Azidation

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Cyclic Hypervalent Iodine Reagents and Iron Catalysts: The Winning Team for Late-Stage C–H Azidation**

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Over the past decades, azides have received increasing attention owing to their exceptional reactivity and versatility in organic chemistry.[1] Their use as non-basic precursors of amines or their easy conversion into nitrene intermediates for further C–N bond transformations have made them key building blocks in chemistry, biology, and material science. In spite of their hailed synthetic utility, their installation into organic molecules traditionally proceeds through substitution reactions, which usually require substrate pre-functionalization. Methods enabling the selective introduction of azides into C–H bonds at a late stage of the synthesis would represent a breakthrough in the field by providing a more efficient entry to these versatile building blocks. Recently, Sharma and Hartwig reported a practical method in which the challenges of reactivity and selectivity associated with the late-stage azidation of C–H bonds were successfully overcome by the combination of an azidobenziodoxolone reagent and an iron catalyst.[2]

The envisaged azidation reaction requires a reactive, yet stable azide precursor that is tolerant to functional groups and simultaneously acts as a mild oxidant to perform C–H functionalization. In this context, hypervalent iodine reagents appear to be excellent candidates as they display several of the desired properties. They had indeed been applied to azide transfer processes for a long time, but the available reagents were highly unstable at room temperature.[3] In 1994, Zhdankin and co-workers,[4] shortly followed by Kita and co-workers,[5] reported the first examples of cyclic and bench-stable azidobenziodoxol(on)e reagents (**1**–**3**; Figure 1).

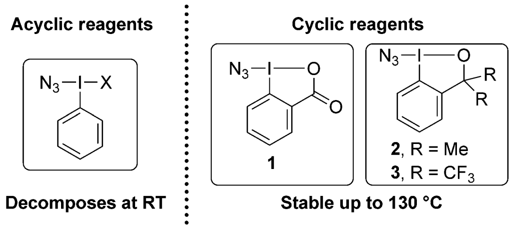
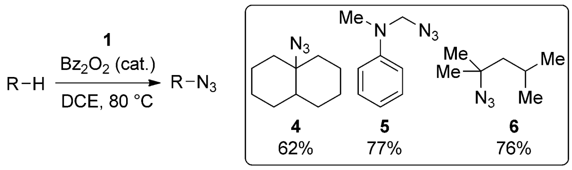


Figure 1. Discovery of stable azidobenziodoxol(on)e reagents.[4,5]

Key for success was the incorporation of the iodine atom into a cyclic structure to give the benziodoxol(on)e core, an approach that has been highly successful for other functional-group-transfer reagents, such as those for the introduction of trifluoromethyl (Togni's reagent)[6] or alkynyl (EBX reagents) groups.[7] Although the main focus of the early work by Zhdankin and co-workers was on stability and structure studies, they also demonstrated the excellent properties of reagent **1** for the azidation of free radicals that were generated by C–H abstraction (Scheme 1).[8] Even though this report represented a crucial advance for late-stage azidation, the method still suffered from low selectivities and efficiencies as radical formation was achieved with benzoyl peroxide as the initiator at 80 °C.



Scheme 1. C–H azidation with azidobenziodoxolone reagent **1**.[8] Bz = benzoyl, DCE = 1,2-dichloroethane.

To tackle the formidable challenge of selective and efficient C–H functionalization, chemists have taken inspiration from metalloenzymes found in nature. For example, cytochromes P450 are able to achieve the selective C–H hydroxylation of many organic molecules by making use of a catalytically active iron center. Important contributions to the field were made by the groups of Que and White, among others, who developed small-molecule iron catalysts for C–H hydroxylation (Scheme 2).[9] Nevertheless, it was not clear whether this important finding would be applicable to other transformations. In this respect, an interesting proof of

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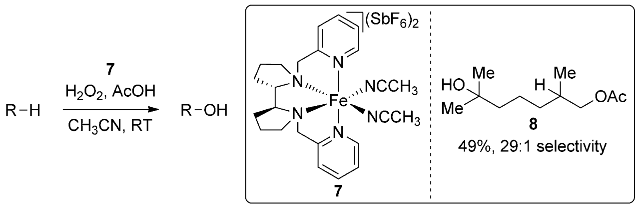
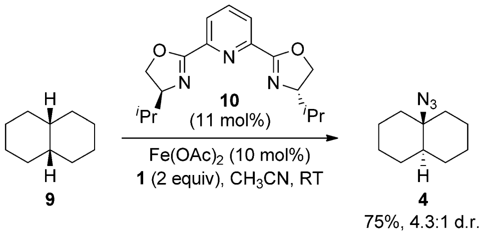


Scheme 2. Iron-catalyzed C−H hydroxylation reported by Chen and White.[9b]

concept was reported by Que and co-workers in 1993, who achieved a C−H azidation reaction using a stoichiometric amount of an iron complex as well as a very simple substrate presenting no selectivity issues.[10]

In the highlighted contribution, Sharma and Hartwig made use of the exceptional properties of azidobenziodoxolone reagent **1** to develop the first iron-catalyzed C−H azidation reaction. The transformation proceeded with enhanced selectivity and efficiency compared to previously reported radical processes. To develop a new C−H azidation method, they started by examining the catalyst used by White and co-workers for C−H hydroxylation in combination with *cis*-decalin (**9**) and reagent **1**. The desired azide **4** could indeed be obtained, albeit only in 4% yield. In order to enhance the reactivity of the iron catalyst, various ligands were then tested, and the simple, commercially available PyBOX ligand **10**[11] finally gave the azide in 75% yield and with a diastereoselectivity of 4.3:1 at room temperature (Scheme 3).



Scheme 3. Iron-catalyzed C−H azidation with azidobenziodoxolone reagent **1**.

With the optimized conditions in hand, they investigated the scope and selectivity of the azidation reaction (Figure 2). The most electron-rich tertiary C−H bond could be azidated selectively to give products **11** and **12**, a result similar to the one obtained for C−H hydroxylation.[9] When more complex substrates bearing different functional groups and numerous C−H bonds were examined, the new iron-catalyzed azidation led to selective mono-azidation (products **13–15**). The use of benzoyl peroxide usually led to low yields and selectivities. Particularly impressive is the direct azidation of complex natural products, such as podocarpic acid derivative **14** or tetrahydrogibberellic acid derivative **15**. The introduced azide could then be used for further diversification of the molecules.

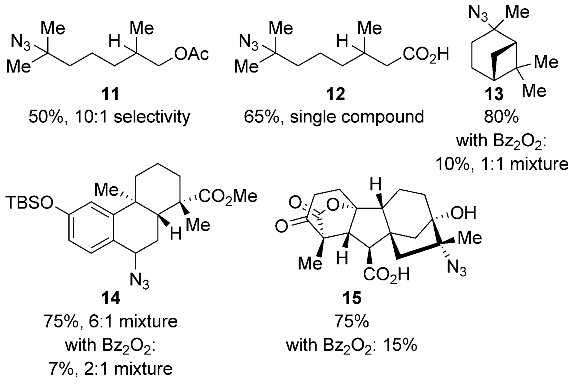


Figure 2. Selected examples of late-stage azidation reactions. TBS = *tert*-butyldimethylsilyl.

Mechanistically, this C−H azidation is very intriguing. Does the role of the iron catalyst only entail the generation of a free radical from a C−H bond under milder and more selective conditions? Indeed, several experiments hinted at the presence of free radicals: The reaction was stereoconvergent and could be inhibited by radical traps, such as (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT). Furthermore, the observed kinetic isotope effect of 5.0 is consistent with C−H bond cleavage being the rate-limiting step. On the other hand, when the azidation of decalin **9** was performed at 80°C with either benzoyl peroxide or iron as a catalyst, different diastereoselectivities were observed. This result suggests that the direct reaction of a free radical with benziodoxolone reagent **1** is not involved in the iron-catalyzed process. The authors proposed that an azido iron complex could consequently be the active azide-transfer reagent. Nevertheless, many other possibilities could also be envisaged, such as activation of the benziodoxolone reagent by the iron catalyst or the reaction of an iron alkyl complex. Furthermore, the identity of the species responsible for C−H abstraction has not yet been investigated.

In summary, by combining the exceptional properties of benziodoxolone reagents and iron catalysts, Sharma and Hartwig have achieved an important breakthrough for the late-stage C−H azidation of complex molecules. Nevertheless, moderate yields and selectivities were still observed for some substrates, and our understanding of the reaction mechanism remains underdeveloped. Indeed, the potential of combining base-metal catalysts and cyclic hypervalent iodine reagents for the discovery of new reactions has just begun to be investigated, and many more exciting discoveries await us in the future.

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compound **1** is relatively stable, in our laboratory, it detonated in two instances. Differential scanning calorimetry (DSC) analysis confirmed its explosive character. Reagent **2** has a much lower explosion potential. See the Supporting Information for details.

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