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# Stereoselective Radical Azidooxygenation of Alkenes

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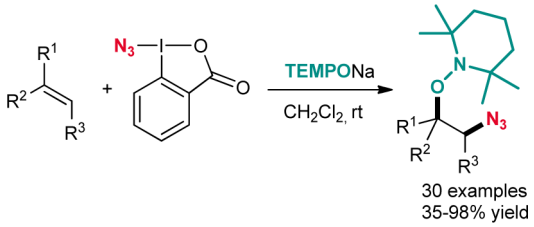
## ABSTRACT




**Radical azidooxygenation of various alkenes is described. A readily prepared $N_3$-iodine(III) reagent acts as a clean $N_3$-radical precursor. Radical generation is achieved with TEMPONa acting as a mild organic reducing reagent. The C-radical generated after $N_3$-radical addition is efficiently trapped by *in situ* generated TEMPO. Yields are good to excellent, and for cyclic systems azidooxygenation occurs with excellent diastereoselectivity.**

Organic azides are highly important compounds which have gained renewed attention due to their intensive use as coupling partners in azide/alkyne cycloaddition (*bona fide* click reaction).[1] Moreover, azides are easily transformed to amines and serve as starting materials for other useful transformations.[2] Alkyl azides are generally prepared *via* ionic substitution of alkyl halides with an inorganic azide as a nucleophile.[3] Hydroazidation of alkenes can be achieved with $HN_3$,[4a] $TMSN_3$,[4b] $TosN_3$,[4c] and $NaN_3$.[4d] Renaud nicely demonstrated the efficiency of radical chemistry for the introduction of azide functionality.[5] In these reactions, alkyl or arylsulfonyl azides were used as C-radical acceptors. However, azidation *via* a reaction of the electrophilic azidyl radical[6a] with an alkene has not been well explored. Azido-phenylselenylation was achieved by radical azidation with $PhI(OAc)_3/NaN_3$ in the presence of PhSeSePh.[6b] In polar solvents, *in situ* generated $N_3I$ reacts with alkenes to the corresponding vicinal azidoiodides *via* an ionic mechanism.[7] In apolar solvents radical type addition can be achieved as judged by the regiochemical outcome of the vicinal difunctionalization.[8] Reaction of $NaN_3$ with ceric ammonium nitrate (CAN) and an alkene was reported to give the corresponding α-azido-β-nitratoalkene likely *via* an initial azidyl radical addition.[6c,d] However, in many cases the azidyl radical was used for C-radical generation *via* H-abstraction and C–N-bond

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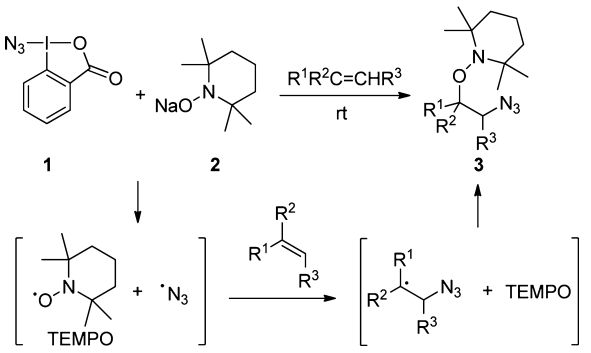
10.1021/ol402106x 

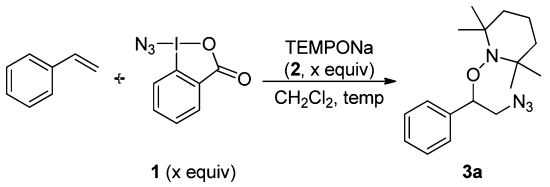
formation in such transformations occurs *via* a subsequent ionic process.[9] Herein we report radical azidooxygenation of various alkenes using azidoiodine(III) reagent **1**[10] as a $N_3$-radical precursor under mild reductive conditions (Scheme 1).[11,12]

**Scheme 1.** Radical Azidooxygenation of Alkenes




We have recently shown that the $CF_3$-radical can be cleanly generated from a $CF_3$-iodine(III) reagent (Togni reagent)[13] by single electron transfer (SET) using TEMPONa **2**[14] as an organic reducing reagent.[15] Based on that result we decided to investigate azidyl radical generation from azidoiodine(III) reagent **1** by reduction with **2**. If SET is conducted in the presence of an alkene, the $N_3$-radical should add to the alkene and the adduct radical generated will be trapped by the 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO)[16] which is formed as a byproduct in the initial SET to eventually give the azidooxygenation product **3** (Scheme 1). Selective cross-coupling of the adduct radical by TEMPO is steered by the persistent radical effect.[17]

**Table 1.** Azidooxygenation of Styrene under Various Conditions




| entry | **1** (equiv) | **2** (equiv) | time (h) | temp (°C) | yield (%)[a] |
|---|---|---|---|---|---|
| 1 | 1.5 | 1.5 | 4 | 20 | 50 |
| 2 | 2 | 2 | 4 | 20 | 57 |
| 3 | 2 | 3 | 4 | 20 | 57 |
| 4 | 3 | 2 | 4 | 20 | 56 |
| 5 | 3 | 3 | 4 | 20 | 65 |
| 6 | 3 | 3 | 3 | 20 | 53 |
| 7 | 3 | 3 | 5 | 20 | 75 |
| **8** | **3** | **3** | **6** | **20** | **94** |
| 9 | 2 | 2 | 6 | 20 | 74 |
| 10 | 2.5 | 2.5 | 6 | 20 | 90 |
| 11 | 3 | 3 | 6 | 0 | 21 |
| 12 | 3 | 3 | 6 | 40 | 93 |

[a] Isolated yields.

The reaction was optimized using styrene as a test substrate. The concentration, solvent, and stoichiometry of the reagents were systematically varied, and **3a** was isolated by purification using $SiO_2$-chromatography. Reactions were conducted by slowly adding a freshly prepared THF solution of TEMPONa (0.875 M) to a $CH_2Cl_2$ solution (0.2 M) of styrene and **1** at rt to give **3a**. Pleasingly, with 1.5 equiv of **1** and **2** each for 4 h the targeted azidooxygenation product **3a** was isolated in a promising 50% yield (Table 1, entry 1). Increasing the amount of reagents **1** and **2** led to a further improvement of the yield, and the best result was achieved upon using a 3-fold excess of **1** and **2** (Table 1, entries 2−5, 9, 10). It is likely that the *in situ* generated azidyl radical is trapped in a side reaction by TEMPO to give an unstable $N_3$-TEMPO derivative which however could not be detected by mass spectrometric analysis. We found that a 6 h reaction time is ideal for this transformation (Table 1, entries 6−8). Other solvents such as $CH_3CN$, THF, and trifluorotoluene provided lower yields (not shown), and running the reaction at a lower temperature afforded a lower yield (Table 1, entry 11). Increasing the temperature to 40 °C did not affect the yield to a large extent (Table 1, entry 12); therefore all other experiments were conducted at rt.

Under optimized conditions various terminal alkenes were tested in the radical azidooxygenation reaction to give the corresponding products **3b**−**v** (Table 2). Styrene derivatives bearing electron-donating substituents at the *para*-position afforded the azides **3c** (4-Me), **3e** (4-*t*-Bu),

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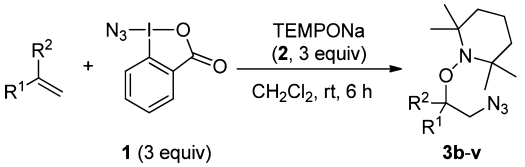
and **3f** (4-MeO) in good to excellent yields (85–98%, Table 2, entries 1, 4, 5). *Ortho*- and *meta*-substituted congeners showed similar reactivity (Table 2, entries 2, 3). As expected due to the electrophilic nature of the $N_3$-radical, styrene derivatives carrying electron-withdrawing substituents provided slightly lower but still good yields (see **3g**–**i**, **3l**–**n**, Table 2, entries 6–8, 11–13).

**Table 2.** Radical Azidooxygenation of Terminal Alkenes




| entry | $R^1$ | $R^2$ | compd | yield (%)[a] |
|---|---|---|---|---|
| 1 | 4-$CH_3C_6H_4$ | H | **3b** | 85 |
| 2 | 3-$CH_3C_6H_4$ | H | **3c** | 89 |
| 3 | 2-$CH_3C_6H_4$ | H | **3d** | 94 |
| 4 | 4-*t*-$BuC_6H_4$ | H | **3e** | 97 |
| 5 | 4-$CH_3OC_6H_4$ | H | **3f** | 98 |
| 6 | 4-$FC_6H_4$ | H | **3g** | 88 |
| 7 | 4-$ClC_6H_4$ | H | **3h** | 84 |
| 8 | 4-$BrC_6H_4$ | H | **3i** | 88 |
| 9 | 4-$PhC_6H_4$ | H | **3j** | 73 |
| 10 | β-naphthyl | H | **3k** | 90 |
| 11 | 4-$NCC_6H_4$ | H | **3l** | 60 |
| 12 | 4-$CF_3C_6H_4$ | H | **3m** | 72 |
| 13 | 4-$AcOC_6H_4$ | H | **3n** | 52 |
| 14 | 4-pyridyl | H | **3o** | 57 |
| 15 | $PhCH_2CH_2$ | H | **3p** | 35[b] |
| 16 | BuO | H | **3q** | 66 |
| 17 | *N*-carbazyl | H | **3r** | 84 |
| 18 | $C_6H_5$ | $CH_3$ | **3s** | 96 |
| 19 | $C_2H_5$ | $C_2H_5$ | **3t** | 77 |
| 20 | -$CH_2(CH_2)_4CH_2$- | | **3u** | 80 |
| 21 | 2-Allyl$C_6H_4$ | H | **3v** | 80 |

[a] Isolated yields. [b] Using 5 equiv of **1** and 5 equiv of **2**.

β-Vinylnaphthalene afforded a 90% yield of **3k**, and a slightly lower yield was achieved with *para*-vinylbiphenyl (see **3j**, 73%) likely due to the inductive effect exerted by the second phenyl group (Table 2, entries 9, 10). However, the aliphatic alkene, 4-phenylbut-1-ene, was not a good substrate and **3p** was isolated in only a 35% yield (Table 2, entry 15). It is known that the azidyl radical reacts slowly with unactivated aliphatic terminal alkenes.[6a] Importantly, this reactivity difference can be used for highly regioselective azidooxygenation as shown in the reaction of *ortho*-allylstyrene to give the benzylic alkoxyamine **3v** in good yield (80%, entry 21). Azidation at the less reactive allyl group did not occur under the applied conditions. Electron rich enol ethers or enamines gave good results (Table 2, entries 16, 17). Terminal aliphatic alkenes if activated by an additional alkyl group at the β-position such as in 2-ethylbut-1-ene or methenylcyclohexane afford in good to excellent yields the corresponding tertiary alkoxyamines (see **3t**,**u** in Table 2, entries 19, 20).

To address the diastereoselectivity of the novel process we investigated the azidooxygenation of internal alkenes (Figure 1). Selectivity was determined by $^1$H NMR analysis of the crude product. β-Methylstyrene reacted under the standard conditions with complete regioselectivity to **3w** which was isolated in 95% yield. Azide **3w** was formed with 4.3:1 diastereoselectivity, and assignment of the relative configuration was based on the allylic A[1,3]-strain model.[18,19] Very low selectivity but good yield was obtained in the transformation of *trans*-stilbene (**3x**, dr = 1:1.1, 88%). Dihydronaphthalene and indene reacted with excellent *trans*-selectivity and complete regioselectivity to produce the corresponding azides **3y** and **3z** in excellent yields. Complete *trans*-selectivity but slightly lower yields were achieved for the radical azidooxygenation of cyclohexene and dihydropyran (see **3aa** and **3ab**). For electronic reasons only one regioisomer was formed in the reaction of the cyclic enol ether. Norbornene was transformed with complete *exo*-selectivity for the initial $N_3$-radical addition and perfect *trans*-selectivity in the TEMPO trapping step (**3ac**), and also benzofuran reacted with complete regio- and diastereoselectivity (**3ad**) in good yield.

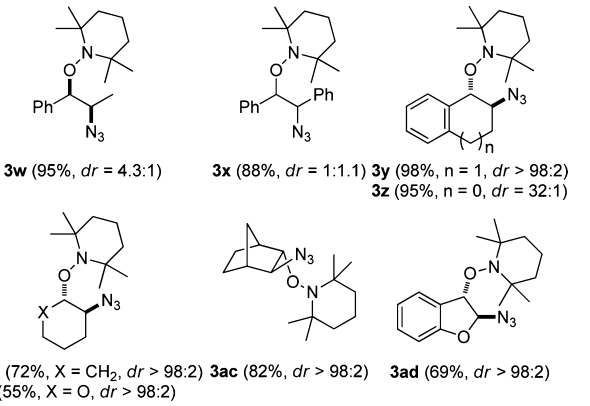



**Figure 1.** Products obtained by diastereoselective radical azidooxygenation of internal alkenes.

To document the potential of the azidooxygenation products as building blocks in the synthesis we investigated the follow up chemistry. Chemical modification of the azide functionality was studied first using **3a** as the substrate (Scheme 2). Azide reduction was achieved by treating **3a** with $CuSO_4$/$NaBH_4$ in MeOH at 0 °C to provide amine **4** in 95% yield.[20] Benzotriazole **5** (82%) was readily obtained by the reaction of *in situ* generated benzyne with **3a**,[21] and as expected, **3a** was a suitable substrate for a Cu-catalyzed [3 + 2] alkyne/azide cycloaddition (CAAC; see **6**, 84%).[1]

The alkoxyamine moiety in these azidooxygenation products offers unique and diverse reactivity.[16b] For example, oxidation of that functionality in **3a** with *meta*-chloroperbenzoic acid (MCPBA) at rt afforded the

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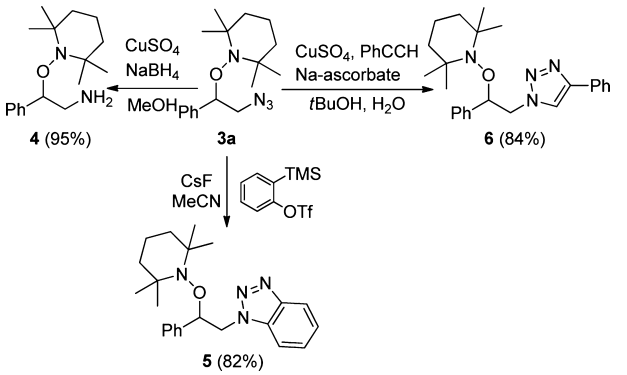
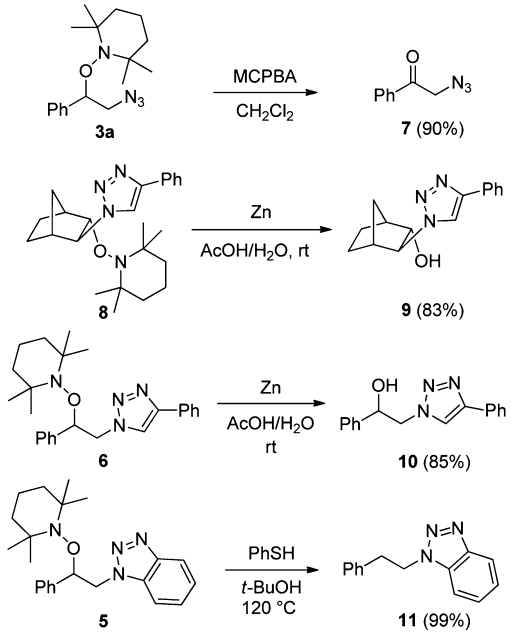
(19) All compounds reported were prepared as racemates.
(20) Rao, H. S. P.; Siva, P. *Synth. Commun.* **1994**, *24*, 549–555.
(21) Reddy, B. V. S.; Praneeth, K.; Yadav, J. S. *Carbohydr. Res.* **2011**, *346*, 995–998.

**Scheme 2.** Transformation of the Azide Functionality in **3a**

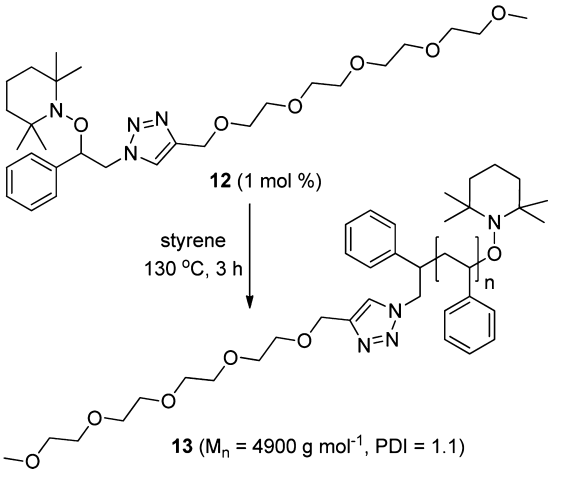



**Scheme 3.** Diverse Reactivity of the Alkoxyamine Functionality




α-azidoketone **7** in 90% yield (Scheme 3).[22] The N−O bond in alkoxyamines can be readily cleaved under mild conditions. Alkoxyamine **8**,[23] obtained by CAAC of **3ac** with phenyl acetylene, was converted to alcohol **9** by using Zn in $AcOH/H_2O$ at rt.[24] In analogy, we obtained alcohol **10** starting from triazole **6**. TEMPO-derived benzylic alkoxyamines have weak C−O bonds which at higher temperature are cleanly homolytically cleaved.[17] Heating of alkoxyamine **6** in the presence of PhSH as a radical reducing reagent provided the deoxygenated triazole **11** in quantitative yield.

**Scheme 4.** NMP of Styrene Using **12** as Initiator/Regulator




To further document the potential of these bifunctional aminoxygenation products we successfully used **3a** for the preparation of a diblock copolymer. CAAC of **3a** with a pegylated alkyne gave alkoxyamine **12** (72%, see Supporting Information) which was then used as a radical initiator/mediator for the nitroxide mediated radical polymerization of styrene (NMP, Scheme 4).[17] NMP using 1 mol % of **12** in neat styrene at 130 °C for 3 h provided the diblock copolymer **13** ($M_n$ = 4900 g/mol, PDI = 1.10, 51% conversion) convincingly documenting that the chemistry presented is very well suited for the preparation of NMP initiators.

In conclusion, we reported a novel method for radical azidation using readily prepared $N_3$−I(III)-reagent **1** and TEMPONa, generated from commercially available TEMPO and sodium. In these processes TEMPONa first acts as a mild organic reducing reagent (SET) for $N_3$-radical generation under formation of TEMPO which subsequently reacts as an oxidant for adduct C-radical trapping. The azidooxygenation works efficiently on various styrene derivatives and on electron-rich alkenes. Experiments are easy to conduct, and products are generally obtained in good to excellent yields. For cyclic systems the vicinal difunctionalization occurs with excellent diastereoselectivity. Importantly, the products obtained are highly useful materials for further chemical manipulations as documented by various transformations.

**Acknowledgment.** We thank the Deutsche Forschungsgemeinschaft (DFG) for supporting our work.

**Supporting Information Available.** Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(23) The structure of **8** was also characterized by X-ray analysis. CCDC 936564 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/-conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44(1223)336-033, E-mail: deposit@ccdc.cam.ac.uk].

(24) N−O cleavage leaving the azide functionality intact was not possible.