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Iron-Catalysed Remote C(sp^3)-H Azidation of *O*-Acyl Oximes and *N*-Acyloxy Imidates

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Abstract: The azido group occupies an important position in modern organic chemistry, broadly used as amine surrogates and as anchors in bioconjugation. Despite their importance, examples of selective direct azidation of inert C(sp^3)–H bonds remain limited and often require strong oxidative conditions. Herein, we highlight the use of *O*-acyl oximes and *N*-acyloxy imidates as directing groups for the selective iron-catalysed azidation of C(sp^3)–H bond with trimethylsilyl azide, giving access to various γ-azido ketones and β-azido alcohols in moderate to excellent yields. The iron catalyst is assumed to play a dual role in these catalytic processes: as a reductant to generate the reactive iminyl and imidate radicals, respectively, and as a redox centre to mediate the azido transfer to the translocated carbon radical.

Keywords: Azides · C–H functionalisation · 1,5-HAT · Iron catalysis · Radical

Alexandre Leclair studied chemistry in France at the University of Nantes. During his master's studies, he moved to Belgium to join the process and development department of Janssen (Johnson & Johnson) as an organic chemistry intern. In 2017, he moved to Switzerland at EPFL to perform his master's thesis under the supervision of Prof. Jieping Zhu working on the development of a new difunctionalisation of alkenes. Alexandre is now a PhD student in the same group working on the development of new remote C–H functionalisation strategies.

1. Introduction

Since its discovery, the azido group has evolved to become an important functional group in organic chemistry. In addition to their high energetic properties, azides have emerged as versatile synthetic building blocks[1] (Fig. 1), playing an important role in the synthesis of complex molecules as a latent amino group. The new developments in azide-alkyne Huisgen cycloaddition[2] and Staudinger ligation[3] have resulted in an enhanced interest in the use of azides as anchors for biological molecules. The small size and good metabolic stability of the azido group have made it particularly suitable for biorthogonal chemistry. It has also been found in some drugs such as zidovudine (AZT), an antiretroviral agent widely used to prevent and treat HIV/AIDS.

1.1 *Aliphatic C–H Azidation*

One of the most reliable methods to access aliphatic azides involves a nucleophilic substitution of alkyl (pseudo)halides by alkali azides, thereby requiring pre-functionalised organic substrates. The direct azidation of C–H bonds would without doubt offer straightforward access to functionalised molecules, which, in turn, could allow for further late stage structural diversifications of complex molecules.

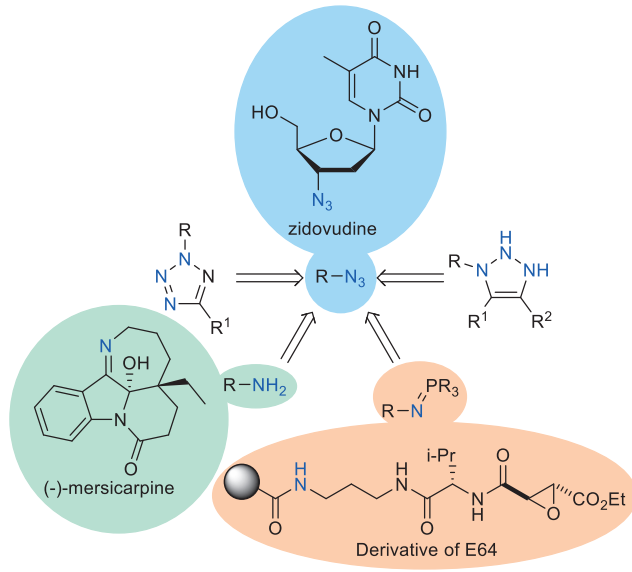

Fig. 1. Azides, versatile building blocks and relevant applications: for the total synthesis of (-)-mersicarpine;[4] zidovudine (AZT), an antiretroviral drug; derivative of E64 as probe for the analysis of Cathepsin cysteine proteases.[5]

Despite the recent development of C–H functionalisation methodologies, reports for the direct azidation of aliphatic C–H bonds remain limited to oxidative conditions. Thus, hypervalent iodinane species with[6] or without[7] metal catalysts, hydrogen abstraction by means of peroxide,[8] persulfate,[9] photoredox conditions[10] or more recently electrochemistry[11] followed by radical trapping with an azide donor have been developed. In addition, Studer reported an elegant remote C–H azidation of sulfonamides using *N*-allylsulfonyl groups as amidyl radical precursors.[12] In

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2020, Stahl *et al.* reported a Cu-catalysed selective benzylic azidation protocol.[13] With few exceptions, a main limitation inherent to most of these methodologies is the lack of regioselectivity and a low tolerance toward easily oxidised functional groups (*e.g.* alkynes) and electron-rich heteroarenes such as furans, indoles.

1.2 *O-acyl Oximes and Remote Functionalisation*

In order to address the problem of site-selectivity during the C–H functionalisation, a common and atom-economic strategy is to use the self-carried functionality to direct the site-selective functionalisation. The most iconic examples are the Hoffman-Löffler-Freytag reaction and the Barton reaction for the remote functionalisation of amines and alcohols, respectively. Both reactions rely on the 1,5-hydrogen atom transfer (1,5-HAT) of the *in situ* formed heteroatom-centred radical to generate a δ-C(sp^3) radical which could then be further functionalised.[14] Due to the high bond dissociation energy (BDE) of N–H and O–H bonds (~105 kcal/mol) relative to C(sp^3)–H bonds (BDE: 90-100 kcal/mol), the 1,5-HAT of amidyl and alkoxyl radicals to generate C(sp^3) radicals are thermodynamically favoured. In addition, the process is also polarity-matched as it takes place between electrophilic amidyl/alkoxyl radicals and nucleophilic aliphatic C–H bonds, thus rendering it kinetically favourable.

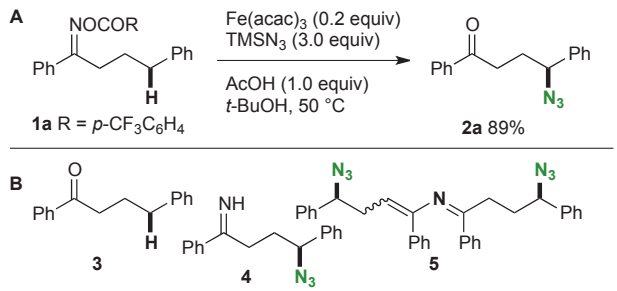
Due to their easy access, *O*-acyl oximes have been widely exploited in organic synthesis over the years. The generation of iminyl radicals from α-imino-oxy acids under oxidative conditions followed by 1,5-HAT and cyclisation of the translocated carbon-centred radicals was reported in 1975 by Forrester *et al.*[15] This remote functionalisation strategy laid dormant for many years until the recent emergence of photoredox catalysis.[16] It is important to note that the iminyl N–H bond is weaker (BDE: ~93 kcal/mol) than most of the C(sp^3)–H bonds, thereby making the 1,5-HAT thermodynamically neutral or unfavourable. In their pioneering studies, Forrester and co-workers demonstrated that the addition of acid is beneficial to the reaction, presumably by the formation of a better hydrogen abstractor iminium radical cation.

At the outset of our work, methods for the functionalisation of translocated carbon-centred radicals were limited to classical radical reactivity, *i.e.* radical addition, homolytic substitution (S_H2) or Minisci-type reactions. Building on our recent works on copper catalysed remote C–H bond functionalisation,[17] and alkene difunctionalisation,[18] we became interested in exploiting the dual catalytic role of metal catalysts: as a reductant to generate the iminyl radical and as a redox centre to functionalise the translocated carbon radical. Herein, we summarise our work on the iron-catalysed γ-C(sp^3)-H azidation of *O*-acyl oximes and *N*-acyloxy imidates offering a new access to γ-azido ketones and β-amino alcohols, respectively, under mild reducing conditions.[19]

2. Iron-catalysed Remote C(sp^3)–H Azidation of O-Acyl Oximes

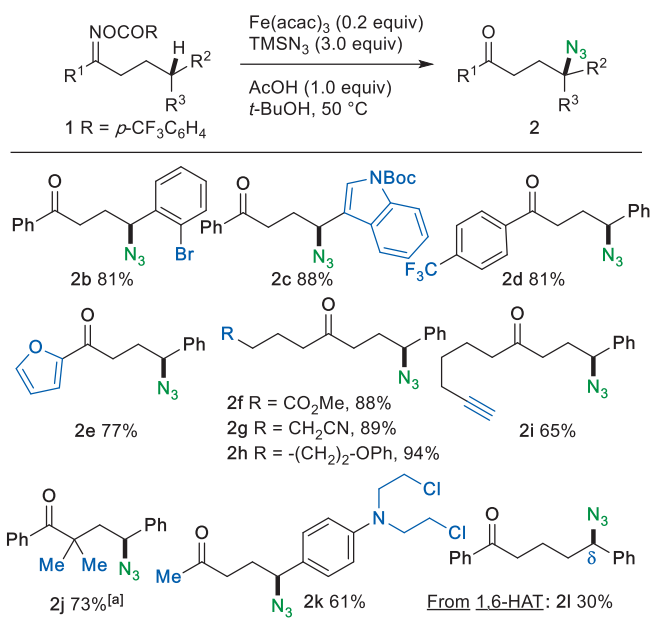
One of the main challenges inherent to this metal-catalysed strategy consisted of finding the right catalyst for the single electron transfer (SET) reduction of the *O*-acyl oximes. Indeed, several metals[20] are known to be competent for the generation of iminyl radicals from *O*-acyl oximes. However, the 1,5-HAT of these intermediates are in general endergonic and reversible.[16a,c] A competitive second SET would convert the iminyl radicals to the iminato-metal species, thereby interrupting the desired domino process.

Our initial investigations were carried out using copper catalysts (Scheme 1). While a trace amount of γ-azido ketone **2a** was indeed isolated under certain conditions, the unfunctionalised ketone **3**, resulting from a double SET and subsequent hydrolysis, was isolated as a major product in most of the cases. In contrast, iron catalysts were found to be generally more effective. After systematic screening of the reaction parameters, varying the iron sources, the ligands, the additives, the solvents and the temperature, the optimum conditions found consisted of simply heating a *t*-BuOH (*c* 0.05 M) solution of oxime **1** and $TMSN_3$ in the presence of AcOH (1.0 equiv) and $Fe(acac)_3$ (0.2 equiv) at 50 °C. Under these conditions, γ-azido ketone **2a** was isolated in 89% yield. Although we believed that the catalytic cycle was initiated by a $Fe^{(II)}$ complex, using $Fe^{(II)}$ catalysts gave the product with much reduced yield. $TMSN_3$ outperformed other nucleophilic sources of azide. The presence of a trace amount of water was critical to avoid the formation of azadiene side product **5** and to guarantee high efficiency of the transformation. In practice, non-anhydrous commercially available *t*-BuOH was the solvent of choice. In agreement with the work of Forrester,[15] the addition of one equivalent of acetic acid improved the efficiency and kinetics of the reaction, presumably by accelerating both the 1,5-hydrogen atom transfer and the hydrolysis of γ-azido imines **4** to ketone **2a**. The reaction could be performed on a gram scale with relatively low impact on the yield.



Scheme 1. Iron-catalysed remote C–H azidation. A. Optimised conditions; B. Intermediate and side-products observed during the optimisation.

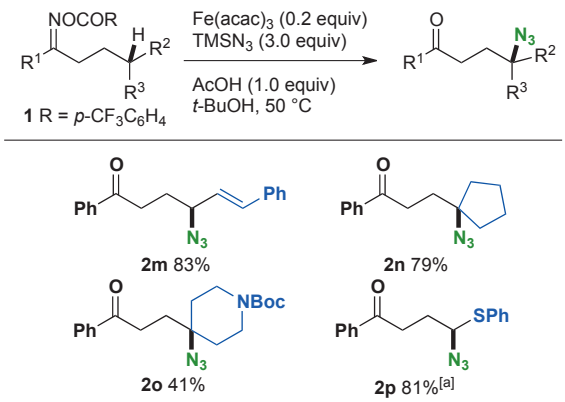
With these optimal conditions in hand, the scope of the transformation was explored (Scheme 2). Electron-poor, electron-rich and heteroaromatic benzylic positions were azidated to provide **2b** and **2c** in high yields. The ketoxime ester aryl substituent



Scheme 2. Selected examples of the distal γ-C(sp^3)–H bond azidation of benzylic positions. [a]at 80 °C.

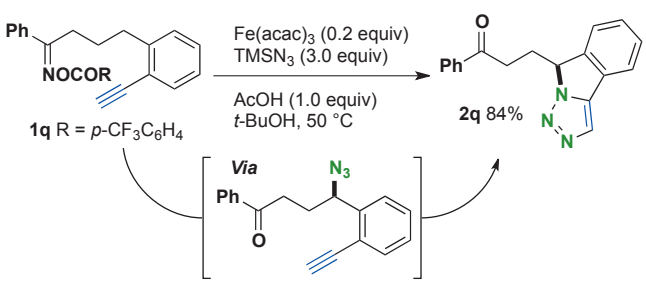
bearing an electron-withdrawing trifluoromethyl group did not alter the outcome of the reaction (**2d**, 81%). The furan substituent (**2e**) was compatible with the reaction conditions, highlighting the difference between these mild reducing conditions and the existing oxidative methodologies. Alkyl *O*-acyl oximes proved to be similarly competent in this transformation, with an excellent functional group tolerance and selectivity being observed (**2f–i**). Interestingly, product **2j**, for which the iminyl intermediate was prone to β-fragmentation, was obtained in good yield. This methodology was also successfully applied to a chlorambucil methyl oxime derivative, an anticancer drug, despite the presence of the sensitive bis(chloroethyl)amine functionality (**2k**). Finally, the possibility of a δ-C(sp^3)-H functionalisation involving a 1,6-HAT of iminyl radical was demonstrated with the isolation of δ-azidoketone **2l**, albeit in a diminished yield.

The azidation of non-benzylic C(sp^3)–H bonds was then examined (Scheme 3). Allylic (**2m**) and tertiary C–H bonds (**2n–o**) were readily functionalised. The functionalisation of a thioether α-position (**2p**) was achieved with excellent synthetic efficiency. More challenging primary and secondary C–H bonds, however, remained inert under our conditions and only the corresponding unfunctionalised ketones were isolated.



Scheme 3. Selected examples of the distal γ-C(sp^3)–H bond azidation of non-benzylic positions. [a]*t*-BuOH/DCE (v/v = 4:1, 0.05 M).

Finally, to further showcase the synthetic potential of this procedure, a domino process was designed (Scheme 4). The reaction of **1q** with $TMSN_3$ under our standard conditions afforded triazole **2q** in 84% yield *via* a domino iminyl radical generation/1,5-HAT/azidation/Huisgen [3+2] cycloaddition sequence.

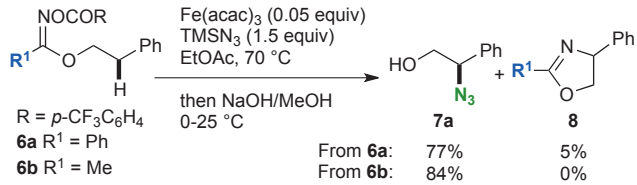


Scheme 4. Domino γ-C(sp^3)–H bond azidation/azide-alkyne [3+2] cycloaddition.

3. Extension to *N*-acyloxy Imidates

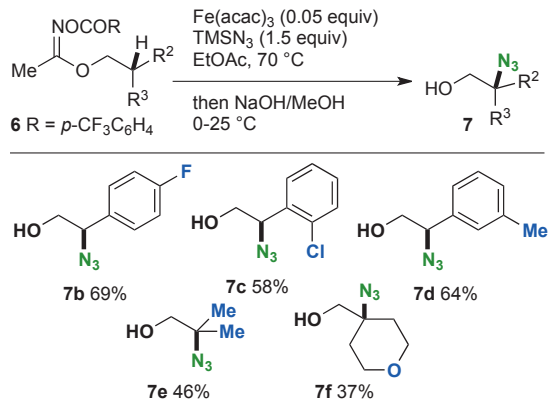
The hydroxyl moiety, an ubiquitous functional group, widely exists in nature (*i.e.* cellulose, sugars) and appears in a large number of bioactive natural molecules, synthetic intermediates and drugs.[21] The development of regioselective C(sp^3)–H functionalisation of alcohols would be an ideal approach to access value-added compounds from bulk chemicals. Unlike the δ-C(sp^3)–H functionalisation of alcohols which has been already intensively studied,[17b,c,22] examples of β-functionalisation remain scarce and are limited to transition-metal catalysed[23] and more recently to visible-light catalysed oxidative transformations.[24]

We envisioned to extend the chemistry of *O*-acyl oximes to *N*-acyloxy imidates, easily accessible from alcohols (Scheme 5). Initial attempts with the previously developed conditions proved to be unsuccessful at first. However, after investigation of the reaction conditions, acetic acid was found to be detrimental to the reaction outcome. Indeed, in the absence of acetic acid, β-azido imidate derivatives were formed as major products together with a trace amount of oxazoline **8**. After saponification of the crude reaction mixture, β-azido alcohol **7a** was obtained in good yield. The fine tuning of the reaction conditions allowed us to reduce both the catalyst and azide loading and ethyl acetate was identified as the solvent of choice. Finally, changing the directing group to the acetimidate **6b** completely suppressed the formation of oxazoline **8**.



Scheme 5. Optimised conditions for the remote C(sp^3)–H azidation of *N*-acyloxy imidates.

The scope of this reaction was then investigated (Scheme 6). Electron-poor and mildly electron-rich benzylic C–H bonds were successfully functionalised in moderate yields (**7b–d**). The presence of strong electron-donating groups on the aromatic ring tended to divert the mechanism and the product was obtained in only low yield. Finally, tertiary C–H bonds could be azidated, albeit with lower efficiency (**7e–f**). Secondary C–H bonds, however, remained untouched under these conditions.



Scheme 6. Selected examples of the remote C(sp^3)–H azidation of *N*-acyloxy imidates.

4. Conclusion

Relying on the capacity of iminyl and imidate radicals to undergo a site-selective 1,5-HAT process, we have developed two

new iron-catalysed distal C(sp^3)–H azidation of *O*-acyl oximes and *N*-acyloxy imidates under mild conditions. In these transformations, the iron catalyst played a dual role: as a reductant to generate the iminyl/imidate radical and as a redox centre to mediate the azide transfer. Under these mild reducing conditions, various γ-azido ketones and β-azido alcohols were synthesized including those bearing easily oxidisable substituents (indole, furan and thioether), complementing therefore other existing oxidative C-H azidation procedures.

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