

# SYNLETT Spotlight 394

## (Trifluoromethyl)trimethylsilane

Compiled by Thi Minh Ha Vuong



This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

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### Introduction

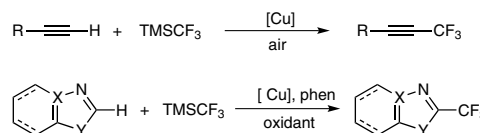
(Trifluoromethyl)trimethylsilane (TMSCF<sub>3</sub>) is a flammable liquid with a boiling point of 54–55 °C, a flash point of –17 °C and density of 0.926 g/mL at 20 °C. It may be harmful if inhaled, swallowed, absorbed through skin and may cause respiratory tract, skin and eye irritation. TMSCF<sub>3</sub> was firstly synthesized by Rupert<sup>1</sup> in 1984 via the condensation reaction of CF<sub>3</sub>Br and TMSCl with (Et<sub>2</sub>N)<sub>3</sub>P. Nowadays, there are various synthetic methodologies to yield this compound. Among them, the approach of Pawelke is considered as the most efficient

method.<sup>2</sup> Following this method, the reaction of CF<sub>3</sub>I and tetrakis(dimethylamino)ethylene formed an in situ mediated complex which reacted directly with TMSCl to afford TMSCF<sub>3</sub> in 94% yield. TMSCF<sub>3</sub> is versatile reagent for trifluoromethylation, such as transition-metal-catalyzed reaction, miscellaneous trifluoromethylation, and addition to carbonyl and imine groups. These reactions are extremely useful approaches in the pharmaceutical and agrochemical industry,<sup>3</sup> because they enhance metabolic stability (metabolic blocking) and alter the compound properties (lipophilicity, binding selectivity).

### Abstract

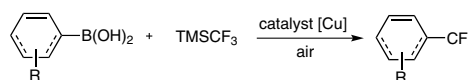
#### (A) Oxidative Trifluoromethylation of Terminal Alkynes and Heteroarenes:

Qing and co-worker described a powerful method for the synthesis of a broad range of trifluoromethylated acetylenes in good yields by using the copper-mediated protocol.<sup>4</sup> Recently, they have developed an alternative copper-catalyzed trifluoromethylation.<sup>5</sup> This method is also applied to the oxidative trifluoromethylation of heteroarenes and highly electron-deficient arenes via C–H activation.<sup>6</sup>



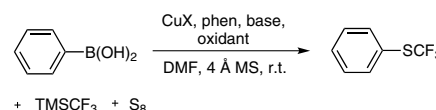
#### (B) Oxidative Trifluoromethylation of Boronic Acids:

Copper-mediated or -catalyzed oxidative cross-couplings of aryl- and alkenylboronic acids with TMSCF<sub>3</sub> under mild condition have been reported.<sup>5,7</sup> This procedure can be employed in the various ranges of functionalized aryl, heteroaryl and alkenyl boronic acids.



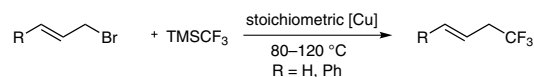
#### (C) Cu-Catalyzed Reaction of Arylboronic Acid with TMSCF<sub>3</sub> and S<sub>8</sub>:

This study provides an efficient and convenient protocol for the synthesis of aryl trifluoromethyl thioethers.<sup>8</sup>



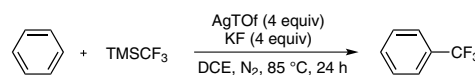
#### (D) Cu-Mediated Nucleophilic Trifluoromethylation of Allyl Halides:

The trifluoromethylated allylic products have been synthesized in good yields.<sup>9</sup>

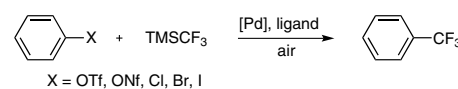


(E) *Ag-Mediated Trifluoromethylation of Arenes:*

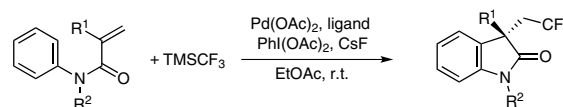
The innovative procedures for silver-mediated CH trifluoromethylation of aromatic substrates were developed by Melanie S. Sanford and co-workers.<sup>10</sup> The mechanism of these reactions is suggested to proceed via an AgCF<sub>3</sub> intermediate.

(F) *Pd-Catalyzed Trifluoromethylation of Aryl Halides and Vinyl Sulfonates:*

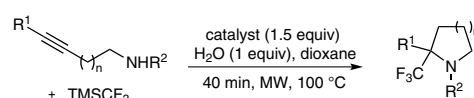
Hartwig,<sup>11</sup> Sanford,<sup>12</sup> Grushin<sup>13</sup> and Buchwald<sup>14,15</sup> have contributed to a notable feature of this reaction.

(G) *Pd-Catalyzed Intermolecular Oxidative Aryltrifluoromethylation of Activated Alkenes:*

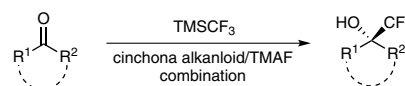
The powerful synthesis of oxidole derivatives containing CF<sub>3</sub> was explored by Liu and colleagues.<sup>16</sup> The desired products were obtained via initial arylpalladation of alkenes, continued by sequential oxidation and reductive elimination of Csp<sup>2</sup> Pd<sup>IV</sup>CF<sub>3</sub> species.

(H) *Synthesis of α-CF<sub>3</sub> N-Heterocycles Through Tandem Nucleophilic Additions:*

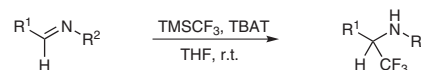
A powerful strategy for the synthesis of precursors of biologically important unnatural cyclic amino acids and fluorinated N-heterocycles by tandem reactions based on amination and trifluoromethylation catalyzed by AgF was reported by Hammond.<sup>17</sup>

(I) *Addition to the Carbonyl Group:*

The catalytic nucleophilic enantioselective trifluoromethylation of carbonyls, including aldehydes,<sup>18</sup> ketones<sup>18</sup> (alkynylketones<sup>19</sup> and aryl ketones<sup>20</sup>), acyltrifluoromethane,<sup>21</sup> acylphosphonates<sup>22</sup> and acylsilanes<sup>23,24</sup> was reported. The addition to related carbonyl compounds (enones, amides, esters, sulfonic, sulfinic, selenic esters and α-keto esters) was also described.<sup>18</sup>

(J) *Addition to Imines, Nitrones, Thiocyanate and Selenocyanate:*

This series of trifluoromethylation by addition allows for generating promising candidates for the pharmaceutical and agrochemical industry.<sup>18</sup>



## References

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