



C–H Activation Hot Paper

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Photochemical Transformations with Iodine Azide after Release from an Ion-Exchange Resin

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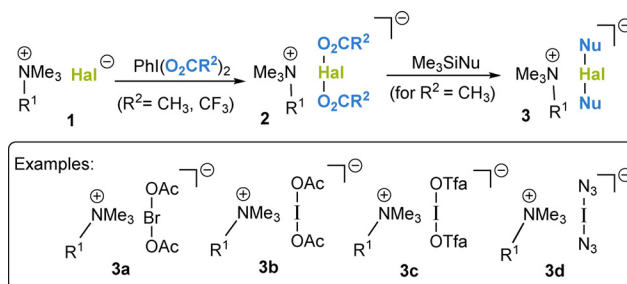
In memory of Prof. Rolf Huisgen

Abstract: This report discloses the photochemical homolytic cleavage of iodine azide after its formation following release from polymer-bound bisazido iodate(I) anions. A series of radical reactions are reported including the 1,2-functionalization of alkenes and the unprecedented chemoselective oxidation of secondary alcohols in the presence of primary alcohols.

The pioneering work of Hassner^[1] introduced iodine azide (IN₃) to the reagent portfolio of preparative organic chemists. However, its explosive character hampered broader synthetic studies. Due to this property, iodine azide is commonly prepared in situ from sodium azide and iodine chloride in polar solvents.^[1,2]

Many years ago we reported on a new class of electrophilic halonium reagents that are obtained by iodine(III)-mediated oxidation of ammonium bromide or iodide (**1**; Scheme 1).^[3] The resulting acylated haloate(I) complexes **2**^[4] can be further diversified by ligand exchange using silylated nucleophiles that yields ate(I) anions in **3a–d**. These reagents have been employed in various transformations with alkenes and alkynes^[5] for the activation of thioglycosides^[6] as well as dithioacetals^[7] and as cooxidants for TEMPO-mediated oxidations.^[8] Chemically, the haloate(I) anions in **3a–d** behave like Br-OAc, I-OAc, I-OTfa, and I-N₃. It can be assumed that these species are liberated from **3a–d** prior to the reaction with different nucleophiles.^[9,10]

With these results in mind we initiated a program for extending the scope of these compounds to photochemical reactions, and the highly useful functionalized ion-exchange resin **3d** was our reagent of choice. This orange-colored polymer is a non-explosive source of iodine azide (**5**) and can be stored in the dark for several months under an argon



Scheme 1. Preparation of haloate(I) complexes. Ac = acetyl, Nu = nucleophile, Tfa = trifluoroacetyl; R¹ = alkyl or polystyrene; the ammonium counterion can be replaced by phosphonium PR₄⁺^[3].

atmosphere at –15 °C without loss of activity. Reactions are commonly terminated by filtration through a piece of cotton that is positioned at the opening of the vial. The polymeric byproduct **4** generated during transformations with **3d** is removed by simple filtration (Scheme 2)^[11] and its regeneration is achieved by exchange of azide with iodide, PhI(OAc)₂-promoted oxidation to **3b**, and ligand exchange with TMSN₃. Principally, polymer-bound iodine azide **3d** resolves the problems arising from the explosive character of iodine azide (**5**). So far photocatalytic reactions with iodine azide (**5**) have not been reported.^[12] Since **3d** is a source of Hal-X species, we assumed that it is ideally suited to generate and study the chemical versatility of the azide radical (**6**) (Scheme 2).^[13]

Huang and Groves determined the bond dissociation energy (BDE) for H-N₃ (**12**) to be 92.7 kcal mol⁻¹,^[14] which indicates that the azide radical (**6**) is a much stronger hydrogen-atom abstractor than iodine or bromine radicals (BDE(H-I) = 71.3 kcal mol⁻¹, BDE(H-Br) = 86.5 kcal

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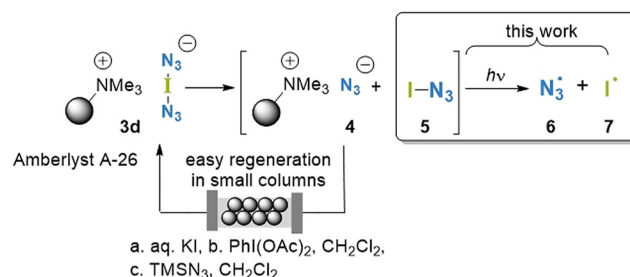
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Scheme 2. Polymer-bound bisazidoiodate(I) **3d**, release of iodine azide (**5**), proposed photochemical generation of the azide radical **6**, and resin regeneration.

mol^{-1}).^[15] Azidoiodinanes **8–10** show similar I–N₃ BDE values to iodine azide (**5**) in the range of 29–35 kcal mol⁻¹ (Figure 1).^[14]

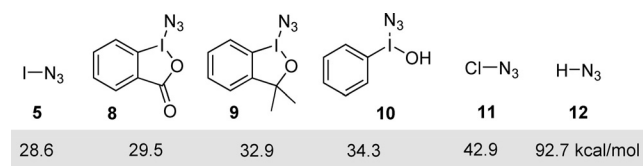


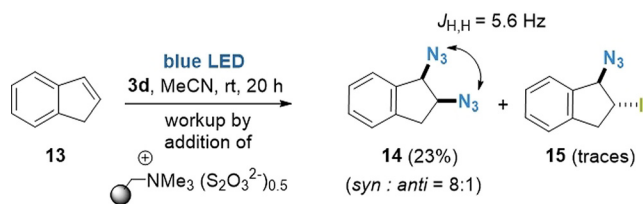
Figure 1. X–N₃ bond dissociation energies (BDE) of common organic halogen azides (**5**, **8–11**) and of HN₃ (**12**).^[14]

To prove that polymer-bound reagent **3d** can serve as a source of azide radicals (**6**) we exposed it to blue LED light (445–510 nm) in the presence of indene (**13**). Under these conditions the *syn*-bisazido adduct **14** formed (Scheme 3). The *anti*-azido-iodination product **15** is commonly formed under nonradical conditions and was only detected in trace amounts. The *syn* stereochemistry in **14** was determined by comparison with literature values.^[16]

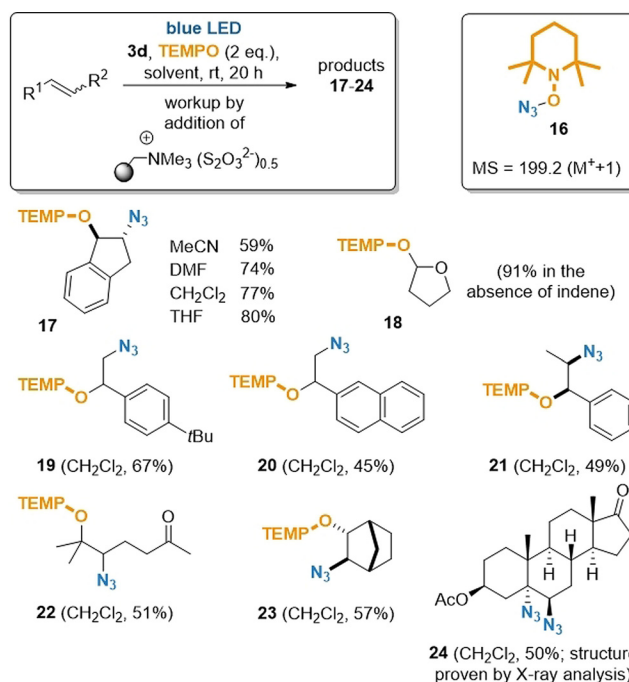
Noteworthy, thiosulfate ion exchange resin was added for reductive workup of all reactions and removal of byproducts such as iodine and IN₃. Thus, the need for hydrolytic workup is bypassed. Further evidence for the presence of a radical process was collected using 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) as a radical-scavenging agent. Consequently, the *anti* 1,2-adduct **17** was formed (Scheme 4).

A brief solvent check demonstrated that besides acetonitrile also DMF, CH₂Cl₂, and THF can be employed. However, in THF oxidized furan **18** was also detected in trace amounts. In the absence of indene (**13**) the radically formed THF adduct **18** was isolated in 91% yield.^[17] There is precedence for radical H abstractions from tetrahydrofurans and other heterocycles when iodide salts are mixed with *t*-butyl hydroperoxide.^[18a] Alternatively, the azide radical (**6**) can be generated from PhI(OAc)₂ and sodium azide which also leads to H radical abstraction from the solvent THF.^[18b] As suggested for bulky TEMPO derivatives, TEMPO–azide adducts can form, serving as an azide radical in a “resting state”.^[19] A sample taken from a reaction mixture consisting of polymer **3d** and TEMPO in acetonitrile was analyzed by HPLC-MS after 2 h and a signal at $m/z = 199.2$ ($M^+ + 1$) was detected which could be TEMPO–N₃ **16**.

Next, the scope of this radical process was extended to several other alkenes. These yielded the corresponding 1,2-addition products **17–23**. 1,2-Disubstituted alkenes commonly



Scheme 3. Radical bisazidation of indene (**13**) by photochemical activation of polymer-bound reagent **3d**.

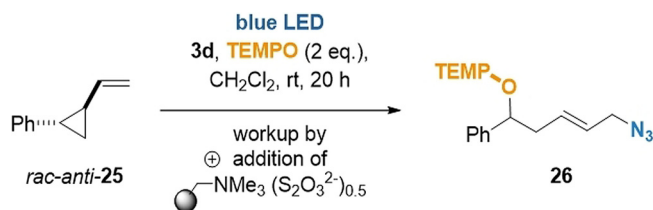


Scheme 4. Radical 1,2-addition of azide and TEMPO to alkenes and formation of **17–24** by photochemical activation of polymer-bound reagent **3d**; structure of TEMPO azide **16** (**16** was also described to be a salt^[19]).

reacted with complete diastereocontrol. Under these conditions, 3-(acetoxy)-androst-5-en-17-one yielded the *anti*-1,2-bisazido adduct **24** in 50% yield and not the azido oxygenation product. The structure of **24** was determined by X-ray crystallographic analysis (see the Supporting Information).^[20] This result is consistent with the observations of Lin and co-workers, who found that aminoxyl radicals are able to catalyze the *anti*-diazidation of alkenes, likely with **16** serving as an azide radical reservoir.^[19] This alternative outcome of the reaction is fostered by increasing steric hindrance around the alkene moiety and the aminoxyl radical.

A radical clock experiment was conducted under the established conditions using vinyl cyclopropane **25** as starting material (Scheme 5). The ring-opened allyl azide **26** was obtained besides the iodoazidated product formed by ionic 1,2-addition to the terminal alkene. The formation of **26** clearly proved the presence of the azide radical (**6**).

It has to be noted that azido-oxygenations of alkenes were reported before by Studer et al., who employed azido benziodoxolone (Zhdankin’s reagent^[21]) in combination with highly reactive TEMPO_{Na} as a reducing agent and

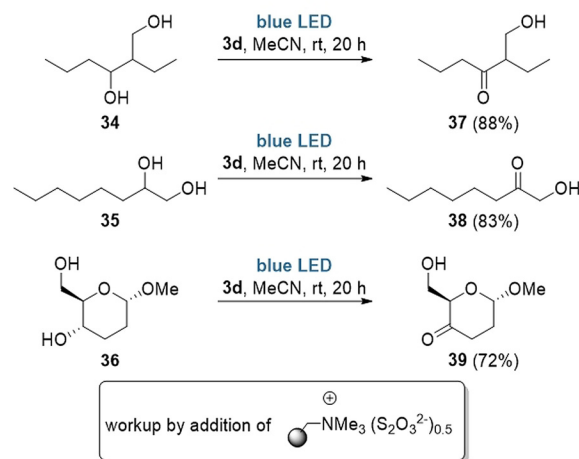


Scheme 5. Radical clock experiment with vinyl cyclopropane **25**.

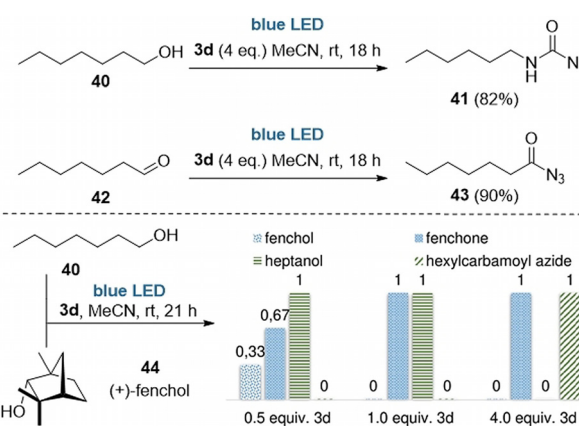
precursor for TEMPO.^[22] A second approach relied on the electrochemical reduction of TEMPO to TEMPO⁺. The resulting metastable charge-transfer complex with azide **16** (TEMPO⁺/N₃⁻) decomposes to TEMPO and the azide radical (**6**).^[23] Recently, Kashya and co-workers published the first photocatalyzed azidoxygenation that relied on trimethylsulfonium [bis(azido)iodate(I)] species, which are generated in situ from trimethylsilyl azide and sulfonium bis-(acetoxy)iodate(I).^[24]

During our studies we also observed an unexpected property of iodine azide (**5**) under photolytic conditions. We found that secondary alcohols are smoothly oxidized to the corresponding ketones while primary alcohols reacted very sluggishly (Schemes 6–8). This unexpected difference of reactivity was substantiated for the diols **34–36** (Scheme 7).^[25] In all cases the secondary hydroxyl group was oxidized with remarkable chemoselectivity, forming hydroxyketones **37–39**. The selective oxidation of the 2,3-deoxyglycoside **36**^[26] to the corresponding uloside **39** is particularly noteworthy and synthetically useful as protecting group chemistry, a typical feature in carbohydrate synthesis, is circumvented.

We found that primary alcohols are also oxidized by the azide radical (**6**). Compared to fenchol (**44**), which was quantitatively oxidized to fenchone (**32**) within seven hours at room temperature, heptanol **40** reacted much more sluggishly. After 20 h hexylcarbamoyl azide (**41**) formed under the typical photolytic conditions in the presence of polymer **3d** (Scheme 8, top). Mechanistically, one can assume that heptanal (**42**) is formed first followed by H abstraction and generation of an acyl radical. When this is trapped by the azide radical (**6**) the acyl azide **43** would form. Next a Curtius rearrangement would yield the corresponding isocyanate, which finally reacts with HN₃. Evidence for this series of events was collected when heptanal (**42**) was exposed to polymer **3d** under the typical photolytic conditions in the presence of polymer **3d**. Acyl azide **43** was isolated in 90% yield. Obviously the Curtius rearrangement did not take place. The number of equivalents HX formed (X = I or N₃) is larger when starting from heptanol (**40**) than from heptanal



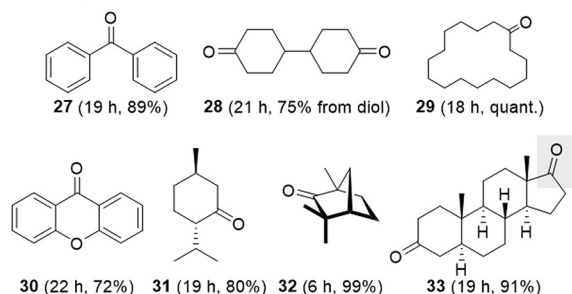
Scheme 7. Chemoselective oxidation of diols **34–36** with functionalized polymer **3d**.



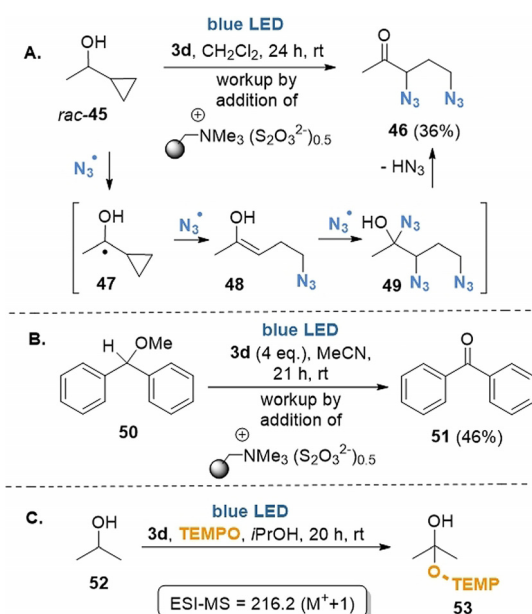
Scheme 8. Oxidation of heptanol (**40**) and heptanal (**42**), competition experiments between (+)-fenchol (**44**) and heptanol (**40**) (ratios determined by ¹H NMR spectroscopic analysis; workup by addition of thiosulfate ion exchange resin and filtration).

(**42**). These promote formation of carbamoyl azide **41** from acyl azide **43**. This chemoselectivity was unequivocally proven in a competition experiment between (+)-fenchol (**44**) and heptanol (**40**) in the presence of different amounts of **3d** (Scheme 8, bottom). Finally, C–H activation similar to that described here was encountered for cyclic and acyclic ethers using strongly oxidizing reagents or transition metal catalysts.^[27–29]

To collect evidence that alcohol oxidations proceed via ketyl radicals, we carried out three experiments. First, we employed 1-cyclopropylethan-1-ol (**45**), which was expected to undergo a rapid ring opening after radical formation (Scheme 9, example A). Treatment of **45** under the established conditions yielded bisazide **46**, a clear indication that a ketyl radical **47** must have formed as an intermediate and subsequent reactions via intermediates **48** and **49** furnished bisazide **46**. Secondly, methyl ether **50** was exposed to the established conditions and the corresponding ketone **51** was isolated as the main product (Scheme 9, example B). Finally, we carried out detailed mass spectrometric studies (LC-ESI-



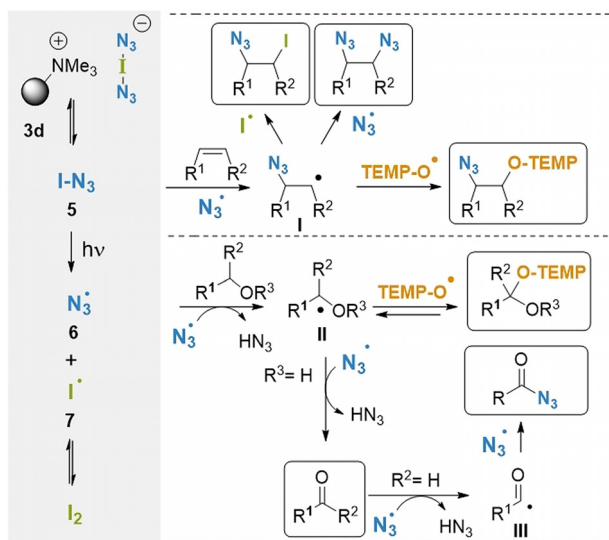
Scheme 6. Oxidation of secondary alcohols with functionalized polymer **3d** and formation of ketones **27–33** (gray mark refers to site of oxidation).



Scheme 9. Three experiments (A–C) that provide evidence for C–H activation and ketyl radical formation during alcohol oxidation.

MS) on the crude mixture collected from the oxidation of isopropanol **52** in the presence of TEMPO. These displayed a signal at $m/z = 216.2$ ($M^+ + 1$) indicative for TEMPO adduct **53**, which, however, could not be isolated (Scheme 9, example C).

With reference to the BDE of IN_3 , and the H-abstraction capability of both radicals, a mechanistic scheme can be summarized (Scheme 10). Polymer-bound iodate(I) complex **3d** provides iodine azide (**5**), which under photocatalytic conditions undergoes homolytic cleavage to yield the azide **6** and iodine radical (**7**). While **7** is able to recombine to form I_2 , the corresponding dimerization of the azide radical (**6**) to form N_6 is not reported. The azide radical (**6**) is able to add to



Scheme 10. Proposed mechanistic considerations for radical processes reported here.

alkenes and the newly formed radical **I** can be trapped by the iodine or the azide radicals **6** and **7** or by TEMPO. The azide radical (**6**) also enforces C–H abstraction next to a C–O bond such as in tetrahydrofuran or alcohols. In the former example this was proven by isolation of the TEMPO adduct, while in the second case the corresponding ketones formed from secondary alcohols via the ketyl radicals **II**. Primary alcohols also form intermediate **II** but the resulting aldehyde undergoes a second C–H abstraction to yield an acyl radical **III**. This is trapped by **6** to yield acyl azides, which may undergo the Curtius rearrangement with final addition of HN_3 to the intermediate isocyanate.

In essence, we have showed that the polymer-bound bisazido(iodate(I)) anion **3d** is the most versatile source of the azide radical (**6**) in photocatalytic reactions.^[30] It performs azidoxygenations of alkenes and C–H abstractions of ethers and alcohols.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: azide radicals · C–H activation · iodine azide · photochemistry · polymer-bound reagents

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- [31] It can be regenerated infinitely (Scheme 2). Chemical changes of the polymer backbone initiated by the radicals formed were not studied here.

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