

Cyclic Hypervalent Iodine Reagents and Iron Catalysis: the Winning Team for Late-Stage C-H Azidation

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Dedication ((optional))

In the past decades azides have received increasing attention due to their exceptional reactivity and versatility in organic chemistry.^[1] Their use as non-basic precursors of amines or their easy conversion to nitrene intermediates for further C-N bond transformations 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 via substitution reactions, which usually require the pre-functionalization of the substrate. Methods allowing the selective introduction of azides into C-H bonds at a late-stage of the synthesis would represent a breakthrough in the field by giving a more efficient entry to these versatile building blocks. Recently, Sharma and Hartwig reported a practical methodology in which the challenges of reactivity and selectivity represented by 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, which is tolerant to functional groups and can at the same time act as a mild oxidant to perform C-H functionalization. In this context, hypervalent iodine reagents appear as excellent candidates, as they display several of the desired properties. They had been indeed applied to azide transfer since 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).

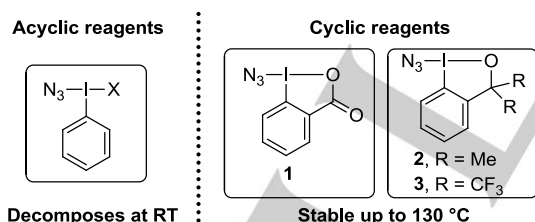
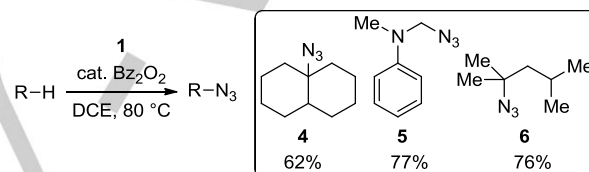


Figure 1. Discovery of stable azidobenziodoxol(on)e reagents.^[4,5]

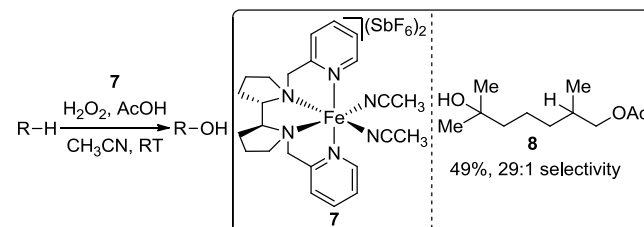
Key for success was the incorporation of the iodine atom into a cyclic structure to give a benziodoxol(on)e core, an approach

which has been highly successful in the case of other functional groups such as trifluoromethyl (Togni's reagent)^[6] or alkynyl (EBX reagents).^[7] Although the main focus of Zhdankin and co-workers' early work was on stability and structure studies, they also demonstrated the excellent properties of reagent **1** for the azidation of free radicals generated by C-H abstraction (Scheme 1).^[8] Even though this represented a crucial advance for late-stage azidation, the method still suffered from low selectivity and efficiency due to radical formation using benzoyl peroxide as initiator at 80 °C.



Scheme 1. C-H azidation with azidobenziodoxolone reagent **1**.^[8]

To tackle the formidable challenge of selective and efficient C-H functionalization, chemists have taken inspiration from metallo-enzymes found in nature. For example, cytochromes P-450 are able to achieve the selective C-H hydroxylation of many organic molecules making use of a catalytic active iron center. An important contribution to the field was achieved when the groups of Que and White among others developed small molecule iron catalysts for C-H hydroxylation (Scheme 2).^[9] Nevertheless, it was not clear if this important finding would be applicable to other transformations. In this respect, an interesting proof-of-concept was demonstrated by Que and co-workers in 1993 for C-H azidation using a stoichiometric amount of an iron complex as well as a very simple substrate without issues of selectivity.^[10]



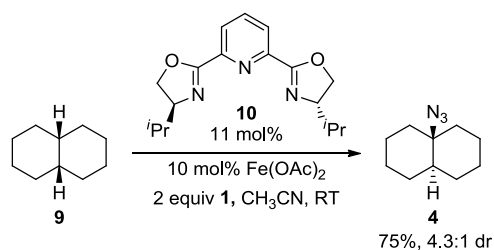
Scheme 2. Iron-catalyzed C-H hydroxylation reported by Chen and White.^[9b]

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

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efficiency when 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 with *cis*-decalin (**9**) and reagent **1**. The desired azide **4** could be indeed obtained, albeit only in 4% yield. In order to enhance the reactivity of the iron catalyst, diverse ligands were then tested and a simple commercially available PyBOX ligand **10**^[11] gave finally the azide in 75% yield and 4.3:1 diastereoselectivity at room temperature (Scheme 3).



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

With the optimized conditions in hand they studied more in details the scope and selectivity of the azidation reaction (Figure 2). They observed that the most electron-rich tertiary C-H bond can 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 were examined bearing different functional groups and numerous C-H bonds, the new iron-catalyzed azidation lead to selective mono-azidation (products **13-15**). The use of benzoyl peroxide led usually to low yield and selectivity. 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. Mechanistically, the new developed C-H azidation is highly intriguing. Is the role of the iron catalyst just to generate 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 butylated hydroxytoluene (BHT). Furthermore, the observed kinetic isotope effect of 5.0 is consistent with C-H bond cleavage as 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 catalyst, different diastereoselectivities were observed. This result suggested that direct reaction of a free radical with the benziodoxolone reagent **1** is not involved in the iron-catalyzed process. The author proposed that an azido-iron complex could be consequently 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 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 yield and selectivity were still observed for some substrates and the understanding of the reaction mechanism remains underdeveloped. Indeed, the potential of combining the design of 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.

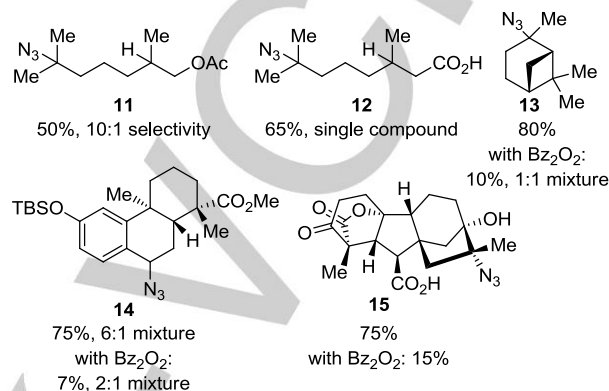


Figure 2. Selected examples of late-stage azidation.

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Keywords: C-H Functionalization • Azides • Iron Catalysis • Hypervalent Iodine • Radicals

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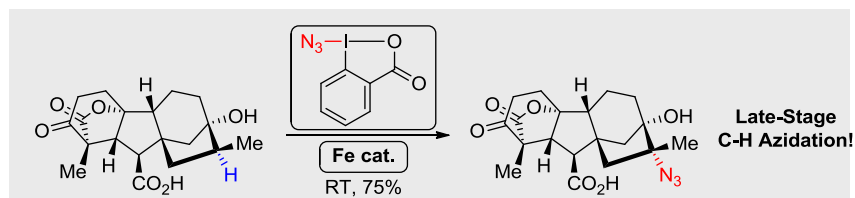
Layout 2:

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Maria Victoria Vita and Jerome Waser *

Page No. – Page No.

**Cyclic Hypervalent Iodine Reagents
and Iron Catalysis: the Winning Team
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1+1 = 3: By combining the exceptional reactivity of cyclic hypervalent iodine reagents and iron catalysts, Sharma and Hartwig achieved the azidation of C-H bonds with unprecedented efficiency and selectivity. The late-stage introduction of azides into complex bioactive molecules will greatly facilitate the synthesis of analogues and accelerate the discovery of new chemical entities.