrate scope because they are usually solid.

Scheme 1 Various dehydrogenative cross-coupling reactions.

Scheme 2 Synthesis of sulfonyl amidines.
Herein, we developed a novel strategy to access to sulfonyl amidines with \(N, N\)-dimethyl aniline and sulfonamide, which provides a direct method to synthesize various sulfonyl amidines containing the structure of aromatic rings.\(^{1,6}\) Comparing to the sp\(^3\) C–H amination\(^1\) and above mentioned reports, this method could be considered as a powerful alternative strategy in direct C=N bond formation.

The optimization of catalytic system was summarized in Table 1. Initially, various readily available catalysts were investigated (Table 1, entries 1-8) and NaI was found to be the best one (Table 1, entry 1). When the amount of 2a was increased, the yield of this conversion was obviously promoted (Table 1, entry 1 vs entry 15). Notably, the oxidant plays an important role in this reaction. As shown in Table 1, anhydrous TBHP (5-6 M in decane) as the oxidant was proved to be the best (80\%, Table 1, entry 16), which is better than TBHP (in water) did (65\%, Table 1, entry 15). When other oxidants were used, 3a cannot be obtained (Table 1, entries 9-14). In order to improve the catalytic effect, various additives were employed into the reaction (Table 1, entries 17-19) and 1,10-phenanthroline (Phen) was best (Table 1, entry 17). Although similar transformations assisted by organocatalysts have been present via the radical intermediate,\(^6\) and the detailed mechanism is not very clean yet. However, from the comparison experiments of with and without the ligand, it indicates that the ligand assists the first part of the transformation, from materials to \(C\).\(^9\)

Under the optimized conditions, the substrates generality was tested, and the results are shown in Table 2. Electron-donating group (such as methyl) on the aniline gave slightly low yield (Table 2, 3b). While electron-withdrawing groups (such as fluoro, chloro, bromo and nitro groups) on the aniline had different influence, and yields of corresponding products 3 were obtained ranging from 28\% to 54\%. Among these substituents, bromo and nitro groups were better than others (Table 2, 3d, 3e and 3i). m-Chloro group on the aniline could also lead to the relatively good yield (Table 2, 3f). All in all, we can see that \(N, N\)-dimethyl anilines without any substituents on the aromatic ring gave the highest yield.

Subsequently, the protocol was applied to the reaction with a range of sulfonamides. To our delight, moderate to good yields were acquired. Both electron-donating groups and electron-withdrawing groups on the aromatic ring could be well tolerated under this conditions (Table 2, 3j-3t). It is noteworthy that heterocycle sulfonamides could give 3u with satisfying yield (60\%).

To gain insight into the reaction mechanism, some additional experiments have been performed as shown in Scheme 3. The model reaction between 1a and 2a was performed under higher temperature (110 °C) in the absence of Phen. 3a was obtained together with many byproducts, which were generated from 2a itself (Scheme 3, eq 1).\(^{10}\) This promoted us to conduct more reactions between 1a and various anilines. When \(N\)-methyl aniline was used instead of 2a, 3a could also be obtained with lower yield and \(N\)-demethyl analog of 3a was not detected (Scheme 3, eq 2). Then we tried to use aniline as the substrate. However, 3a or \(N\)-demethyl analog of 3a was not acquired (Scheme 3, eq 3). In view of above experiments, we can see that the methyl group of 3a probably did not come from TBHP,\(^{11}\) and it is probably from \(N\)-methyl aniline.\(^{21}\) Next, \(N, N\)-dimethylamine was employed.

---

**Table 1** Optimization of the reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Oxidant</th>
<th>Additive</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaI</td>
<td>TBHP</td>
<td>—</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>—</td>
<td>TBHP</td>
<td>—</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>KI</td>
<td>TBHP</td>
<td>—</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>TBAI</td>
<td>TBHP</td>
<td>—</td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td>Li2</td>
<td>TBHP</td>
<td>—</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>Phen(OAc)(_2)</td>
<td>TBHP</td>
<td>—</td>
<td>trace</td>
</tr>
<tr>
<td>7</td>
<td>Cul</td>
<td>TBHP</td>
<td>—</td>
<td>trace</td>
</tr>
<tr>
<td>8</td>
<td>FeCl3</td>
<td>TBHP</td>
<td>—</td>
<td>trace</td>
</tr>
<tr>
<td>9</td>
<td>NaI</td>
<td>O(_2)</td>
<td>—</td>
<td>ND</td>
</tr>
<tr>
<td>10</td>
<td>NaI</td>
<td>K(_2)S(_2)O (_8)</td>
<td>—</td>
<td>trace</td>
</tr>
<tr>
<td>11</td>
<td>NaI</td>
<td>H(_2)O</td>
<td>—</td>
<td>ND</td>
</tr>
<tr>
<td>12</td>
<td>NaI</td>
<td>TBPB</td>
<td>—</td>
<td>ND</td>
</tr>
<tr>
<td>13</td>
<td>NaI</td>
<td>DDQ</td>
<td>—</td>
<td>ND</td>
</tr>
<tr>
<td>14</td>
<td>NaI</td>
<td>DCP</td>
<td>—</td>
<td>ND</td>
</tr>
<tr>
<td>15</td>
<td>NaI</td>
<td>TBHP</td>
<td>—</td>
<td>65</td>
</tr>
<tr>
<td>16</td>
<td>NaI</td>
<td>TBHP</td>
<td>Phen</td>
<td>80</td>
</tr>
<tr>
<td>17</td>
<td>NaI</td>
<td>TBHP</td>
<td>Phen</td>
<td>90(70)*</td>
</tr>
<tr>
<td>18</td>
<td>NaI</td>
<td>TBHP</td>
<td>1H-Benzotriazole</td>
<td>86(67)*</td>
</tr>
<tr>
<td>19</td>
<td>NaI</td>
<td>TBHP</td>
<td>TMEDA</td>
<td>82(52)*</td>
</tr>
</tbody>
</table>

**Table 2** NaI-catalyzed DTCC reactions

| R = H, 3a, 70% | R = 4-Me, 3b, 32% |
| R = 4-Br, 3d, 46% | R = 3-Br, 3e, 32% |
| R = 4-Br, 3f, 53% | R = 3-Cl, 3f, 51% |
| R = 3-Cl, 3g, 51% | R = 4-Br, 3h, 54% |

---

\(^a\) Reaction conditions: benzene sulfonamide (1a, 0.5 mmol), \(N, N\)-dimethyl aniline (2a, 0.7 mmol), catalyst (20 mol%), TBHP (70% aqueous solution, 1.5 mmol), additive (0.05 mmol, if added), toluene (2.0 mL), 110 °C, 12 h, air; \(^b\) LC yield using an internal standard; \(^c\) 2a (2.1 mmol), EtOAc (2.0 mL) as the solvent, 80 °C; \(^d\) TBHP (5-6 M in decane, 1.5 mmol); \(^*\) Isolated yields are given in parentheses.
To our surprise, the dephenylation coupling product \(N,N\)-dimethyl-\(N'\)-phenylsulfonyl)formimidamide was afforded in 45\% yield (Scheme 3, eq 4).

Other substrates were also tested, including \(N,N\)-diethylaniline, \(N\)-ethyl-\(N\)-methylaniline, triethylamine, and trimethylamine, however, only very lower or no conversion was observed.

Subsequently, aniline and benzamide were employed as the substrates to react with \(2a\). However, the desired product could not be generated under the standard condition when aniline was employed as the substrate (Scheme 4, eq 1). And when benzamide reacted with \(2a\), two products were afforded and the ratio was 3:2, which determined by NMR. Interestingly, unexpected \(N\)-methylformanilide was found here while it was not detected in the model reaction between \(1a\) and \(2a\). Without using Phen, only \(N\)-[(methylanilino)methyl]benzamide was obtained with higher yield of 34\% (Scheme 4, eq 3).

Scheme 4. Investigation of the reactions between \(2a\) and aniline or benzamide.

Based on Wan's work, \(2a\) was possibly oxidized to \(N\)-methyl-\(N\)-formyl-aniline by TBHP and then participated in the reaction. So we directly used \(N\)-methyl-\(N\)-formyl-aniline as the substrate, and less amount of desired product \(3a\) was obtained (Scheme 5, eq 1).

Scheme 5. Investigation of the reactions between \(2a\) and aniline or benzamide.

Therefore, it was assumed that the mechanism of the reaction may proceed in a different pathway in our protocol. In addition, it was found that with the base could not afford \(3a\), either. This may prove that it was not a schiff base-involved reaction. Besides, the desired product was not detected when the reaction was carried out in the presence of I\(_2\) and NaOH, which could generate the hypoiodite species in situ and catalyze the C–H functionalization.\(^{11a,11b}\) Next, radical scavengers like TEMPO or BHT (butylated hydroxytoluene) was added to the reaction, and the reaction was inhibited (Scheme 5, eq 2). This suggested that the transformation probably proceeded through a radical progress.

According to prior reports\(^{14}\) and above observation, a plausible reaction mechanism is proposed in Scheme 6. In the first step, TBHP was resolved to generate tert-butoxyl radical and hydroxyl ion in associate with reduction of iodine ion.\(^{13}\) Then tert-butoxyl radical abstracted a hydrogen atom from \(2\) to generate radical \(A\), which subsequently formed iminium ion \(B\) through single electron transfer (SET) with iodine, and this process was well studied and accepted in general.\(^{15-21}\) Afterwards, benzene sulfonamide as a unique nucleophile reagent\(^{16}\) attacked \(B\), followed by deprotonation to form \(C\), which was confirmed by HRMS and proton NMR.\(^{9}\) Sequentially further oxidized by TBHP to produce the desired product \(3.\(^{2,3,27}\)

Scheme 6. Possible reaction pathways.

To our knowledge, various catalytic systems were developed for synthesis of iminium ions from \(N,N\)-dialkylanilines. The scope of catalysts includes Ru,\(^{17}\) Rh,\(^{18}\) Ir,\(^{19}\) Cu,\(^{20}\) Fe,\(^{21}\) Mo,\(^{22}\) Au,\(^{23}\) Re,\(^{24}\) V\(^{25}\) and other complexes.\(^{26}\) However, Nal-catalyzed reaction between \(N,N\)-dialkylaniline and TMS-CN to transform...
hydrogen atoms in one-pot. The further application of our method
NaI. It could be expected that this unanticipated finding would have a
substrates as starting materials and was catalyzed by inexpensive
efficient process use commercially available and abundant
reactions, which provide a novel strategy to generate sulfonyl
for directly constructing new C=N bonds through oxidative DTCC

\[
\begin{align*}
\text{Ph} & \quad + \quad \text{N} \quad \text{S} \\
\text{NaI}, \text{TBHP} & \quad \text{MeOH, } 65 \, ^\circ \text{C, } 5 \text{h} \\
\rightarrow & \quad \text{Ph} \quad \text{N} \quad \text{CN}
\end{align*}
\]

Scheme 7. Control experiment.

Conclusions

In summary, we have discovered a transition-metal-free method
for directly constructing new C=N bonds through oxidative DTCC
reactions, which provide a novel strategy to generate sulfonyl
for directly constructing new C=N bonds through oxidative DTCC

\[
\begin{align*}
\text{Ph} & \quad + \quad \text{N} \quad \text{S} \\
\text{NaI}, \text{TBHP} & \quad \text{MeOH, } 65 \, ^\circ \text{C, } 5 \text{h} \\
\rightarrow & \quad \text{Ph} \quad \text{N} \quad \text{CN}
\end{align*}
\]

Scheme 7. Control experiment.

Conclusions

In summary, we have discovered a transition-metal-free method
for directly constructing new C=N bonds through oxidative DTCC
reactions, which provide a novel strategy to generate sulfonyl
for directly constructing new C=N bonds through oxidative DTCC

\[
\begin{align*}
\text{Ph} & \quad + \quad \text{N} \quad \text{S} \\
\text{NaI}, \text{TBHP} & \quad \text{MeOH, } 65 \, ^\circ \text{C, } 5 \text{h} \\
\rightarrow & \quad \text{Ph} \quad \text{N} \quad \text{CN}
\end{align*}
\]

Scheme 7. Control experiment.

Conclusions

In summary, we have discovered a transition-metal-free method
for directly constructing new C=N bonds through oxidative DTCC
reactions, which provide a novel strategy to generate sulfonyl
for directly constructing new C=N bonds through oxidative DTCC

\[
\begin{align*}
\text{Ph} & \quad + \quad \text{N} \quad \text{S} \\
\text{NaI}, \text{TBHP} & \quad \text{MeOH, } 65 \, ^\circ \text{C, } 5 \text{h} \\
\rightarrow & \quad \text{Ph} \quad \text{N} \quad \text{CN}
\end{align*}
\]

Scheme 7. Control experiment.

Conclusions

In summary, we have discovered a transition-metal-free method
for directly constructing new C=N bonds through oxidative DTCC
reactions, which provide a novel strategy to generate sulfonyl
for directly constructing new C=N bonds through oxidative DTCC

\[
\begin{align*}
\text{Ph} & \quad + \quad \text{N} \quad \text{S} \\
\text{NaI}, \text{TBHP} & \quad \text{MeOH, } 65 \, ^\circ \text{C, } 5 \text{h} \\
\rightarrow & \quad \text{Ph} \quad \text{N} \quad \text{CN}
\end{align*}
\]

Scheme 7. Control experiment.

Conclusions

In summary, we have discovered a transition-metal-free method
for directly constructing new C=N bonds through oxidative DTCC
reactions, which provide a novel strategy to generate sulfonyl
for directly constructing new C=N bonds through oxidative DTCC

\[
\begin{align*}
\text{Ph} & \quad + \quad \text{N} \quad \text{S} \\
\text{NaI}, \text{TBHP} & \quad \text{MeOH, } 65 \, ^\circ \text{C, } 5 \text{h} \\
\rightarrow & \quad \text{Ph} \quad \text{N} \quad \text{CN}
\end{align*}
\]

Scheme 7. Control experiment.

Conclusions

In summary, we have discovered a transition-metal-free method
for directly constructing new C=N bonds through oxidative DTCC
reactions, which provide a novel strategy to generate sulfonyl
for directly constructing new C=N bonds through oxidative DTCC

\[
\begin{align*}
\text{Ph} & \quad + \quad \text{N} \quad \text{S} \\
\text{NaI}, \text{TBHP} & \quad \text{MeOH, } 65 \, ^\circ \text{C, } 5 \text{h} \\
\rightarrow & \quad \text{Ph} \quad \text{N} \quad \text{CN}
\end{align*}
\]

Scheme 7. Control experiment.

Conclusions

In summary, we have discovered a transition-metal-free method
for directly constructing new C=N bonds through oxidative DTCC
reactions, which provide a novel strategy to generate sulfonyl
for directly constructing new C=N bonds through oxidative DTCC

\[
\begin{align*}
\text{Ph} & \quad + \quad \text{N} \quad \text{S} \\
\text{NaI}, \text{TBHP} & \quad \text{MeOH, } 65 \, ^\circ \text{C, } 5 \text{h} \\
\rightarrow & \quad \text{Ph} \quad \text{N} \quad \text{CN}
\end{align*}
\]

Scheme 7. Control experiment.

Conclusions

In summary, we have discovered a transition-metal-free method
for directly constructing new C=N bonds through oxidative DTCC
reactions, which provide a novel strategy to generate sulfonyl
for directly constructing new C=N bonds through oxidative DTCC

\[
\begin{align*}
\text{Ph} & \quad + \quad \text{N} \quad \text{S} \\
\text{NaI}, \text{TBHP} & \quad \text{MeOH, } 65 \, ^\circ \text{C, } 5 \text{h} \\
\rightarrow & \quad \text{Ph} \quad \text{N} \quad \text{CN}
\end{align*}
\]

Scheme 7. Control experiment.


