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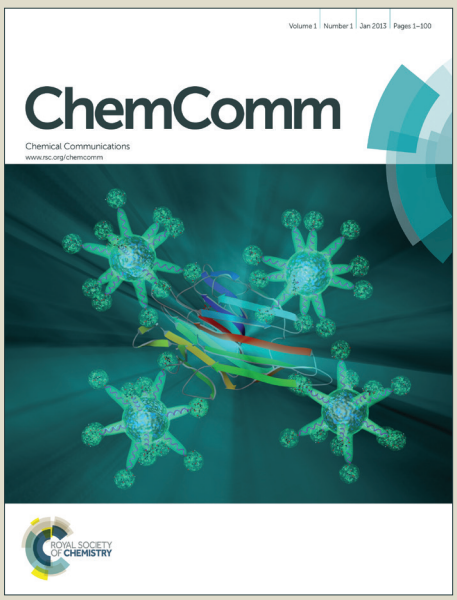

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Radical Aminooxygenation of Alkenes with *N*-fluoro-benzenesulfonaminde (NFSI) and TEMPONa

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Reaction of various alkenes with commercially available *N*-fluorobenzenesulfonimide (NFSI) and TEMPONa provides the corresponding aminooxygenation products in moderate to good yields. Single electron transfer from readily generated TEMPONa to NFSI allows for clean generation of the corresponding bissulfonylamidyl radical along with TEMPO. N-radical addition to an alkene and subsequent TEMPO trapping provides the corresponding aminooxygenation product.

Chemistry comprising C-centered radicals is very abundant.[1] However, radical transformations occurring *via* N-centered radicals have received far less attention in synthesis.[2,3] In most cases, N-centered radicals are generated *via* cleavage of a reactive N-X bond.[2] Along these lines, the commercially availables *N*-fluorobenzenesulfonimide (NFSI)[4] is an interesting reagent. In fact, initially introduced for electrophilic fluorination[4] it has more recently been shown that NFSI also engages in radical transformations. Fluorination of alkyl radicals by NFSI was disclosed by Sammis et al.[5] Zhang and coworkers found that NFSI in combination with CuCl allows for radical amidation of benzylic CH bonds.[6] The same group later presented Cu-catalyzed radical-type vicinal aminocyanation[7a] and aminofluorination[7b] with NFSI as the amine donor. Kanai et al.[8] and we[9] further explored Cu-catalyzed radical amination of alkenes by using NFSI as a reagent and direct radical arene amidations with NFSI have also been reported.[10]

We have recently initiated a program towards vicinal radical difunctionalization of alkenes and already disclosed azidooxygenation,[11a] oxyarylation,[11b] trifluoromethylamin-oxylation,[11c] hydroxyarylation[11d] and aminoazidation.[9]

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† Electronic Supplementary Information (ESI) available: Experimental procedures and spectral data for all compounds. CCDC reference number 1043955 (**2q**).

In some of these cases the readily prepared TEMPONa salt[11a-c] (TEMPO, 2,2,6,6-tetramethylpiperidine-N-oxyl radical)[12] was used as an organic single electron transfer (SET) reducing reagent. NFSI has a reduction potential of E° = -0.78 versus SCE[13] and therefore it is expected that NFSI is readily reduced by TEMPONa.

Based on these facts, we planned to develop a radical alkene aminooxygenation[14] with NFSI and TEMPONa as reagents. The novel approach is presented in Scheme 1. TEMPONa first reduces NFSI to generate NaF, the bisulfonamidyl radical along with TEMPO. N-radical addition to the alkene followed by trapping of the adduct radical with TEMPO will afford the targeted aminooxygenation product. Notably, selective cross coupling of the adduct radical with TEMPO is controlled by the Persistent Radical Effect which describes the highly selective cross coupling between a persistent and a transient radical.[15]

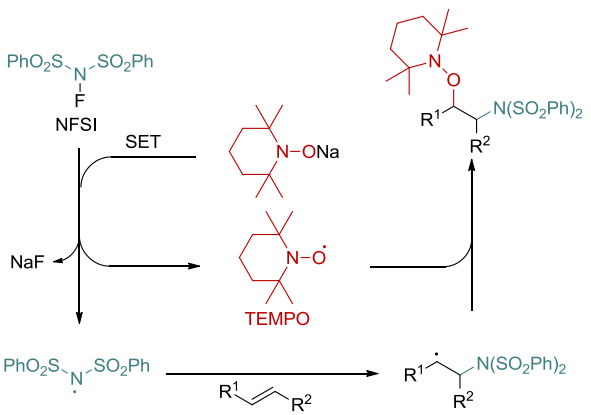
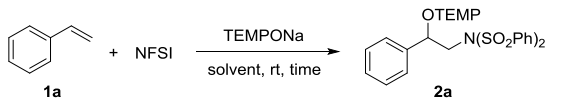


Figure 1 Radical alkene aminooxygenation.

Initial experiments were conducted with styrene as a radical acceptor. Styrene (5 equiv) and NFSI (1 equiv) were dissolved in DCM and a freshly prepared THF solution of TEMPONa (1.2 equiv,

see Supporting Information) was slowly added over 4 h at room temperature *via* syringe pump. Pleasingly, the targeted aminooxygenation product **2a** was isolated in 46% yield (Table 1, entry 1). Reaction in THF was less efficient but in $PhCF_3$[16] a slightly improved yield was obtained (entries 2, 3). We then decided to use TEMPONa and NFSI in excess (3 equiv each) and noted an improved yield (55%, entry 4). Diluting the TEMPONa solution gave a worse result (entry 5) and the best yield was achieved upon extending reaction time to 6 h (90%, entry 6). We assumed that due to a low TEMPO concentration during reaction telomerization might occur to some extent. Therefore, a small amount of TEMPO (0.05 equiv) was added. However, yield dropped to 65% (entry 7). Lowering concentration and amount of reagents or increasing reaction time did not lead to a higher yield (entries 8-11).

Table 1 Optimization studies.



1a 2a

entry	TEMPONa (equiv)[a]	NFSI (mol%)	solvent	Time (h)	yield[b] (%)
1[c]	1.2	1.0	DCM	4	46
2[c]	1.2	1.0	THF	4	41
3[c]	1.2	1.0	$PhCF_3$	4	47
4	3.0	3.0	$PhCF_3$	4	55
5	3.0[d]	3.0	$PhCF_3$	4	51
6	**3.0**	**3.0**	**$PhCF_3$**	**6**	**90**
7[e]	3.0	3.0	$PhCF_3$	6	65
8[f]	2.0[d]	1.0	$PhCF_3$	6	59
9[f]	2.0[d]	2.0	$PhCF_3$	6	52
10	2.0[d]	2.0	$PhCF_3$	6	55
11	2.0[d]	2.0	$PhCF_3$	15	70

[a]TEMPONa soulution in THF (1.7 molar) used. [b]Isolated yield. [c]Styrene (5 equiv) used. [d]TEMPONa solution in THF (0.85 molar) used. [e]TEMPO (0.05 equiv) was added. [f]Styrene (2 equiv) used.

Under optimized conditions (Table 1, entry 6) scope and limitation of the radical aminooxygenation were explored by testing alkenes **1b-t**. Reaction of *ortho*, *meta* and *para*-methyl substituted styrene worked well and the corresponding products **2b-d** were isolated in good yields (66-70%, Scheme 2). As expected, the *para*-*tert*-butyl-styrene and *para*-vinyl-biphenyl were also good substrates (see products **2e**,**f**). However, a significantly lower yield was achieved in the transformation of β-vinyl-naphthalene to **2g**. Aminooxygenation of halogenated styrene derivatives was efficient and TEMPO-adducts **2h-k** were obtained in 60-73% isolated yields. The CF_3-derivative **1l** delivered a lower yield of product **2l**.

We were very pleased to observe that also unactivated aliphatic alkenes undergo radical aminooxygenation as shown by the successful preparation of compounds **2m** and **2n**. The bissulfonylamidyl radical generated from NFSI is an electrophilic amidyl radical. Therefore, reaction should be particularly efficient with electron-rich alkenes. In fact, aminooxygenation of vinyl ether **1o** provided **2o** in 77% yield. In this case we added a small amount of TEMPO (0.05 equiv) to suppress telomerization. As expected, reaction with the electron-poor methyl acrylate did not work and the targeted product **2p** was not identified in the reaction mixture.

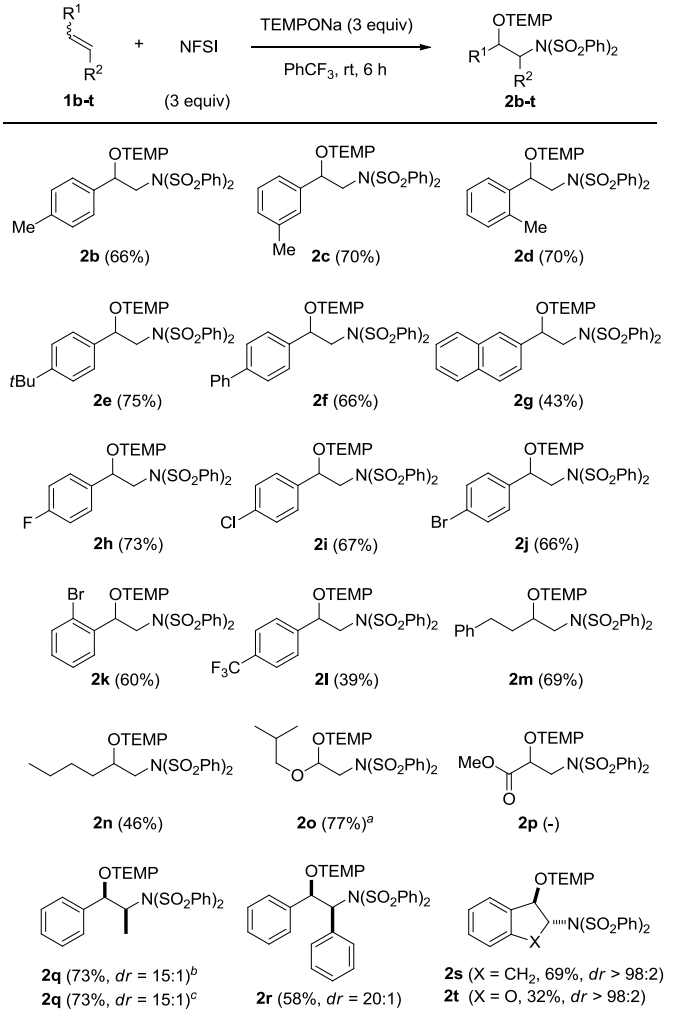


Figure 2 Aminooxygenation of various alkenes. [a]Conducted in the presence of TEMPO (0.05 equiv). [b]With *trans*-β-methyl styrene. [c]With *cis*-β-methyl styrene.

We also investigated the diastereoselectivity of the aminooxygenation and found *trans*-β-methyl-styrene to react in good yield (73%) and good diastereoselectivity (*dr* = 15:1) to **2q**. The relative configuration for **2q** was unambiguously assigned by X-ray crystallography (Figure 3).[17] It is obvious for a radical process that *cis*-β-methyl-styrene provided **2q** with the same selectivity.

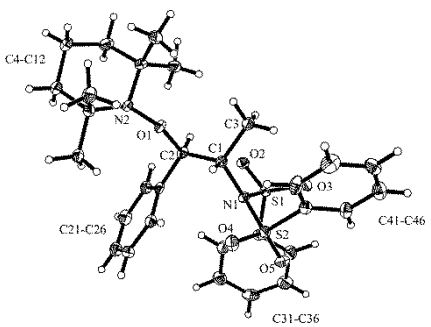


Figure 3 Crystal structure of compound **2q**. (Thermals ellipsoids are shown with 50% probability).

trans-Stilbene was converted to **2r** which was obtained in good yield and very high selectivity (*dr* = 20:1). The relative configuration of the major isomer of **2r** was assigned in analogy to **2q**. Excellent stereocontrol was also achieved in the transformation of indene and **2s** was isolated as a single diastereoisomer in 69% yield. Dearomatizing vicinal bisfunctionalization of benzofuran to give **2t** is possible with the new method. Notable, reaction occurred with complete stereocontrol and regiocontrol, albeit in moderate yield.

We next investigated whether tertiary alkoxyamines can be prepared *via* this novel route. To this end, 2-substituted alkenes were reacted under optimized conditions. Surprisingly, in the transformation of 2-ethyl-butene (**3a**) the targeted aminooxygenation compound was not identified and bissulfonamide **4a** was isolated in good yield (75%) and complete *E*-selectivity (Figure 4). This alkene derives from the tertiary alkoxyamine which under the applied reaction conditions undergoes regio- and stereoselective TEMPOH elimination to give **4a**. In analogy, alkenes **4b-d** were obtained *via* aminooxygenation and subsequent TEMPOH elimination. TEMPOH elimination to **4c** occurred with complete regioselectivity. However, in case of **4d** along with the allylamide also the enamide **4d'** was formed.[18]

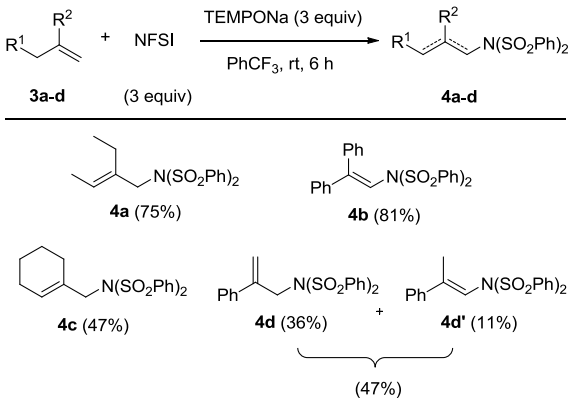


Figure 4 Allylic and vinylic amidation.

Finally, to show the synthetic value of our new method, we investigated follow-up chemistry on aminooxygenation product **2a** (Figure 5). N-O bond cleavage in **2a** was readily achieved with Zn under mild conditions (rt) to give alcohol **5** in a quantitative yield (99%). *meta*-Chloroperbenzoic acid (MCPBA) mediated oxidation of **2a** in CH_2Cl_2 provided ketone **6** in excellent yield (89%) and β-amidoethylbenzene **7** was obtained by a radical deoxygenation reaction (96%).[11b] Treatment of **2a** with Mg in HOAc/NaOAc/DMF according to a literature procedure[19] gave sulfonamide **8** in quantitative yield.

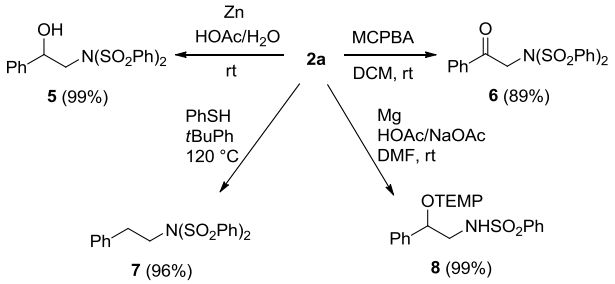


Figure 5 Follow-up chemistry.

In summary, we have shown that readily prepared TEMPONa efficiently reduces NFSI to generate the corresponding bissulfonamidyl radical along with TEMPO. If reduction is conducted in the presence of an alkene, amidyl radical addition followed by TEMPO trapping provides the vicinal aminooxygenation products in moderate to good yields. Vicinal radical bisfunctionalization works on electron-rich alkenes whereas electron-poor radical acceptors, such as methyl acrylate, did not provide the aminooxygenation compounds. With 1,2-disubstituted alkenes good to excellent diastereoselectivities can be achieved. Moreover, we have shown that the aminooxygenation products can be readily further chemically manipulated. Reductive cleavage of the N-O bond of the TEMPO moiety provides the corresponding alcohol in excellent yield. C-O bond cleavage is realized quantitatively by a radical deoxygenation procedure and the TEMPO alkoxyamine entity can be oxidatively converted to the ketone functionality. If 2-substituted alkenes are used as radical acceptors, aminooxygenation products are not stable and TEMPOH elimination under the reaction conditions provides the corresponding products of an allylic or vinylic amidation.

Author Contributions

The manuscript was written by A.S.; Y.L. and M.H. ran all experiments.

Notes

The authors declare no competing financial interest.

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