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Xiangyan Yi,<sup>a,b</sup> Jiajun Feng,<sup>a,b</sup> Fei Huang<sup>\*a,b</sup>, and Jonathan Bayldon Baell<sup>\*b,c</sup>

## Metal-free C-C, C-O, C-S and C-N Bond Formation Enabled by SBA-15 Supported TFMSA

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The intermolecular C-C, C-O, C-S and C-N bonds construction between diazo compounds and acyclic, cyclic 1,3-dicarbonyl compounds, thiophenol, alkynes were developed by using a TFMSA@SBA-15, thus providing a metal-free and eco-friendly platform for forging those chemical bonds.

C-C and C-X (X = O, C, N) bonds exist widely in drug or bioactive molecules.<sup>1</sup> A wide range of transition-metal catalyzed insertion reactions between diazo compounds and various nucleophiles forging those chemical bonds above have become indispensable to organic synthetic field.<sup>2</sup> In this regard, the most used metal catalysts are Rh<sup>3</sup> and Cu,<sup>4</sup> which were first developed to promote the formation of metal-carbenoid intermediates. Metal carbene species can undergo corresponding transformations, forming C-C, C-O, C-S and C-N bonds. Subsequently, transition metal complexes and salts like Fe,<sup>5</sup> Ru,<sup>6</sup> Pd,<sup>7</sup> Sc,<sup>8</sup> In,<sup>9</sup> Au,<sup>10</sup> Ag<sup>11</sup> and Ir<sup>12</sup> have been employed as activator of diazo to catalyze formation of those chemical bonds. Although the process of those reactions can be controlled by sophisticated metal, the cost of preparation of metal catalysts and ligands raise serious barrier in economy. Meanwhile, the issue of transition-metal residue contained in metal catalysts allows those protocols are limited in the pharmaceutical industries (< ppm level).<sup>13</sup> Consequently, as a mean to improve applicability and maneuverability, the research on utilization of organic molecular as a substitute for metal catalysts will be significant. We targeted a new protic acid as the activator of diazo. Based on achievements in Lewis acids14 and Brønsted acid15 activation of diazo compounds. We questioned whether trifluoromethanesulfonic acid (strongest protic acid, TFMSA) could be used to meditate C-C, C-O, C-S and C-N bonds formation. In addition, we envisioned that the higher catalytic efficiency can be exhibited through immobilizing the protic acid on mesoporous silica, according to excellent physical properties of this material and the high oxophilicity of Si helps to the formation of six-membered cyclic structure that increases the electrophilicity of proton in protic acid.<sup>16</sup> Guided by this den idea, herein we would like to elaborate the development of such TFMSA@SBA-15 (only 2 mol%) catalyst catalyzed four chemical bonds



**Scheme 1** Intermolecular C-C, C-O, C-S and C-N bonds construction by pervious contributions and this work.

<sup>&</sup>lt;sup>a.</sup> School of Food Science and Pharmaceutical Engineering, Nanjing Normal University, Nanjing, 210023, China.

<sup>&</sup>lt;sup>b.</sup> School of Pharmaceutical Sciences, Nanjing Tech University, Nanjing, 211816, China.

<sup>&</sup>lt;sup>c</sup> Medicinal Chemistry Theme, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria 3052, Australia.

E-mail: huangfei0208@yeah.net, jonathan.baell@monash.edu

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construction between diazo compounds and acyclic, cyclic 1,3-dicarbonyl compounds, thiophenol, alkynes.

Our investigation began with a search for a nonmetallic catalyst for intermolecular C-C, C-O, C-S and C-N bonds formation through diazo compounds. We examined the activity of various protic acids toward the reactions between ethyl 2-diazoacetate (1a) and 5methylcyclohexane-1,3-dione (2a) to check the feasibility of C-O bond formation (see SI for detail). The results are displayed in (Fig. 1a). The reaction mentioned above did not deliver the desired results with high yield in the presence of acids such as AcOH, CSA, TFA and MsOH. However, the use of some strong acids like TsOH,  $H_2SO_4$ , HCl and HClO<sub>4</sub> gave the product (**3a**) remarkably better yield. Gratifyingly, when TFMAS (pKa =-14) was used as a catalyst, the isolated yield of product (3a) reached the highest. These results also revealed that the correlation between catalytic activity of acid and its pKa value, strong protic acid was necessary for giving the best results, whereas weak acid was ineffective with starting material unchanged.



**Fig. 1** (a) Screening various protic acids with different pKa in C-O bond formation. (b) Study on TFMSA@SBA-15 in C-C, C-O, C-S and C-N bonds formation reactions. (c) TFMSA@SBA-15 SEM images and TEM images. (d) FT-IR spectra of SBA-15 and TFMSA@SBA-15. Reaction condition see SI for details.

To minimize the catalyst amount, as well as the improvement of acid operation, a heterogeneous catalyst, TFMSA@SBA-15, was prepared by immobilizing TFMSA on solid support (SBA-15). Improved results were obtained in each model reactions, affording excellent

isolated yields in C-C (80%), C-O (95%), C-S (85%) and Ce N (88%) bond products, respectively (Fig. 2b). Therefore, it was concluded that TFMSA@SBA-15 (2 mol%) was the best catalyst for those reactions (TON=50).

Next, the morphology of TFMSA@SBA-15 were observed by scanning electron microscopy (SEM). As shown in (Fig. 2c), an overall perspective of TFMSA@SBA-15 can be seen clearly and it presents ordered mesoporous channels. Fluorine and sulfur elements were confirmed via EDS. In addition, the transmission electron microscope images (Fig. 2c) demonstrated that strongly acidic condition didn't cause structural damage to the highly ordered mesoporous channels.

The binding mode between TFMSA and SBA-15 was further analysed by flourier transform infrared (FT-IR) in (Fig. 2d). For the pure SBA-15 samples, two peaks were observed at 807 cm<sup>-1</sup> and 1078 cm<sup>-1</sup>, which can be attributed to Si-O bond group in samples. After treatment with TFMAS, a band was observed at 641 cm<sup>-1</sup> that arise from stretching vibration of the sulfonic group. Moreover, a redshift in the symmetric stretching vibration band from 1078 to 1046 cm<sup>-1</sup> was observed, simultaneously, another redshift ranging from 807 to 796 cm<sup>-1</sup> was observed. Thus, we deduce that the adsorption of TFMSA on SBA-15 preferentially occurred through Si-O binging<sup>16</sup> during the preparation TFMSA@SBA-15 process.



 $\label{eq:scheme 2} \begin{array}{l} \mbox{Scheme 2} \mbox{ Intermolecular C-C bonds formation through $\alpha$-diazo compounds. Reaction conditions: 1 (0.5 mmol), 2 (2.5 mmol), TFMSA@SBA-15 (2 mol%), DCE (3 mL), 60 °C, isolated yield. \end{array}$ 

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With the advent of this efficient heterogeneous catalytic system, we investigated the scope of the reaction between  $\alpha$ -diazoesters and acyclic 1,3-dicarbonyl substrates firstly. A variety of  $\alpha$ -diazoesters

dicarbonyl substrates firstly. A variety of α-diazoesters with either OMe, F, or isobutyl, allyl, benzyl phenyldiazoacetates, were successfully formed the desired C-C bond products in 68-87% yields. It was noted that the presence of an electron-withdrawing group in the phenyl ring increased the yield to 87% (**3b**). Electron-donating group, such as methoxy, decreased the yield (**3c**). 2-Naphthyl-diazoacetates also afforded the corresponding products (**3g**) in 65% isolated yield, while lower reactivity was observed for heteroaryl system (**3h**) and alkyl 1.3-diketone (**3i**).



Scheme 3 Intermolecular C-O bonds formation through  $\alpha$ -diazo compounds. Reaction conditions: 1 (0.5 mmol), 4 (1.5 mmol), TFMSA@SBA-15 (2 mol%), DCE (3 mL), 60 °C, isolated yield.

Interestingly, TFMSA@SBA-15 exclusively furnished the C-O bond product for cyclic 1,3-dicarbonyl substrates, without formation of the C-C bond products. The results may be attributed to the different enol forms of acyclic diketone (*cis*-enol) and cyclic diketone (*trans*enol).<sup>11</sup>

Then TFMSA@SBA-15 was also proved be an efficient catalyst for solvent-free C-S bond formation in room temperature between  $\alpha$ -diazoester and thiophenol in the scheme 4. Not only substituted phenyldiazoacetates but also ethyl diazoacetate could participate in S-H insertion reaction to give products with moderate to good yield (65-85%) in 5-50 mins.



**Scheme 4** Intermolecular C-S bonds formation through α-diazo compounds. Reaction conditions: **1** (0.5 mmol), **6** (1.5 mmol), TFMSA@SBA-15 (2 mol%), rt, isolated yield, <sup>*a*</sup>DCE (3 mL).

To our delight, this catalyst applied to those reactions between various alkynes and  $\alpha$ -diazo compounds as well. In general, good yields (70-93%) were obtained in this 1,3-dipolar cycloaddition reaction. Presumably due to hindered aryl migration, phenyldiazoacetate (**9e**) afforded relatively poor yield compared with ethyl diazoacetate (**9a**). The highest TOF is up to 600 h<sup>-1</sup>.



As an indication of the possible potential of this catalytic system, those reactions were carried out on the 1 g scale and the catalyst can be reused 4 times (see SI for detail). Based on related precedents<sup>11,15-18</sup> and the structure of catalyst, a plausible mechanism was proposed. Firstly,  $\alpha$ -diazo compound activated by protonation of the carbon atom in C-N bond.<sup>11,17</sup> Meanwhile, carbocation is nucleophilic attacked by acyclic, cyclic 1,3-dicarbonyl substrates, thiophenol to

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form C-C,<sup>11</sup> C-O<sup>15</sup>, C-S bond and regenerate the catalyst. Particularly, there is a 1,3-diplor cycloaddition for C-N bond formation between  $\alpha$ -diazo compounds and alkynes after protonation of alkynes.<sup>18</sup>



In conclusion, for the first we have demonstrated that organic acid is able to catalyse the insertion and cycloaddition reactions between diazo compounds and acyclic, cyclic 1,3-dicarbonyl substrates, thiophenol, alkynes. Employing catalyst loadings as low as 2 mol%, good yield was obtained in those reactions of formation C-C, C-O, C-S and C-N bond, when TFMSA was immobilized on SBA-15. Particularly, the reaction of S-H insertion reaction proceeds under solvent-free conditions and remarkably short time with high yields. We believe that this work may open for new possibility of organic molecular catalyzed insertion and cycloaddition reactions, offering a green and feasible entry to industrial application.

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### **Conflicts of interest**

There are no conflicts to declare.

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