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# Iron-Catalyzed Chemoselective Azidation of Benzylic Silyl Ethers

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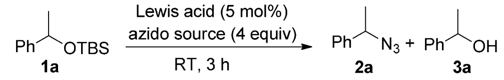
Silyl ethers are traditionally used for the protection of alcohols and are stable in the presence of most nucleophiles, owing to the low leaving-group ability of the siloxy groups.[1] Carbon nucleophiles, such as allylsilanes[2] and enol acetates,[3] can react with silyl ethers in the presence of suitable Lewis acids. Furthermore, the bromination, thiocyanation, and isothiocyantion of silyl ethers in an ionic liquid were also developed.[4] Although azides are important because, for example, they can be transformed into triazoles by the Huisgen reaction[5] and into amines by reduction,[6] there are only a few methods for the azidation of silyl ethers; this transformation can be accomplished by the use of $n\mathrm{Bu_4NN_3}$ as an azido source in the presence of $\mathrm{PPh_3}$ and either 2,3-dichloro-5,6-dicyanobenzoquinone[7] or 2,4,6-trichloro[1,3,5]triazine.[8] In these reports, nonprotected (free) alcohols[9] are more reactive than silyl ethers toward nucleophilic attack of the azide anion and primary alcohols are preferentially converted into the corresponding primary azido products in the presence of secondary and tertiary alcohols. We now demonstrate a novel iron-catalyzed azidation of silyl ethers, the reaction conditions allowing chemoselective transformation of secondary and tertiary benzylic silyl ethers in the presence of primary benzylic silyl ethers. Moreover, secondary and tertiary benzylic silyl ethers undergo azidation more efficiently relative to that of the corresponding free benzylic alcohols, and many reactive functional groups, such as alkyl chlorides,[10] α,β-unsaturated esters,[11] and aldehydes,[12] were stable under the azidation conditions.

Our research group has been focusing on the development of an efficient method for preparing pharmaceutically useful azido derivatives[13] and we wondered whether the direct azidation of silyl ethers, which are normally stable under nucleophilic-substitution conditions, was possible. Fortunately, $\mathrm{AuCl_3}$ (5 mol %) facilitated the desirable azidation of 1-phenylethanol TBS ether (**1a**) in the presence of 4 equivalents of $\mathrm{TMSN_3}$ in $\mathrm{(CH_2Cl)_2}$ at room temperature (Table 1, entry 1). $\mathrm{FeCl_3}$ and $\mathrm{FeBr_3}$, which are cheaper and more common Lewis acids, were found to be suitable catalysts (Table 1, entries 2 and 3), whereas the reaction using either $\mathrm{FeCl_2}$, $\mathrm{Fe(OAc)_2}$, $\mathrm{InCl_3}$, $\mathrm{AuCl_3}$, TMSOTf, or TFA as a catalyst gave no reaction or inefficient transformations.[14] Chlorinated solvents, such as $\mathrm{CH_2Cl_2}$, $\mathrm{CHCl_3}$, and $\mathrm{(CH_2Cl)_2}$, were more effective than either toluene or THF.[14] The azidation reaction was most efficient when conducted in $\mathrm{(CH_2Cl)_2}$ (Table 1, entries 2, and 5–7). Furthermore, $\mathrm{TMSN_3}$ was a more effective azide source than either $\mathrm{NaN_3}$ or DPPA (Table 1, entries 8 and 9).

Table 1. Azidation of benzylic *sec*-TBS ether (**1a**).



| Entry | Azido source | Lewis acid | Solvent | Yield of **1a**/**2a**/**3a** [%][a] |
|---|---|---|---|---|
| 1 | $\mathrm{TMSN_3}$ | $\mathrm{AuCl_3}$ | $\mathrm{(CH_2Cl)_2}$ | 78/20/0 |
| 2 | $\mathrm{TMSN_3}$ | $\mathrm{FeCl_3}$ | $\mathrm{(CH_2Cl)_2}$ | 15/78/0 |
| 3 | $\mathrm{TMSN_3}$ | $\mathrm{FeBr_3}$ | $\mathrm{(CH_2Cl)_2}$ | 5/75/0 |
| 4 | $\mathrm{TMSN_3}$ | TMSOTf | $\mathrm{(CH_2Cl)_2}$ | 25/48/14 |
| 5 | $\mathrm{TMSN_3}$ | $\mathrm{FeCl_3}$ | $\mathrm{CH_2Cl_2}$ | 46/46/0 |
| 6 | $\mathrm{TMSN_3}$ | $\mathrm{FeCl_3}$ | $\mathrm{CHCl_3}$ | 20/68/0 |
| 7 | $\mathrm{TMSN_3}$ | $\mathrm{FeCl_3}$ | toluene | 62/19/0 |
| 8 | $\mathrm{NaN_3}$ | $\mathrm{FeCl_3}$ | $\mathrm{(CH_2Cl)_2}$ | 55/21/24 |
| 9 | DPPA | $\mathrm{FeCl_3}$ | $\mathrm{(CH_2Cl)_2}$ | complex mixture |

[a] Yield was determined by $^1$H NMR spectroscopy. DPPA = diphenylphosphoryl azide, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

The substrate scope was next examined (Table 2).[15] Whereas the azidation of TBS, TES, and TIPS ethers derived from 1-phenylethanol (**1a–c**) required a large excess (4 equivalents) of $\mathrm{TMSN_3}$ and long reaction times (3–6 hours) to complete the reaction (Table 1 and Table 2; entries 1 and 2), the azidation of the corresponding TMS ether (**1d**), which is less sterically hindered, was complete within 30 minutes when **1d** was treated with 5 mol % of $\mathrm{FeCl_3}$ and only 1.1 equivalents of $\mathrm{TMSN_3}$, thus affording **2a** in good yield (Table 2, entry 3). Notably, when the nonprotected alcohol (**3a**) was treated under the same reaction conditions (Table 2, entry 3), a longer reaction time was necessary and **2a** was obtained in a very low yield (28 %) together with the generation of dimeric compound **4** as the main product [Eq. (1)]. This result suggests that the present azidation does not proceed by the deprotection of **1a** to give **3a**. **1e**

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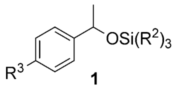
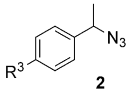
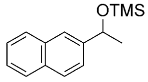
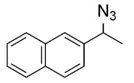
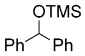
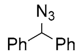
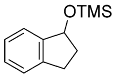
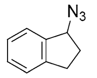
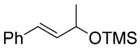
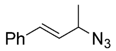
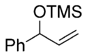
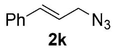
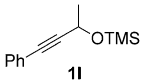
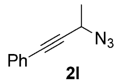
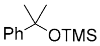
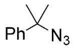
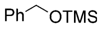
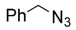
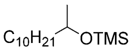
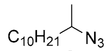
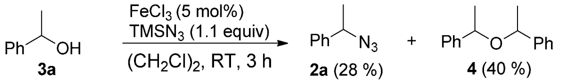
Table 2. Scope and limitations.[a]

$$\underset{\mathbf{1}}{\mathrm{R^1\text{-}OSi(R^2)_3}} \xrightarrow[\mathrm{(CH_2Cl)_2,\ RT}]{\mathrm{FeX_3\ (5\ mol\%)},\ \mathrm{TMSN_3\ (1.1\ equiv)}} \underset{\mathbf{2}}{\mathrm{R^1\text{-}N_3}}$$

| Entry | Substrate | Product | X | $t$ [min] | Yield [%] |
|---|---|---|---|---|---|
| |  **1** |  **2** | | | |
| 1[b] | **1b**: $R^3=H$<br>$Si(R^2)_3=TES$ | **2a**: $R^3=H$ | Br | 180 | 48 |
| 2[b] | **1c**: $R^3=H$<br>$Si(R^2)_3=TIPS$ | **2a**: $R^3=H$ | Br | 360 | 71 |
| 3 | **1d**: $R^3=H$<br>$Si(R^2)_3=TMS$ | **2a**: $R^3=H$ | Cl | 30 | 71 |
| 4 | **1e**: $R^3=MeO$<br>$Si(R^2)_3=TMS$ | **2e**: $R^3=MeO$ | Cl | 15 | 88 |
| 5 | **1f**: $R^3=Cl$<br>$Si(R^2)_3=TMS$ | **2f**: $R^3=Cl$ | Br | 60 | 79 |
| 6 |  **1g** |  **2g** | Cl | 10 | 96 |
| 7 |  **1h** |  **2h** | Cl | 15 | >99 |
| 8 |  **1i** |  **2i** | Cl | 10 | 96 |
| 9 |  **1j** |  **2j** | Cl | 45 | 99 |
| 10 |  **1k** |  **2k** | Br | 120 | 74 |
| 11[c] |  **1l** |  **2l** | Br | 240 | 69 |
| 12 |  **1m** |  **2m** | Cl | 360 | 99 |
| 13 |  **1n** |  **2n** | Br | 180 | trace |
| 14 |  **1o** |  **2o** | Br | 180 | trace |

[a] Reactions were performed using $FeCl_3$ or $FeBr_3$ as the catalyst. Since similar yields were obtained using both catalysts, the better results are described in Table 2. [b] 4 equiv of $TMSN_3$ was used. [c] 35 mol% of $FeBr_3$ and 2 equiv of $TMSN_3$ were used.



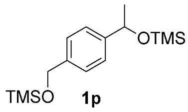
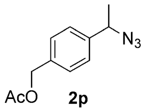
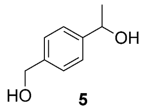
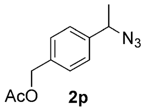
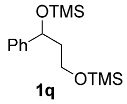
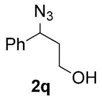
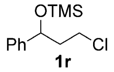
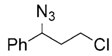
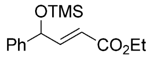
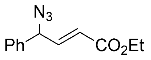
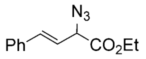
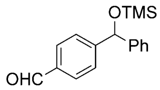
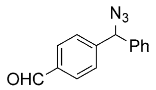
(1)

and **1f** bearing electron-donating and electron-withdrawing groups, respectively, on the aromatic ring and TMS ethers derived from 1-naphthylethanol, diphenylmethanol, and 1-indanol (**1g–i**) efficiently underwent the azidation with high yields (Table 2, entries 4–8). TMS ethers derived from allyl and propargyl alcohols (**1j–l**) could also be used as substrates to afford the corresponding allylic and propargyl azides (**2j–l**), in which the double bond is in the more thermodynamically stable position, that is, in conjugation with the phenyl group (Table 2, entries 9–11). The reaction was also applicable to the TMS ether derived from tertiary benzylalcohol **1m** (Table 2, entry 12), whereas primary benzyl TMS ether **1n** and nonbenzylic secondary alkyl alcohol TMS ether **1o** were inactive toward the azidation probably because of the lower stability of the corresponding benzyl cations that are formed upon elimination of the siloxy group. Encouraged by these results, the chemoselectivity of the transformation was investigated by using a substrate containing both a primary and a secondary silyl ether (Table 3; entries 1 and 3).

When **1p**, which contains both a primary and a secondary silyl ether, was subjected to the reaction conditions (5 mi-

Table 3. Chemoselective azidation.[a]

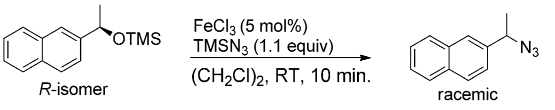
$$\underset{\mathbf{1}}{\mathrm{R\text{-}OTMS}} \xrightarrow[\mathrm{(CH_2Cl)_2,\ RT}]{\mathrm{FeX_3\ (5\ mol\%)},\ \mathrm{TMSN_3\ (1.1\ equiv)}} \underset{\mathbf{2}}{\mathrm{R\text{-}N_3}}$$

| Entry | Substrate | Product | X | $t$ [min] | Yield [%] |
|---|---|---|---|---|---|
| 1[b] |  |  | Br | 5 | 90 |
| 2[b] |  **5** |  **2p** | Cl | 120 | 53 |
| 3[c] |  **1q** |  **2q** | Br | 30 | 82 |
| 4 |  **1r** |  **2r** | Br | 5 | 77 |
| 5[d] |  **1s** |  **2sa**<br> **2sb** | Cl | 60 | 66<br>27 |
| 6[e] |  **1t** |  **2t** | Br | 20 | 68 |

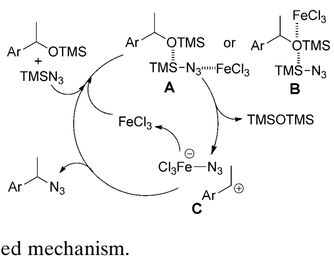
[a] Reactions were performed using either $FeCl_3$ or $FeBr_3$ as the catalyst. Because the use of these catalysts led to similar yields, the better results are described. [b] The product was isolated after acetylation of the resulting primary benzyl alcohol moiety resulting from the deprotection of the primary benzylic TMS ether during the reaction. [c] 20 mol% of $FeBr_3$ and 2 equiv of $TMSN_3$ were used at 0 °C; because there was partial desilylation of the primary TMS ether during the reaction, the reaction was quenched by the addition of TBAF so as to ensure complete conversion into the alcohol product (**2q**). [d] The reaction was carried out using 7 mol% of $FeCl_3$ and 1.5 equiv of $TMSN_3$. [e] The reaction was carried out using 10 mol% of $FeCl_3$ and 2 equiv of $TMSN_3$ at 0 °C.

nutes, room temperature), only the secondary benzylic TMS ether moiety was transformed into the azido group, thus giving **2p** in good yield.[16] However, the azidation of nonsilylated substrate **5** resulted in a lower yield of product and required a longer reaction time (2 hours) for the total consumption of **5** (Table 3, entries 1 and 2). Additionally, **1q** was also chemoselectively converted into the secondary azido product (**2q**) in a modest yield (Table 3, entry 3). Alkylhalides, α,β-unsaturated esters, and aldehydes are easily converted into the corresponding alkylazides, β-azido esters, and nitriles, respectively, when treated with azide anion.[6,10–12] However, substrate **1r**, which bears an alkylchloride moiety, chemoselectively underwent the azidation at the secondary benzylic TMS ether moiety to give the corresponding benzylic azide (**2r**) (Table 3, entry 4). Moreover, **1s**, which contains both an allylalcohol TMS ether and an α,β-unsaturated ester substructure, was transformed into a mixture of α- and γ-azidated esters (**2sa** and **2sb**) as an isomeric mixture resulting from the chemoselective azidation associated with the elimination of the siloxy moiety (Table 3, entry 5). Although **2sa** and **2sb** were separated by silica-gel column chromatography, each isolated product (**2sa** and **2sb**) underwent smooth isomerization into the other isomer by the rapid rearrangement of the allylic azide group. The conversion of the aromatic aldehyde moiety of **1t** into a nitrile could be prevented by conducting the azidation reaction at 0°C and the azidated product (**2t**) was obtained in a good yield (Table 3, entry 6).

When a solution of **1e** in $CDCl_3$ in the presence of 5 mol% of $FeCl_3$ and 1 equivalent of $TMSN_3$ at room temperature, as aged for a period of 15 minutes, was analyzed using $^{29}Si$ NMR spectroscopy, it was shown that hexamethyldisiloxane (TMSOTMS, 7.33 ppm) was formed as the reaction progressed.[17] When an enantiomerically pure sample of a benzylic TMS ether was subjected to the azidation conditions, the resulting benzylic azide was obtained in racemic form [Eq. (2)], thus revealing that the azidation proceeds via a carbocation intermediate (Scheme 1, **C**). The proposed mechanism is shown in Scheme 1. The oxygen atom of the silyl ether could be either activated by coordination to both Lewis acids or by coordination to a complex of the Lewis acids, $TMSN_3$ and $FeCl_3$ (intermediates **B** and **A**, respectively).[18,19] The corresponding carbocation species (**C**), which is generated upon elimination of TMSOTMS, reacts with azide anion to give the benzylic azido product.[20]



(2)



Scheme 1. Proposed mechanism.

In conclusion, we have shown that benzylic silyl ethers undergo efficient azidation using $TMSN_3$ in the presence of $FeCl_3$ as a general, cheap, and safe Lewis acid. The present azidation occurs smoothly under mild reaction conditions and in short reaction times to give the azido products in high yield. Moreover, the reaction is chemoselective, in that secondary and tertiary benzyl silyl ethers are transformed selectively in the presence of primary benzyl silyl ethers, and alkyl chloride, α,β-unsaturated ester, and aldehyde moieties are stable under the reaction conditions.

## Experimental Section

**Typical procedure for the azidation**: To a solution of silylether (0.2 mmol) in $(CH_2Cl)_2$ (0.2 M: 1 mL) was added trimethylsilylazide (0.22 mmol) and either $FeCl_3$ or $FeBr_3$ (0.01 mmol: 5 mol% with respect to the substrate) at room temperature under argon. After stirring the reaction mixture until the substrate was completely consumed, as determined by TLC analysis, water was added to the reaction mixture and the resulting mixture was extracted with $CH_2Cl_2$. The combined organic layer was dried with $Na_2SO_4$, and concentrated in vacuo. The residue was purified by silica-gel column chromatography using cyclohexane/EtOAc (10:1) as the eluent.

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**Keywords:** azides · chemoselectivity · ethers · homogeneous catalysis · iron

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[14] Details of the optimization of reaction conditions using other acids and solvents are shown in the Supporting Information.

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[16] The silylated primary alcohol was deprotected during the aqueous work-up and the obtained free alcohol could not be isolated from the reaction mixture, which contained indeterminable side products. Therefore, **2p** was isolated as an acetate through acetylation.

[17] An $^{29}$Si NMR spectrum of a solution of **1e** in the presence of 5 mol% of FeCl$_3$ and 1 equiv of TMSN$_3$ at RT, as aged for a period of 15 minutes, is shown in the Supporting Information.

[18] The formation of the combined Lewis acid derived from TMSCl and InCl$_3$ was suggested in Ref. [3].

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