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**Title:** Iron-Mediated Azidomethylation or Azidotrideuteromethylation of Active Alkenes with Azidotrimethylsilane and Dimethyl Sulfoxide

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# Iron-Mediated Azidomethylation or Azidotrideuteromethylation of Active Alkenes with Azidotrimethylsilane and Dimethyl Sulfoxide

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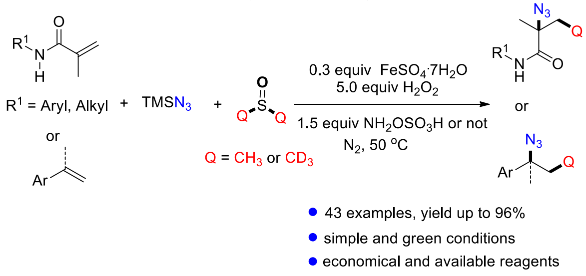
**Abstract.** A radical azidomethylation of various alkenes with azidotrimethylsilane and dimethyl sulfoxide has been achieved under mild reaction conditions, and the method efficiently introduces common and valuable azide and methyl groups into organic compounds. Control experiments such as capturing of the intermediate and gram-scale reactions of the developed system as well as further transformations of the products of the reaction are presented.

**Keywords:** Azidomethylation; Azidotrimethylsilane; Dimethyl sulfoxide; Alkenes; Radical reactions

Organic azides are important nitrogen-containing compounds that are widely used in organic synthesis,[1] biology,[2] medicine,[3] materials chemistry[4] and so on. Organic azides have also attracted much attention from chemists as valuable building blocks.[5] In recent years, many methods for incorporating azides into organic molecules have been reported. Among these methods, the carboazidation,[6] diazidation,[7] oxyazidation,[8] azidophosphonation[9] and haloazidation[10] of azides with alkenes have become active areas of research. Methyl and trideuteromethyl groups, which cause “methyl effects”, can impact the chemical and biological properties of organic compounds.[11] A variety of methylation[12] or trideuteromethylation[13] reactions have been reported by a number of different groups. Inspired by literature precedent, we speculated that if azide and methyl groups could be simultaneously introduced into alkenes, useful organic azides could be produced.

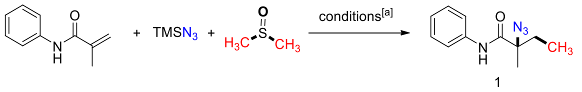
The Liu[14] group reported a copper-catalysed trifluoromethylazidation of alkenes that generated $CF_3$-containing alkyl azides. A photoredox-promoted trifluoromethylazidation of alkenes was reported by the Masson[15] group. However, an efficient protocol for the azidomethylation of alkenes has not been sufficiently well-developed. Recently, we have achieved an iron-mediated free radical α-chloro-β-methylation of *N*-arylacrylamides with dimethyl sulfoxide.[16] A key research focus of our group is the development of azidomethylations of alkenes with low-cost azide regents and methyl or trideuteromethyl sources. Based on our previous work,[17] we finally reported a free radical azidomethylation of active alkenes with azidotrimethylsilane and dimethyl sulfoxide under conditions analogous to those used for the Fenton reaction[18] (Scheme 1).



**Scheme 1.** Azidomethylation or Azidotrideuteromethylation of Activated Alkenes.

Initially, azidotrimethylsilane, dimethyl sulfoxide and *N*-phenylmethacrylamide were selected as the model substrates to optimize the reaction system (Table 1, also see the Supporting Information for details). Product 1 was obtained in 46%, 83% and 76% yields when the reaction was stopped after 1, 2 or 3 h respectively (entries **1-3**). The desired product was isolated in 67% and 70% yields when 1 and 2 equivalents of azidotrimethylsilane were added into the system, respectively (entries **4** and **5**). Both reaction temperature and concentration affected the yield of the product (entries **6-9**). The yields of the final product were reduced when we decreased the amount of hydrogen peroxide (entries **10-12**). Varying the amount and type of catalysts resulted in lower yields of the desired product (entries **13-18**). Excitingly, we found that the azidomethylation product was generated in 86% yield when ferrous sulfate heptahydrate was used as the catalyst, which makes it a better catalyst than other iron salts. The optimum conditions are N-phenylmethacrylamide (1 equiv., 0.3 mmol), azidotrimethylsilane (1.5 equiv., 0.45 mmol), dimethyl sulfoxide (3 mL), ferrous sulfate heptahydrate (0.3 equiv., 0.09 mmol) and hydrogen peroxide (30%, 5 equiv., 1.5 mmol) at 50 °C under $N_2$ for 2 h in a sealed tube.

**Table 1.** Optimization of the Standard Conditions[a].

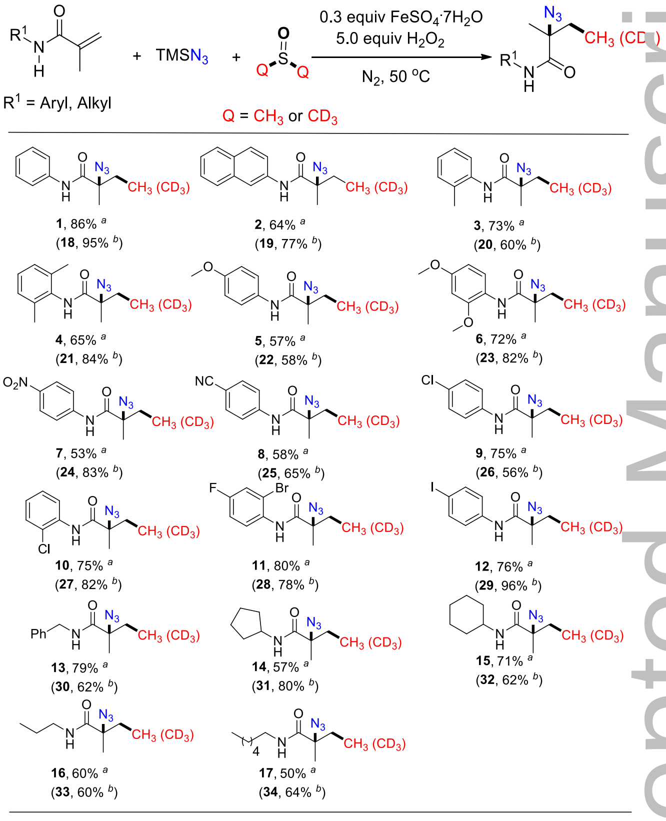


| No. | Catalyst (equiv) | $H_2O_2$ (equiv) | $TMSN_3$ (equiv) | DMSO (mL) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1[c] | $FeCl_2$ (0.3) | 5 | 1.5 | 3 | 46 |
| 2 | $FeCl_2$ (0.3) | 5 | 1.5 | 3 | 83 |
| 3[d] | $FeCl_2$ (0.3) | 5 | 1.5 | 3 | 76 |
| 4 | $FeCl_2$ (0.3) | 5 | 1 | 3 | 67 |
| 5 | $FeCl_2$ (0.3) | 5 | 2 | 3 | 70 |
| 6[e] | $FeCl_2$ (0.3) | 5 | 1.5 | 3 | 77 |
| 7[f] | $FeCl_2$ (0.3) | 5 | 1.5 | 3 | 67 |
| 8 | $FeCl_2$ (0.3) | 5 | 1.5 | 1 | 58 |
| 9 | $FeCl_2$ (0.3) | 5 | 1.5 | 2 | 77 |
| 10 | $FeCl_2$ (0.3) | 2 | 1.5 | 3 | 52 |
| 11 | $FeCl_2$ (0.3) | 3 | 1.5 | 3 | 67 |
| 12 | $FeCl_2$ (0.3) | 4 | 1.5 | 3 | 76 |
| 13 | $FeCl_2$ (0.1) | 5 | 1.5 | 3 | 58 |
| 14 | $FeCl_2$ (0.2) | 5 | 1.5 | 3 | 61 |
| 15 | $FeCl_2$ (0.4) | 5 | 1.5 | 3 | 67 |
| 16 | $FeF_3$ (0.3) | 5 | 1.5 | 3 | 40 |
| **17** | **$FeSO_4·7H_2O$** (0.3) | **5** | **1.5** | **3** | **86** |
| 18 | FeS (0.3) | 5 | 1.5 | 3 | 40 |

[a] Reaction conditions: *N*-phenylmethacrylamide (1 equiv., 0.3 mmol), 50 °C, $N_2$, 2 h. [b] Isolated yields. [c] 1 h. [d] 3 h. [e] 25 °C. [f] 80 °C.

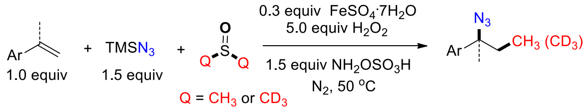
The substrate scope under the standard conditions is shown in Table 2. Both dimethyl sulfoxide and deuterated dimethyl sulfoxide could act as effective methyl sources in the reaction system (**1**-**34**). *N*-phenyl- and *N*-naphthyl-substituted acrylamides gave the corresponding azidomethylation or azidotrideuteromethylation products in 64-95% yields (**1**, **2**, **18** and **19**). The 2-methyl-, 4-methoxyl-, 2,6-dimethyl- and 2,4-dimethoxyl-substituted substrates were all well-tolerated in the reaction and afforded the desired products in good yields, which showed that steric effects had only a small impact on the reaction system (**3**-**6** and **20**-**23**). The effects of the electronic demands of the substituents were not obvious, and various acrylamides modified with electron-withdrawing or electron-donating groups gave the corresponding products in 53-83% yields (**5**-**8** and **22**-**25**). The substrates with halogen substituents, such as F, Cl, Br and I, provided the desired products in moderate to high yields (**9**-**12** and **26**-**29**). Notably, *N*-alkylacrylamides were also tolerated in the reaction system and afforded products **13**-**17** and **30**-**34** in 50-80% yields.

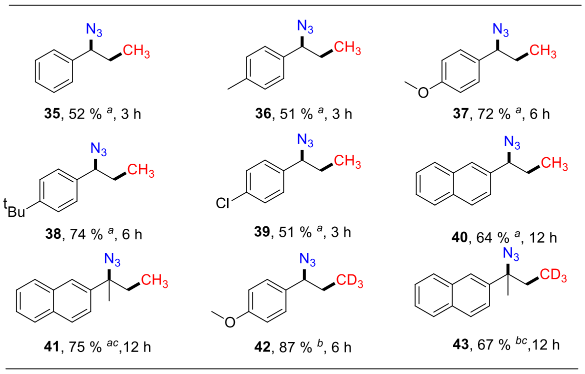
**Table 2.** Azidomethylation or Azidotrideuteromethylation of Acrylamides.



[a]Reaction conditions: acrylamide (1 equiv., 0.3 mmol), $TMSN_3$ (1.5 equiv., 0.45 mmol), DMSO (3 mL), $FeSO_4·7H_2O$ (0.3 equiv., 0.09 mmol), hydrogen peroxide (5 equiv., 1.5 mmol), 50 °C, $N_2$, 2 h, isolated yields. [b]Reaction conditions: acrylamide (1 equiv., 0.3 mmol), $TMSN_3$ (1.5 equiv., 0.45 mmol), DMSO-$d_6$ (1 mL), $FeSO_4·7H_2O$ (0.3 equiv., 0.09 mmol), hydrogen peroxide (5 equiv., 1.5 mmol), 50 °C, $N_2$, 3 h, isolated yields.

**Table 3.** Azidomethylations of Styrenes.

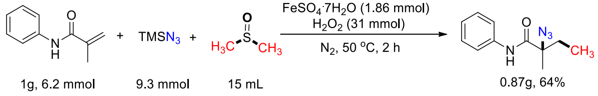




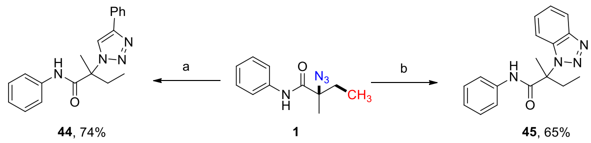
[a] Reaction conditions: styrene (1 equiv., 0.3 mmol), $TMSN_3$ (1.5 equiv., 0.45 mmol), $NH_2OSO_3H$ (1.5 equiv., 0.45 mmol), DMSO (2 mL), $FeSO_4·7H_2O$ (0.3 equiv., 0.09 mmol), hydrogen peroxide (5 equiv., 1.5 mmol), 50 °C, $N_2$, isolated yields. [b] DMSO-$d_6$ (1 mL) instead of DMSO, isolated yields. [c] No $NH_2OSO_3H$ was added to the system.

Styrenes were also well-tolerated in the reaction system. Styrene provided product **35** in 52% yield. The 4-methyl-, 4-methoxyl-, 4-tert-butyl- and 4-chloro-substituted styrenes all reacted efficiently and afford the corresponding products in 51-74% yields (**36-39**). 2-Vinylnaphthalene and 2-(prop-1-en-2-yl)naphthalene could undergo azidomethylation or azidotrideuteromethylation and provide the desired products in good yields (**40-41** and **43**). When 4-methoxystyrene was reacted with deuterated dimethyl sulfoxide, product **42** was isolated in 87% yield.

Meanwhile, the reaction could be conveniently scaled up to the gram level, and it afforded product **1** in 64% yield (Scheme 2). We also carried out some transformations to verify the practical applicability of the azidomethylation adducts. Product 1 was reacted with phenyl acetylene to generate triazole **44** in 74% yield (Scheme 3a). Triazole **45** was prepared in 65% yield via the corresponding transformation reaction (Scheme 3b).

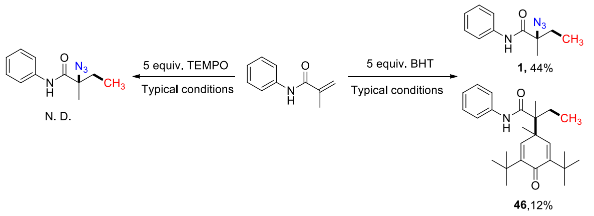


**Scheme 2.** Gram-Scale Synthesis of Product 1.

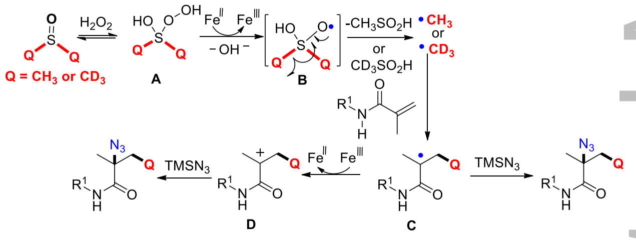


**Scheme 3.** Transformation Reactions of Product 1. Reaction conditions: (a) phenyl acetylene (2 equiv.), CuI (0.2 equiv.), $Et_3N$ (2 equiv.), $CH_3CN$ (3 mL), 25 °C, 3 h; (b) 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (2 equiv.), CsF (0.5 equiv.), $CH_3CN$ (3 mL), 70 °C, 68 h.

Control experiments were conducted to elucidate the reaction mechanism (Scheme 4). When TEMPO was added to the system, there was no reaction. Intermediate **C** was successfully captured by BHT and formed product **46** in 12% yield, which suggested that a free radical was involved in the reaction mechanism. Based on experimental date and previous studies,[16, 17d, 19] a plausible mechanism was proposed as described in Scheme 5. First, hydrogen peroxide reacted with dimethyl sulfoxide and produced intermediate **A**. A hydroxy ion and free radical **B** were prepared from **A** via a heterolysis reaction. Next, **B** underwent β-cleavage to form a methyl free radical and the by-product, methylsulfinyl acid. Then, the methyl free radical added to the double bond of the acrylamide to generate new carbon-centred free radical **C**, which was captured by BHT. Finally, the desired product was prepared from the reaction of **C** with azidotrimethylsilane. Intermediate **C**, which could be oxidized by Fe(III), afforded carbocation **D**, and the final product was generated from the reaction of azidotrimethylsilane with **D**.



**Scheme 4.** Control Experiments.



**Scheme 5.** Plausible Mechanism.

In conclusion, a free radical-based azidomethylation of activated alkenes with azidotrimethylsilane and dimethyl sulfoxide has been developed. It offers a convenient, low-cost and mild method for preparing organic azides. This protocol can be scaled up, and the products can be subjected to other useful transformations. Further studies on azidomethylation reactions and applications of azidomethylated products are ongoing in our laboratory.

# Experimental Section

### *General Experimental Procedure for the Reaction*

A mixture of acrylamide (1 equiv., 0.3 mmol), $TMSN_3$ (1.5 equiv., 0.45 mmol), DMSO (3 mL), $FeSO_4·7H_2O$ (0.3 equiv., 0.09 mmol), and $H_2O_2$ (5 equiv., 1.5

mmol) was stirred at 50°C in a sealed tube (15 mL) under nitrogen for 2 h. When the reaction was finished, the mixture was extracted with water and ethyl acetate, condensed under vacuum and purified by column chromatography to afford the final product.

The mixture of acrylamide (1 equiv., 0.3 mmol), $TMSN_3$ (1.5 equiv., 0.45 mmol), DMSO-$d_6$ (1 mL), $FeSO_4{\cdot}7H_2O$ (0.3 equiv., 0.09 mmol), and $H_2O_2$ (5 equiv., 1.5 mmol) was stirred under the standard conditions. After the reaction was finished, the desired product was isolated by the same work-up procedure.

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**COMMUNICATION**

# Iron-Mediated Azidomethylation or Azidotrideuteromethylation of Active Alkenes with Azidotrimethylsilane and Dimethyl Sulfoxide

*Adv. Synth. Catal.* **Year**, *Volume*, Page – Page

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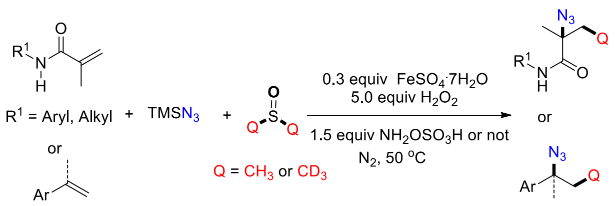

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