

*“Mild oxidative Csp<sup>3</sup>-H bond functionalization applied for  
the synthesis, ring expansion and derivatization of  
heterocycles”*

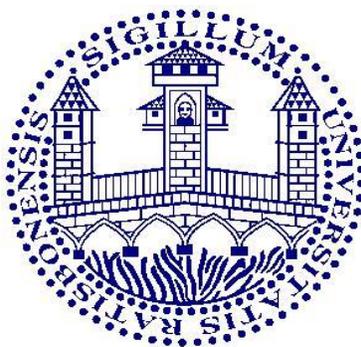
Dissertation

Zur Erlangung des Doktorgrades der Naturwissenschaften

**Dr. rer. nat**

an der Fakultät für Chemie und Pharmazie

der Universität Regensburg



vorgelegt von

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*El bastón, las monedas, el llavero,  
La dócil cerradura, las tardías  
Notas que no leerán los pocos días  
Que me quedan, los naipes y el tablero,  
Un libro y en sus páginas la ajada  
Violeta, monument de una tarde  
Sin duda inolvidable y ya olvidada,  
Una ilusoria aurora. ¡Cuántas cosas,  
Limas, umbrales, atlas, copas, clavos,  
Nos sirven como tácitos esclavos,  
Ciegas y extrañamente sigilosas!  
Durarán más allá de nuestro olvido;  
No sabrán nunca cuq nos hemos ido.  
(Las Cosas – Jorge Luis Borges)*

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# 1

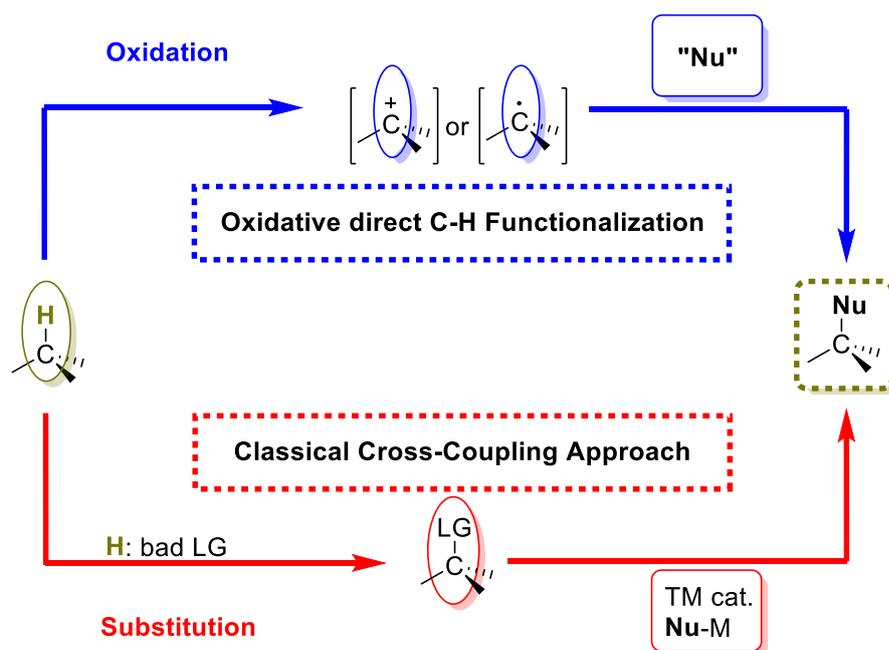
## Introduction

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## 1.1 Csp<sup>3</sup>-H bond oxidative functionalization: An introduction

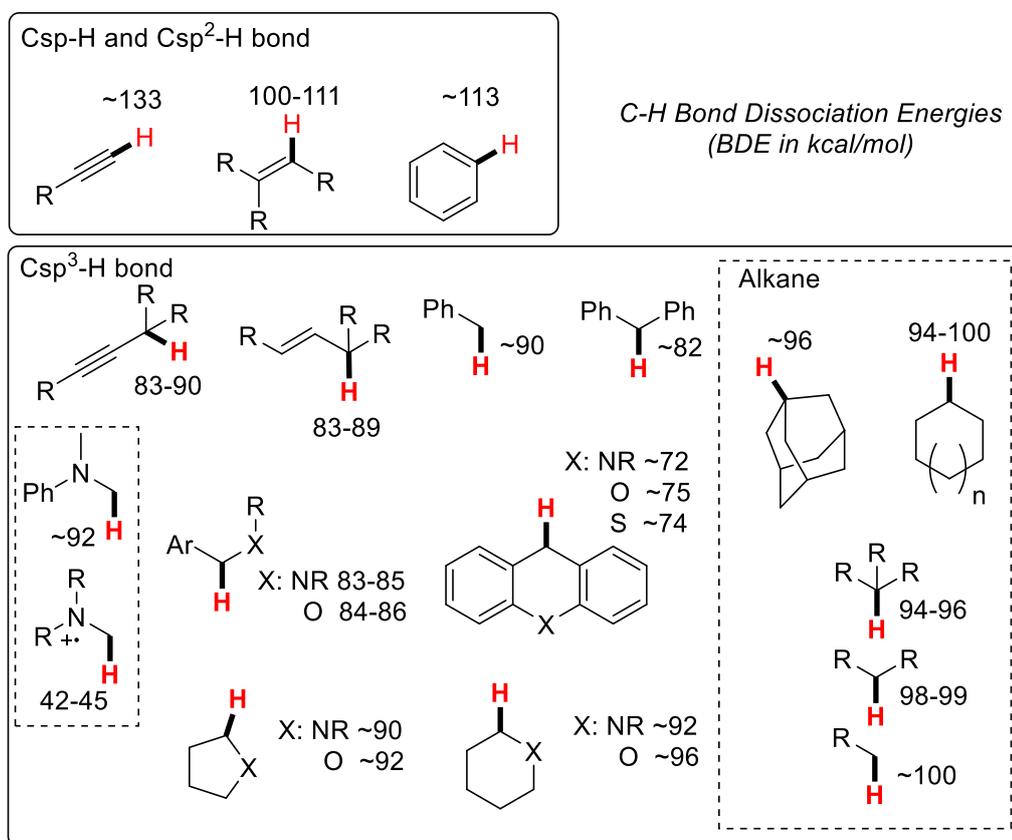
Csp<sup>3</sup>-H bonds are omnipresent in synthetic and natural compounds.<sup>1</sup> From small neurotransmitters to big bio-polymers, all the organic compounds are essentially chains or rings of consecutive carbon atoms covered each with one or more hydrogen atoms, occasionally followed by heteroatoms (such as oxygen, nitrogen or halogen). Although such heteroatoms are essential for common organic synthetic strategies, nature has engineered various approaches to introduce high value fragment in molecules by simple activation of Csp<sup>3</sup>-H bond in a regioselective manner,<sup>2</sup> for example what is observed in the biosynthesis of several alkaloids.<sup>2a,2f,2e</sup> Indeed, one of the biggest challenges, easily tackled by nature, is the similar high energy of the different present Csp<sup>3</sup>-H bonds,<sup>3</sup> which hinders achieving a complete regioselectivity without abusing of synthetic steps. As it follows, the scientific community is far to carry out similar and almost perfect strategies, and the most general methodology on the functionalization of Csp<sup>3</sup>-H bond still relief in standards cross-coupling approaches involving a pre-insertion of a good leaving group (LG), which drives the next reaction, typically a nucleophilic substitution or a transition metal (TM) catalysed coupling (Scheme 1).<sup>4</sup> It is important to notice that, even though the C-H bond in sp<sup>2</sup> and sp carbons have higher dissociation energy compared to Csp<sup>3</sup>-H, the intrinsic proprieties of unsaturated carbon chains lead to easier and extremely regio-selective direct functionalization of Csp<sup>2</sup>-H or Csp-H bond, such as standard Heck and Sonogashira cross-coupling reactions.<sup>5,6</sup>



**Scheme 1.** Direct oxidative C-H functionalization vs. cross coupling.

Another important issue is the incompatibility of the enrolled reagents with the functional groups in the molecule, especially when strong organometallic nucleophiles are involved.<sup>4</sup> Thus, to avoid this controversy other unwanted protection/deprotection steps are required. Therefore, Csp<sup>3</sup>-H functionalization reactions inspired by nature's high efficiency and chemoselectivity are highly desirable and an ongoing endeavour in synthetic chemistry. In this regard, one of the most promising approach is the dehydrogenative or (mono-) oxidative functionalization of Csp<sup>3</sup>-H bonds. Among this approach, several other similar C-H bond direct functionalization strategies were successfully developed. For example, other interesting methodologies involve the C-H bond activation by a transition metal or by metal-carbene formation,<sup>7,8</sup> the activation by hydrogen radical abstraction through an *in situ* generated N-centered radical,<sup>9</sup> radical halogenations,<sup>10</sup> the

more classical Friedel-Crafts-type reactions or the simple deprotonation-substitutions (via acid-base) not involving a C-H oxidation of the reaction partner.<sup>11</sup> The dehydrogenative or (mono-) oxidative functionalization of Csp<sup>3</sup>-H strategy was just a dream at the beginning of the last century, but in the last 20 years chemists explored massively this approach, resulting to a relentless flow of outstanding applications that try to elude the poor regioselectivity among similar Csp<sup>3</sup>-H bonds. In general, such approaches rely on the symmetry of the desire target, or on steric hindrance, to exclude specific site. However, the intrinsic nature of Csp<sup>3</sup>-H bonds, i.e. different influences from adjacent functional groups, lead to slightly but exploitable changes of dissociation energy between diverse C-H bonds (Scheme 2).<sup>12</sup> As consequence, the choice of the right oxidative system has a major role in scheduling a strategy with the outlook of a complete regioselective C-H bond functionalization on a substrate with several possible active sites. In this fashion, it would be noteworthy to analyse the current evolution in Csp<sup>3</sup>-H functionalization based on an oxidant perspective, while discussing the advantage and disadvantage of each class of oxidant.

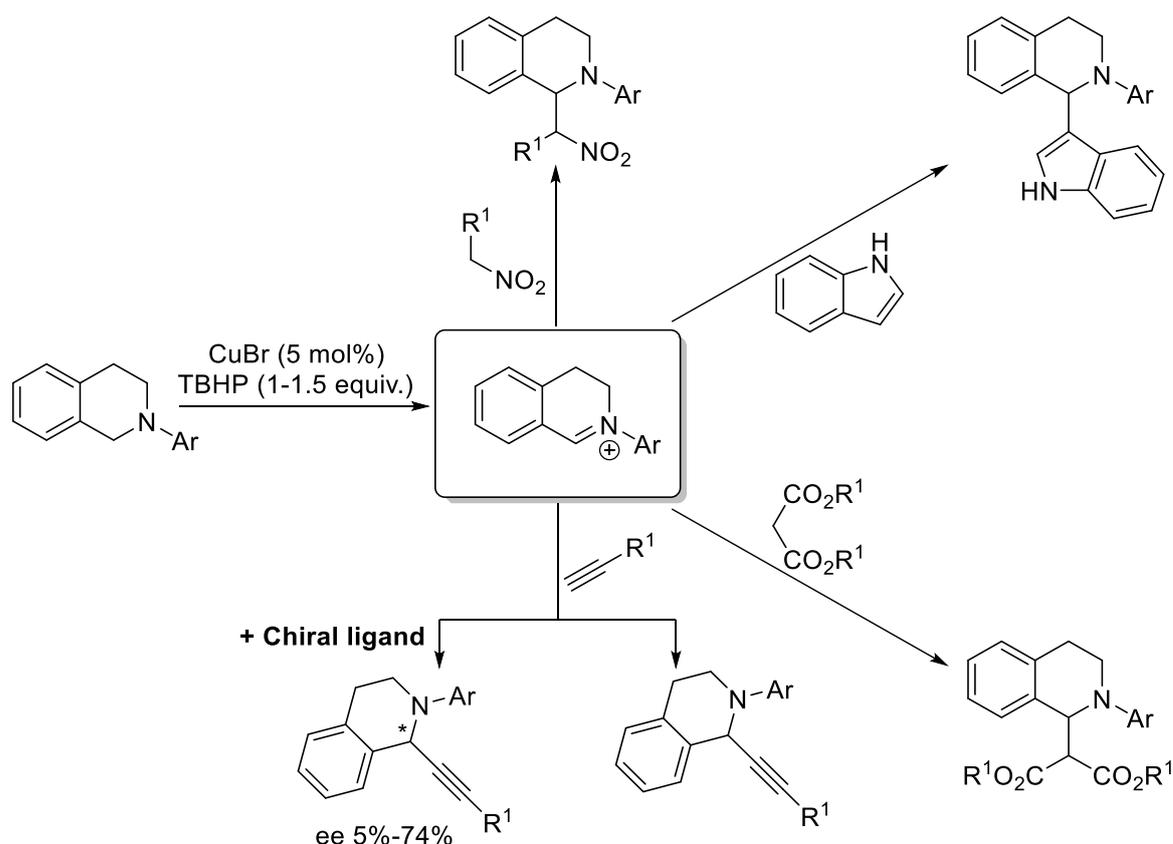


**Scheme 2.** BDEs of C-H bonds of standard substrates.

## 1.2 Peroxides as Oxidants

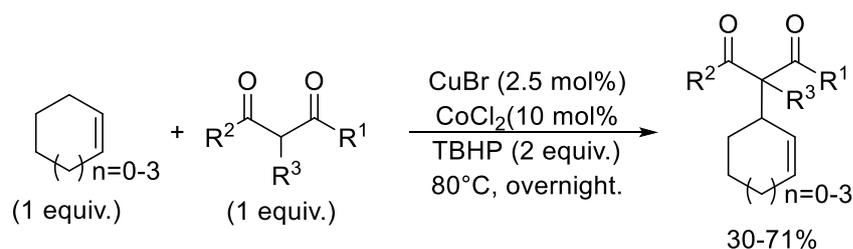
The most representative examples of dehydrogenative and (mono-)oxidative Csp<sup>3</sup>-H bond functionalization involved strong radical hydroxyperoxide oxidants such as *tert*-butyl hydroxylperoxide (TBHP). Besides the general low selectivity of this reactant, several reported procedures employ it as terminal or as primary oxidant, generally paired with copper or iron based catalysts.<sup>13</sup> Metal catalysis results in many cases essential to achieve not only in the C-X bond formation, but to enhance the selectivity and to help the activation of the hydroxyperoxide at lower temperatures. However, when such strong peroxides are employed, it is essential to avoid sensitive functional groups and to target substrates with a highly distinct oxidizable site.

Between 2004 and 2006, C. S. Li and co-workers published plenty of outstanding examples on copper catalysed Csp<sup>3</sup>-H bond activation involving TBHP as oxidant.<sup>14</sup> Among these publications, it resulted doubtless that tetrahydroisoquinoline is a special target when such strategies are applied (Scheme 3). From the pioneering work reported in 2004, in which alkynes were the chosen reaction partners, several different nucleophiles have been successfully employed. However, the methods are limited to nucleophiles that are stable in such oxidative environment. In addition, Li's group showed that it was possible to extend, this methodology to different Csp<sup>3</sup>-H bonds in  $\alpha$  to a nitrogen atom, such as in dimethyl anilines or cyclic amines.<sup>14a,14d</sup> Noteworthy, it was possible to perform the addition of an alkyne in asymmetric manner by adding a chiral ligand (Scheme 3).<sup>14b</sup>



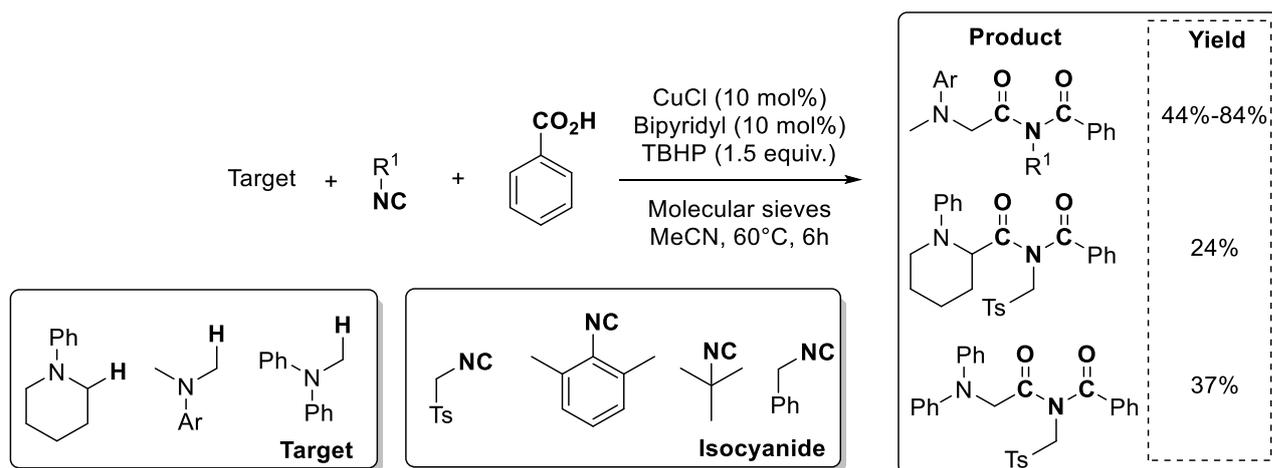
**Scheme 3.** Various TBHP mediated C-H functionalization of THIQ.

In addition, the C.-J Li's group achieved the THBP-mediated functionalization of allylic C-H bond of cyclic alkenes using copper and cobalt as dual catalytic system (Scheme 4).<sup>14f</sup>



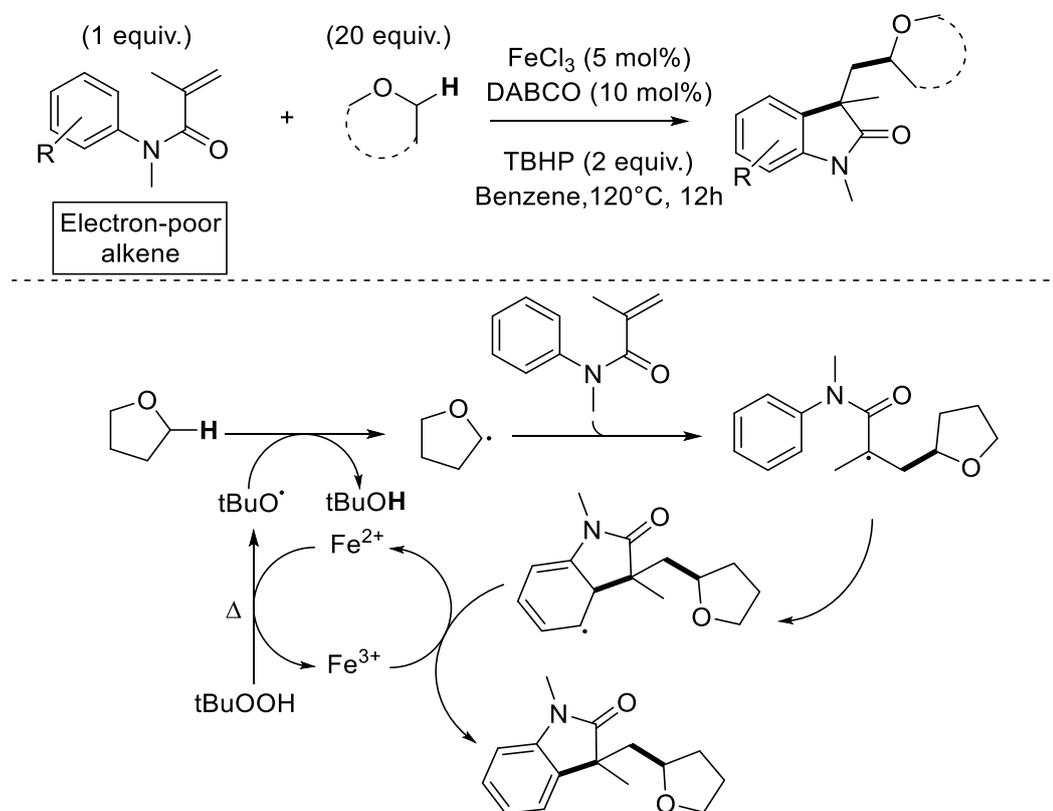
**Scheme 4.** Cobalt/Copper dual catalysis for the functionalization of allylic C-H bond.

In 2010, T. Xie and co-workers published an interesting Ugi-type three-component reaction involving THBP/copper-mediated Csp<sup>3</sup>-H direct functionalization of N,N-dimethyl anilines.<sup>15</sup> The proposed strategy appears a valid option for the synthesis of  $\alpha$ -amino imides, but it has some limitations regarding the scope. This methodology is not applicable to electron-rich anilines, highly electron-poor anilines and *ortho* unsubstituted aryl isocyanides. In addition, the reaction is limited to aryl carboxylic acids. The yields are reasonable, but a poor reactivity is observed when the target is not a N,N-dimethyl aniline (Scheme 5).



**Scheme 5.** THBP-mediated C-H bond functionalization/Ugi-type reaction.

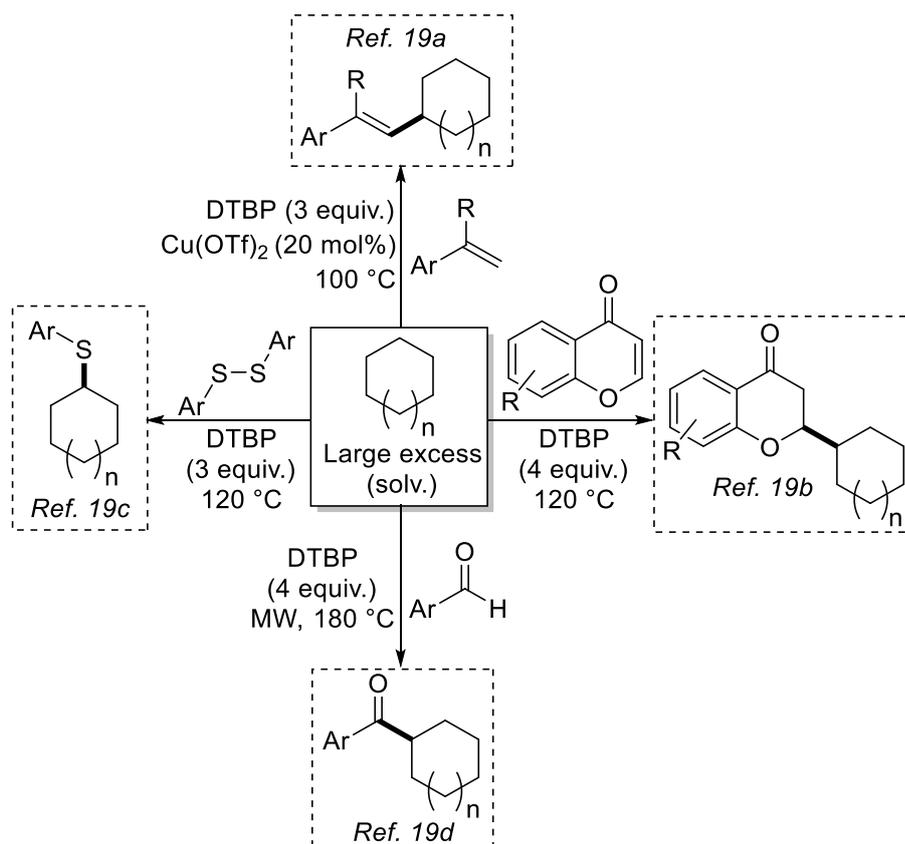
TBHP is not only able to mediate the activation of Csp<sup>3</sup>-H bonds close to a nitrogen. For example, in 2013 the group of J.-H. Li proposed an interesting strategy for the formation of oxo-indolines by addition of ether-radicals, formed via TBHP-mediated HAT process, to electron-poor alkenes (Scheme 6).<sup>16</sup>



**Scheme 6.** Synthesis of oxo-indolines by C-H functionalization/cascade reaction.

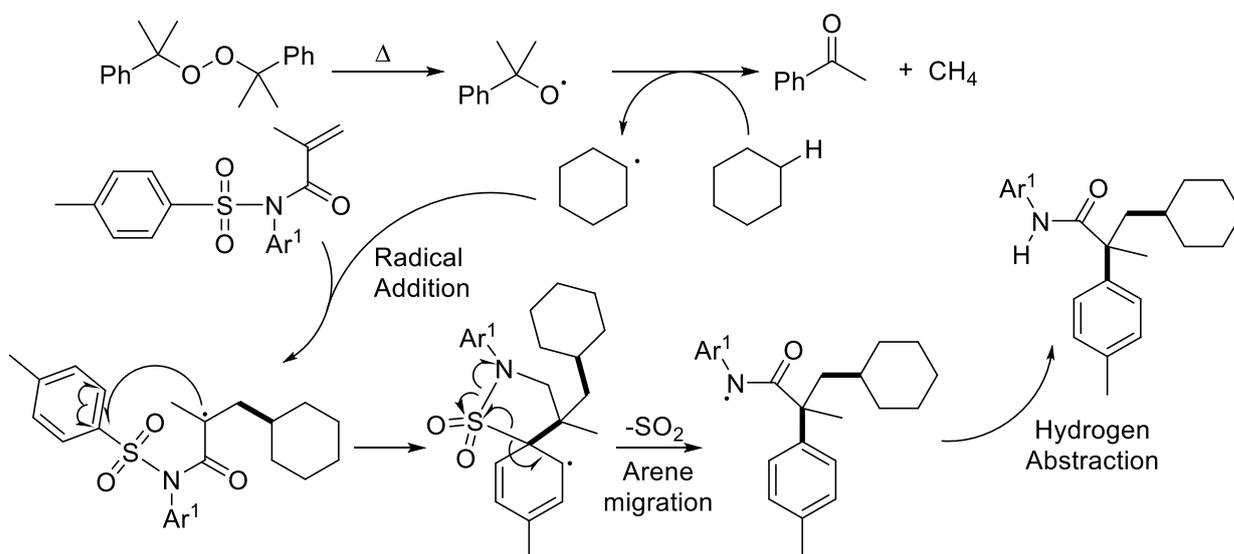
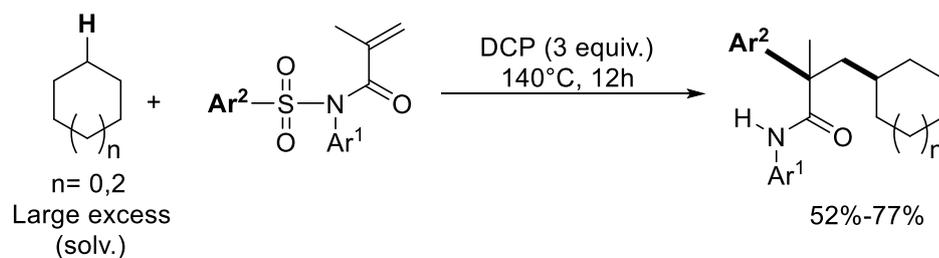
In this case, the reaction is performed under iron catalysis, which promotes both the activation of the TBHP and the SET process to restore the aromaticity to form the desired product. Although the reaction works relatively well with linear and cyclic ethers, diethers, cyclic thioethers and methyl piperidines, the strategy is restricted to symmetric substrates. Furthermore, the employed high temperature (120 °C) and the requested large amount of ethers (20 equiv.) limits the procedure to small scale reaction with cheap and temperature-stable ethers. It is interesting to notice that in 2015 H. Ge and co-workers published a similar Csp<sup>3</sup>-H bond activation for the addition of ethers on coumarin and flavon derivatives.<sup>17</sup>

Even though TBHP can perform efficient C-H bond functionalization on several targets and the copper/TBHP system could be considered a benchmark in the C-H bond activation, the high reactivity of TBHP limits the scope, especially considering a late stage functionalization of sensitive substrate. Thus, the attention was shifted to more tolerating oxidants such as dialkyl or diacyl peroxides,<sup>18</sup> from which the formation of the active radical species is considerable slower. The dialkyl and diacyl peroxides, such as di-*tert*-butyl peroxide (DTBP), dicumyl peroxide (DCP) and dibenzoyl peroxide (BPO), were then explored in many Csp<sup>3</sup>-H bond functionalization reactions, including rather inert substrates. In fact, in recent years, the mediated Csp<sup>3</sup>-H bond activation of cyclic symmetric alkanes resulted a potent methodology for the alkylation of several radical acceptors.<sup>19</sup> The most notably examples are involving simple alkenes,<sup>19a</sup> chromones,<sup>19b</sup> dithiols<sup>19c</sup> or aldehydes<sup>19d</sup> (Scheme 7).



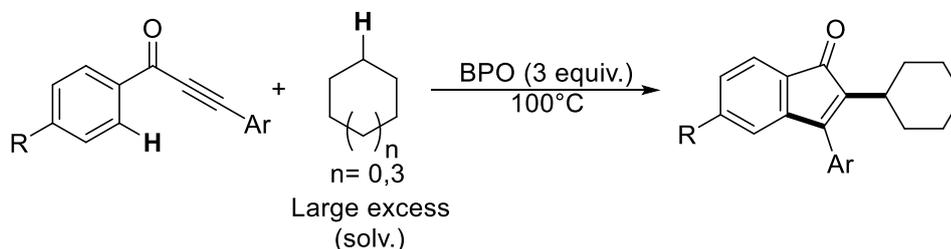
**Scheme 7.** Di-*tert*-butyl peroxide mediated C-H functionalization of alkenes.

The generated alkyl radical intermediate can also be involved in cascade reactions.<sup>20</sup> For example, C. Zhu and co-workers reported in 2015 the synthesis of novel quaternary carbon centres by a DCP promoted free radical cascade process concerning a radical addition/SO<sub>2</sub> elimination/arene migration (Scheme 8).<sup>20a</sup> Several N-aryl-N-(arenylsulfonyl)methacrylamides were used efficiently apart from substrate bearing strongly electron-poor or bulky *ortho* substituents.



**Scheme 8.** Alkyl radical addition to electron-poor alkane.

More recently, J.-T. Yu and his collaborators proposed another interesting cascade reaction, implicating a benzoyl peroxide mediated Csp<sup>3</sup>-H bond activation/carboannulation of ynones with alkanes (Scheme 9).<sup>20b</sup> The activation of alkanes presents some important limitations due to the required typical high temperature to achieve both the activation of the peroxide and the HAT on the alkane. Furthermore, there is a poor regioselectivity for the functionalization on linear and not symmetric substrate. Other notable target molecules suitable for the Csp<sup>3</sup>-H bond activation by diacyl or dialkyl peroxides are benzylic, moieties<sup>21a, 21c</sup> amides<sup>21b</sup> or ethers<sup>21d</sup>.



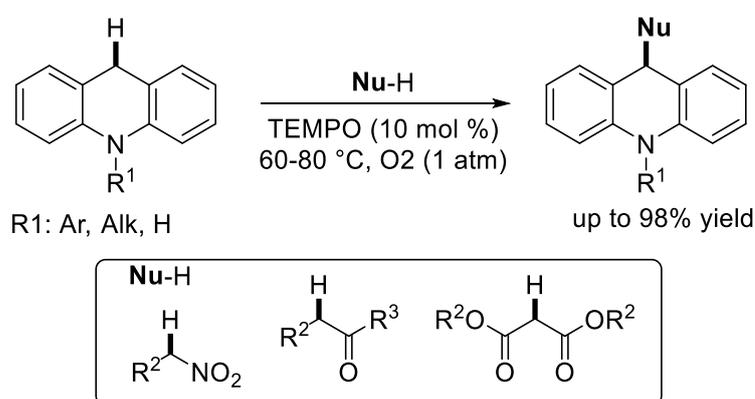
**Scheme 9.** Benzoyl peroxide mediated Csp<sup>3</sup>-H bond activation/carboannulation of ynones.

### 1.3 Benzoquinones and Oxygen as Oxidant

Benzoquinones are another class of oxidants that have been employed in various oxidative Csp<sup>3</sup>-H functionalization applications, such as direct cross dehydrogenative coupling (CDC) reactions mediated by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) reported by C.-J. Li and co-workers.<sup>22</sup> Nevertheless, the main concern about these oxidative agents is their high intrinsic toxicity.<sup>23</sup> Therefore, oxygen has attracted a great attention in the past few years as one of the greenest and cheapest oxidants.<sup>24</sup> Unfortunately, its reactivity as oxidant is poor. As a result, there are only few examples where oxygen was used without any additive, such as metal catalysts or terminal oxidants. In such cases, oxygen is involved in an auto-oxidative process with those substrates that may form a peroxide intermediate at the targeted Csp<sup>3</sup>-atom, which acts as the real catalytic oxidant.<sup>25</sup> Thus, currently oxygen itself cannot be evaluated as an efficient active oxidation agent in this chemistry, except when used as secondary oxidant.

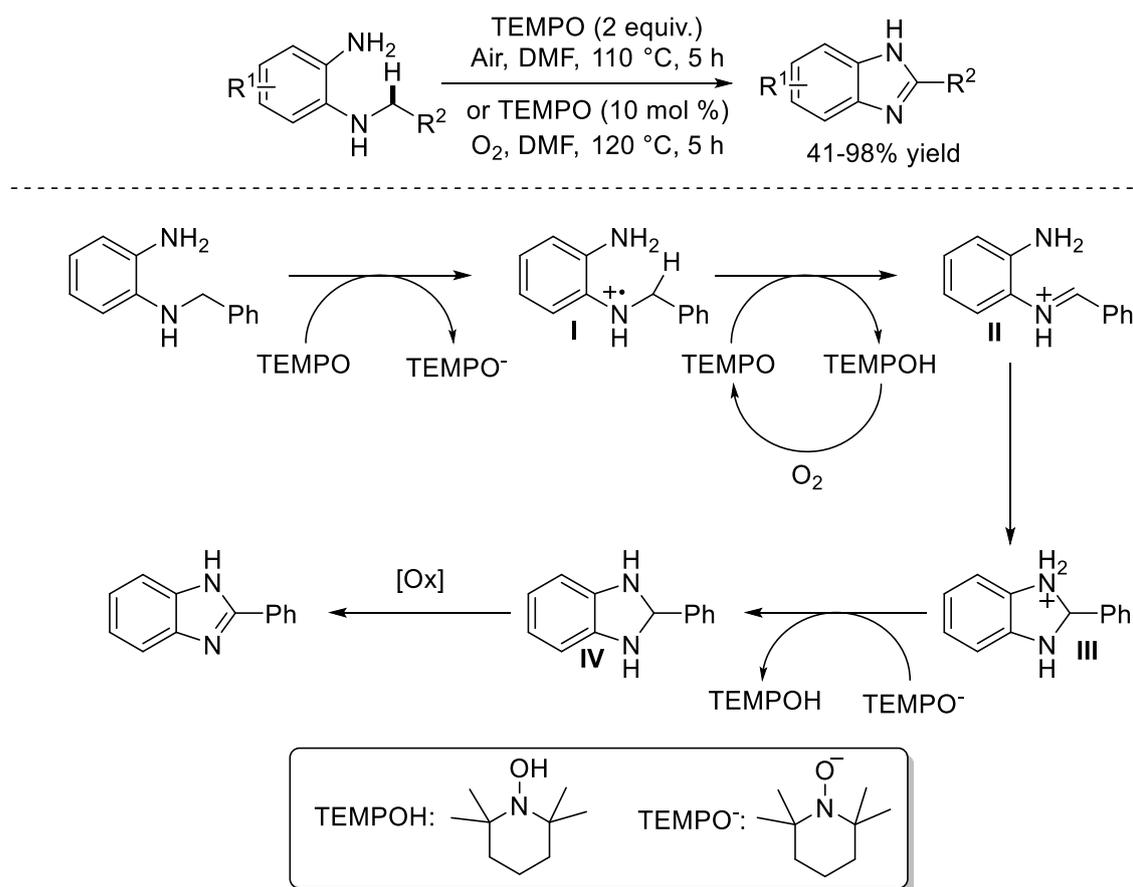
### 1.4 Stable N-Oxyl radicals as Oxidants

Since the first synthesis of the persistent 2,2,6,6-tetramethylpiperidinyloxy radical (TEMPO, E<sup>0</sup><sub>ox</sub> = 0.76V/ E<sup>0</sup><sub>red</sub> = 1.48V) by Lebedev and Kazarnovskii in 1959,<sup>26</sup> the interest around stable radical nitroxides have relentlessly increased. Among stable N-oxyl radicals, TEMPO is well known as highly versatile oxidant and it has recently been used in C-H coupling reactions, including oxidative Csp<sup>3</sup>-H bond functionalization. The first TEMPO/O<sub>2</sub> induced example of such transformation was reported by N. Jiao and co-workers in 2012.<sup>27</sup> Thus, the simple reaction between acridanes and carbonyl based nucleophiles in the presence of a catalytic amount of TEMPO, under oxygen atmosphere at 60 °C, led to the corresponding C-9 substituted coupling product in moderate to excellent yields. Although the mechanism of this transformation is still unknown, the author proposed that oxygen is involved in both the oxidation of the substrate and the reactivation of the generated TEMPO-OH to TEMPO radical (Scheme 10).



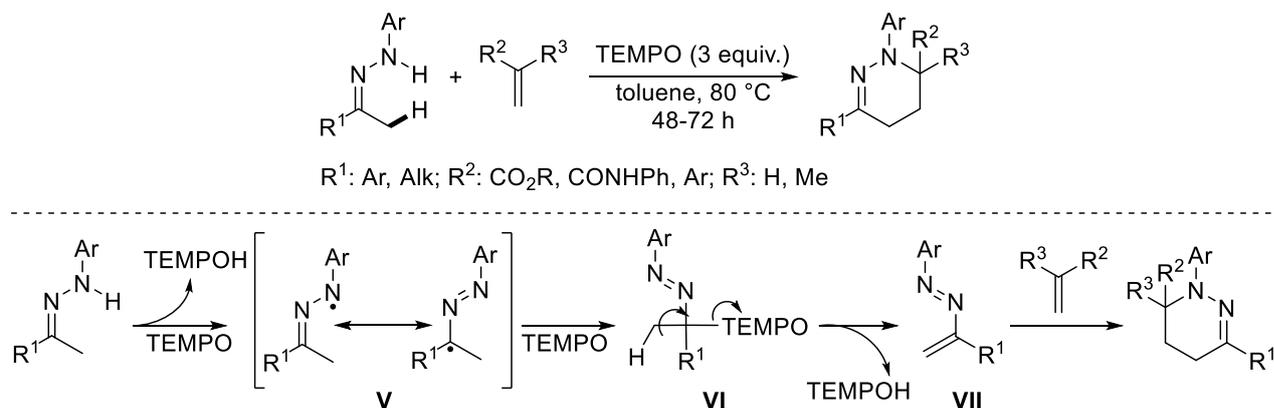
**Scheme 10.** TEMPO-mediated C-C coupling of acridanes.

In 2014 D. Xue and Y. Long have presented an efficient TEMPO/air mediated intramolecular Csp<sup>3</sup>-H amination of N-substituted 1,2-phenyldiamines (Scheme 11).<sup>28</sup> In this case, a stoichiometric amount of TEMPO was employed at 110 °C to afford multisubstituted benzimidazoles in poor (N-alkyl) to excellent (N-aryl) yields. Notably the reaction could also be carried out with catalytic amount of TEMPO, but then an oxygen atmosphere was required to achieve a similar efficiency. The proposed mechanism involves a first TEMPO-mediated single electron transfer (SET) process to form a radical cation **I**, followed by a hydrogen abstraction. The generated iminium intermediate **II** can easily evolve to the bicyclic aromatic product by nucleophilic addition (**III**) and final aerobic oxidation via the intermediate **IV**.



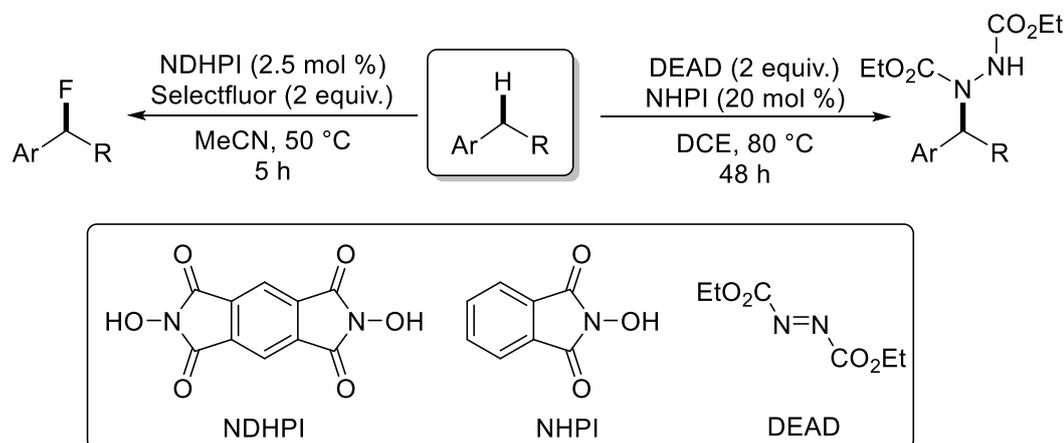
**Scheme 11.** TEMPO/O<sub>2</sub> oxidation system in Csp<sup>3</sup>-H bond amination/intramolecular cyclization reactions.

Recently, B. Han and co-workers described an elegant and novel TEMPO-mediated intermolecular aza-Diels-Alder reaction by oxidative C-H functionalization of ketohydrazone (Scheme 12).<sup>29</sup> The authors proposed that two equivalents of TEMPO are necessary to achieve such transformation: i) the first molecule extracts the hydrogen radical from the hydrazone moiety **V** and ii) the second stabilizes the radical intermediate **VI**, which undergo a Cope-like TEMPOH elimination leading to the active hetero-diene **VII**. Moderate to good yields on the Diels-Alder adduct could be obtained, though only stabilized dienophiles and aromatic hydrazines were well tolerated in this reaction.



**Scheme 12.** TEMPO-mediated oxidative aza-Diels-Alder reaction

The applications of other stable persistent N-oxyl radicals in Csp<sup>3</sup>-H functionalization are few and, in general, the radical oxidant has a marginal role in the oxidation system.<sup>30</sup> Nevertheless, in-situ generated N-oxyl radicals from N-hydroxyphthalimide-like molecules are reported as efficient catalytic mediators in Csp<sup>3</sup>-H bond functionalization such as nitrations and fluorinations (Scheme 13).<sup>31</sup>



**Scheme 13.** N-Hydroxyphthalimides as N-oxyl-like oxidant precursors.

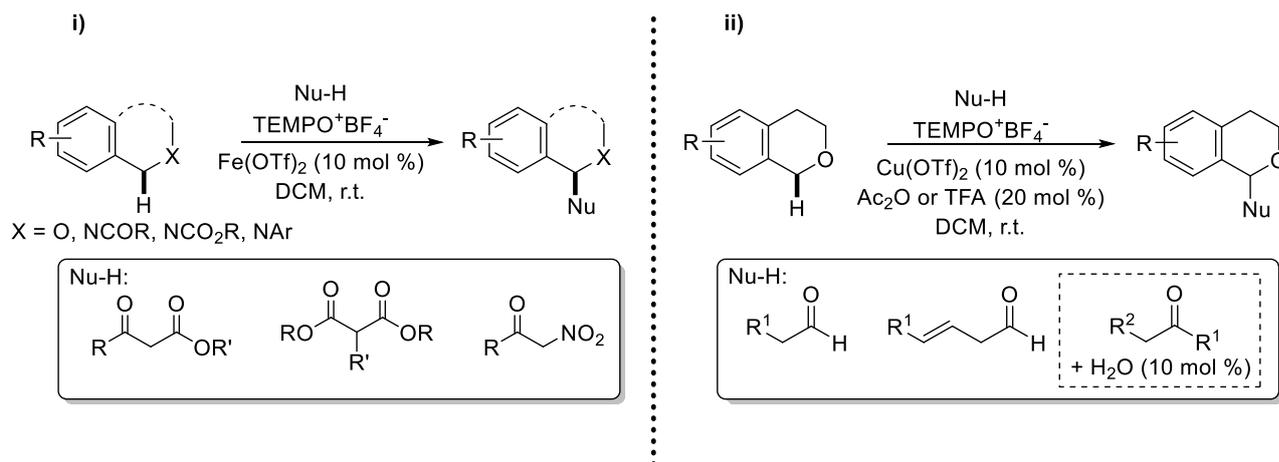
## 1.5 Cationic organic oxidants

### 1.5.1 Hydride Abstractors

This section will cover ionic oxidants, which do not involve a radical intermediate but proceed by a direct hydride abstraction from the substrate. In this regard, N-oxammonium and carbenium salts have recently been established as the standard classes of oxidants of this type.

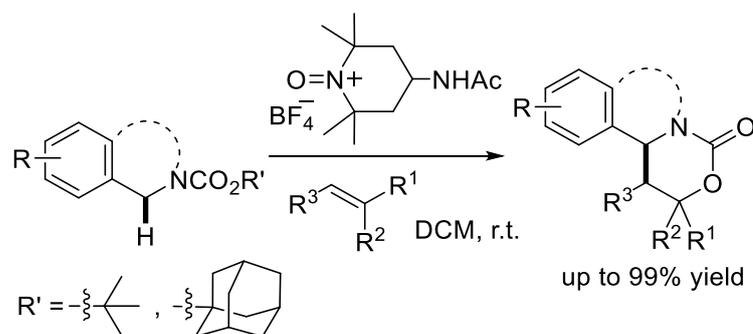
#### *Oxoammonium salts*

The first example of oxidative Csp<sup>3</sup>-H bond functionalization employing a TEMPO oxoammonium salt was reported in 2010 by García Mancheño and co-workers (Scheme 13, i).<sup>32</sup>



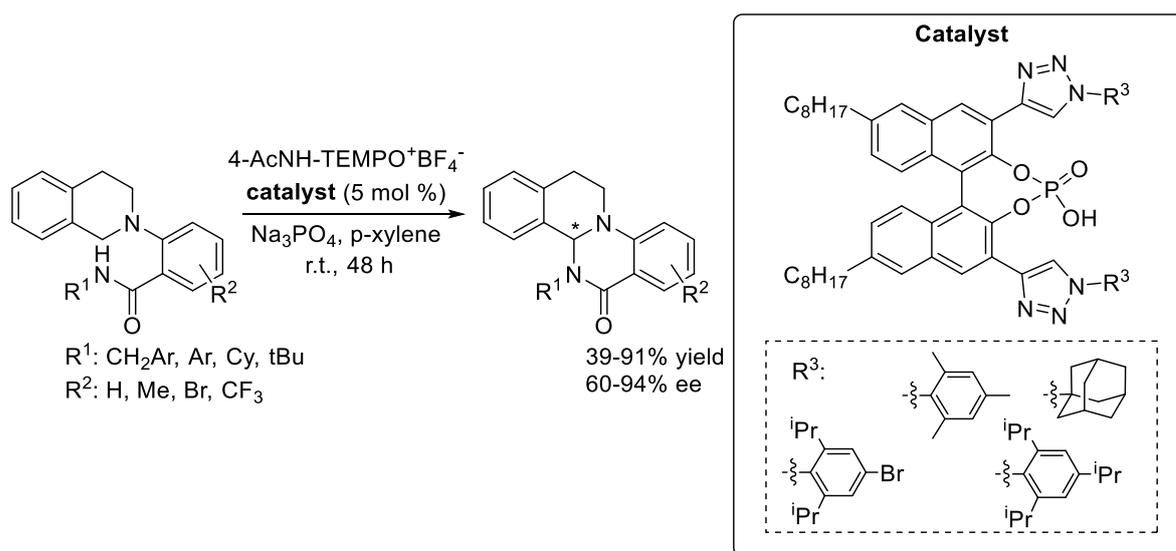
**Scheme 13.** TEMPO<sup>+</sup>BF<sub>4</sub><sup>-</sup> mediated CDC reaction with carbonyl.

In this pioneering work, different activated carbon pronucleophiles, such as malonates or keto ester compounds, were involved in the reaction with various benzyl ethers and amines under iron catalysis. In the absence of the metal catalyst, the main products of the reaction resulted both the oxygenated dimer and the oxidation product of the starting material. Therefore, it was postulated that the catalyst served only as a Lewis acid in the C-C coupling, facilitating the slow re-opening of this dimer intermediate to the active oxonium or iminium species. In 2011, the same group extended the procedure to less reactive C-H-based nucleophiles such as alkyl and  $\alpha,\beta$ -unsaturated aldehydes (Scheme 13, ii). Slightly changes of the condition were necessary to enrol such nucleophiles: a different lewis acid catalyst (copper(II) instead of iron(II)) and a catalytic amount of acetic anhydride or acetic acid.<sup>33</sup> Later on, the first example of Csp<sup>3</sup>-H functionalization/intermolecular cyclization tandem reaction of N-carbamoyl tetrahydroisoquinolines and benzyl carbamates mediated by the 4-acetoamido TEMPO salt (4-AcNH-TEMPO<sup>+</sup>BF<sub>4</sub><sup>-</sup>) was reported by García Mancheño and co-workers (Scheme 14).<sup>34</sup> This fascinating way to obtain the oxazinone ring involves the reaction of olefins with benzylic carbamates bearing a leaving group. The initially employed Boc-protecting group led to a mixture of the desired product along with the one derived from the reaction with 2-methylpropene formed *in situ* by elimination of Boc group under the employed conditions. The next choice of adamantyl carbamate as uncommon protecting group was inspired by the Bredt's rule, which negate the formation of a double bond on tertiary "bridge" carbon of polycyclic systems. This solution dramatically changed the efficiency of the reaction, since the leaving adamantyl carbocation cannot produce a competitive alkene by further elimination.



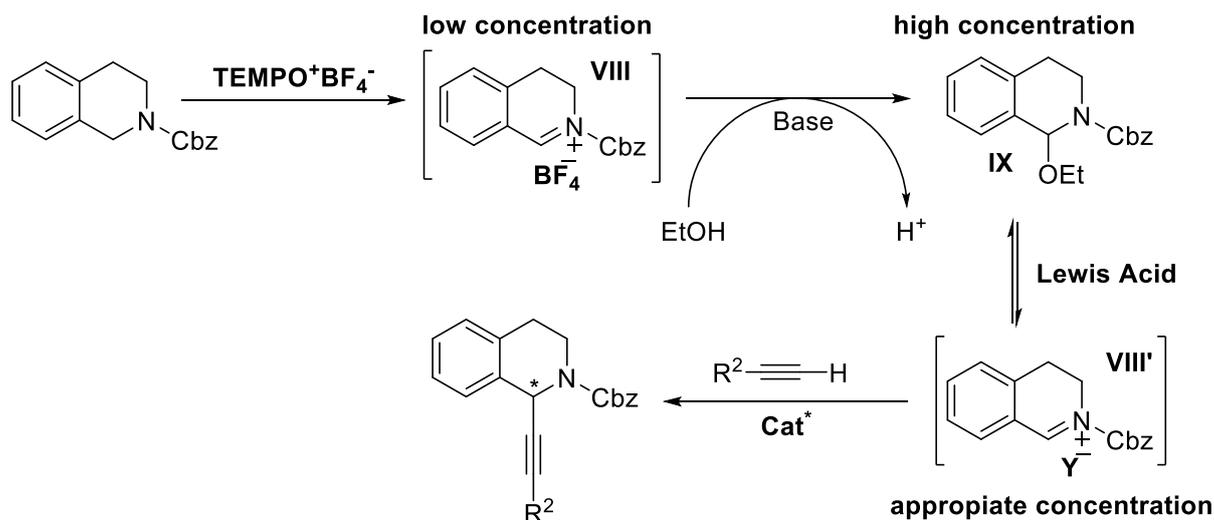
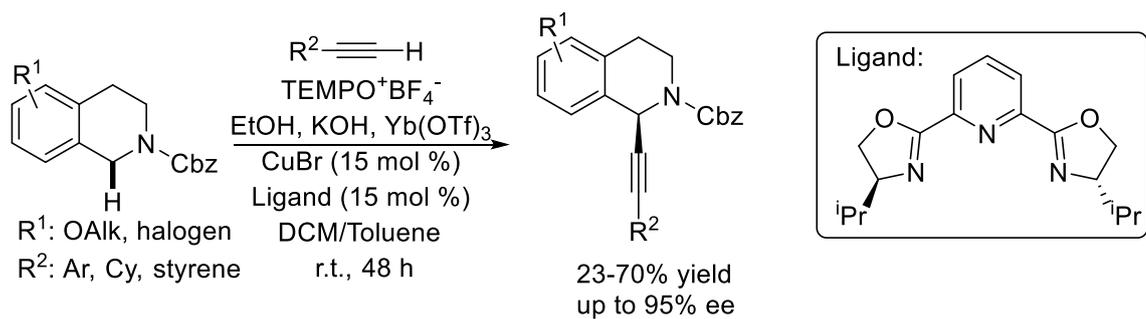
**Scheme 14.** 4-AcNH-TEMPO<sup>+</sup>BF<sub>4</sub><sup>-</sup> in Csp<sup>3</sup>-H functionalization /intermolecular cyclization tandem reaction to oxazinones.

In 2013 D. Toste and co-workers designed a prominent example of intramolecular enantioselective annulation (Scheme 15).<sup>35</sup> Following the good results obtained in the intermolecular cyclization reported by García Mancheño, Toste's group developed an attractive 4-AcNH-TEMPO<sup>+</sup>BF<sub>4</sub><sup>-</sup> promoted asymmetric Csp<sup>3</sup>-H amination of N-(2-benzamide)-tetrahydroisoquinolines catalyzed by chiral 3,3'-triazolyl BINOL-derived phosphates. Various bulky protecting groups were tolerated on the amide moiety and good to excellent enantioselectivities were achieved.



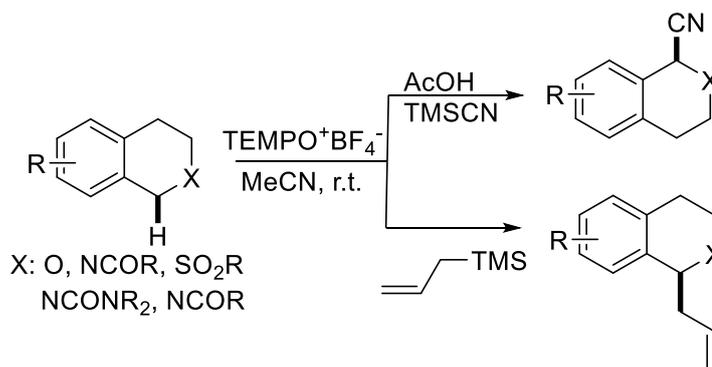
**Scheme 15.** Chiral phosphate-catalyzed oxidative asymmetric Csp<sup>3</sup>-H functionalization/intramolecular cyclization.

In 2015 L. Liu described a further enantioselective Csp<sup>3</sup>-H functionalization reaction of N-carbamoyl tetrahydroisoquinolines using a TEMPO salt as oxidant (Scheme 16).<sup>36</sup>



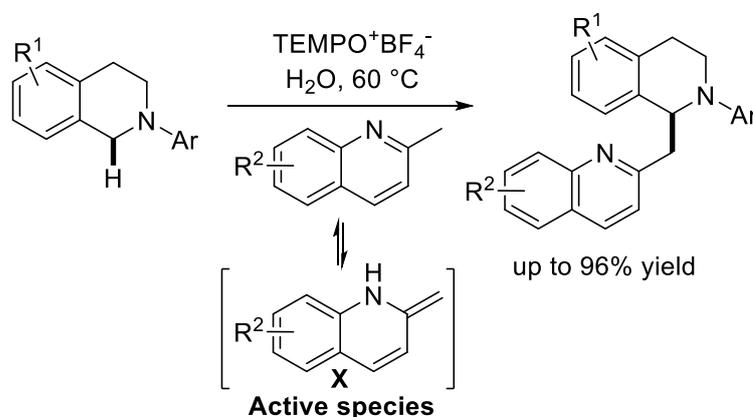
**Scheme 16.** TEMPO salt-mediated asymmetric alkylations.

Thus, the coupling of terminal alkynes catalyzed by chiral copper complexes was reported. However, in this manner the generated catalytic Cu-nucleophile could not effectively react with the highly unstable acyliminium species. The authors proposed an intelligent way to improve the efficiency of the reaction by trapping the iminium intermediate **VIII** with ethanolate. It was then possible to activate the generated alkoxy species **IX** to slowly regenerate the ionic active intermediate **VIII'** by enrolling a metal Lewis acid catalyst. Despite the moderate yields, the enantiomeric excesses proved to be in most the cases around 90%. An extension of possible nucleophiles able to participate in the Csp<sup>3</sup>-H functionalization of tetrahydroisoquinolines (THIQs) has been proposed by Q. Wang and co-workers. Between 2014 and 2015 the group published two different applications of Csp<sup>3</sup>-H functionalization mediated by the TEMPO<sup>+</sup>BF<sub>4</sub><sup>+</sup> salt involving TMS-based nucleophiles (Scheme 17).<sup>37,38</sup> The first example was a metal-free α-cyanation with trimethylsilyl cyanide performed in acetonitrile at room temperature.<sup>37</sup> In this case, the addition of acetic acid was necessary to inhibit the decomposition of the oxidant. Moreover, this procedure could also be extended to isochromanes.



**Scheme 17.** Csp<sup>3</sup>-H bond functionalization with TMS-based nucleophiles.

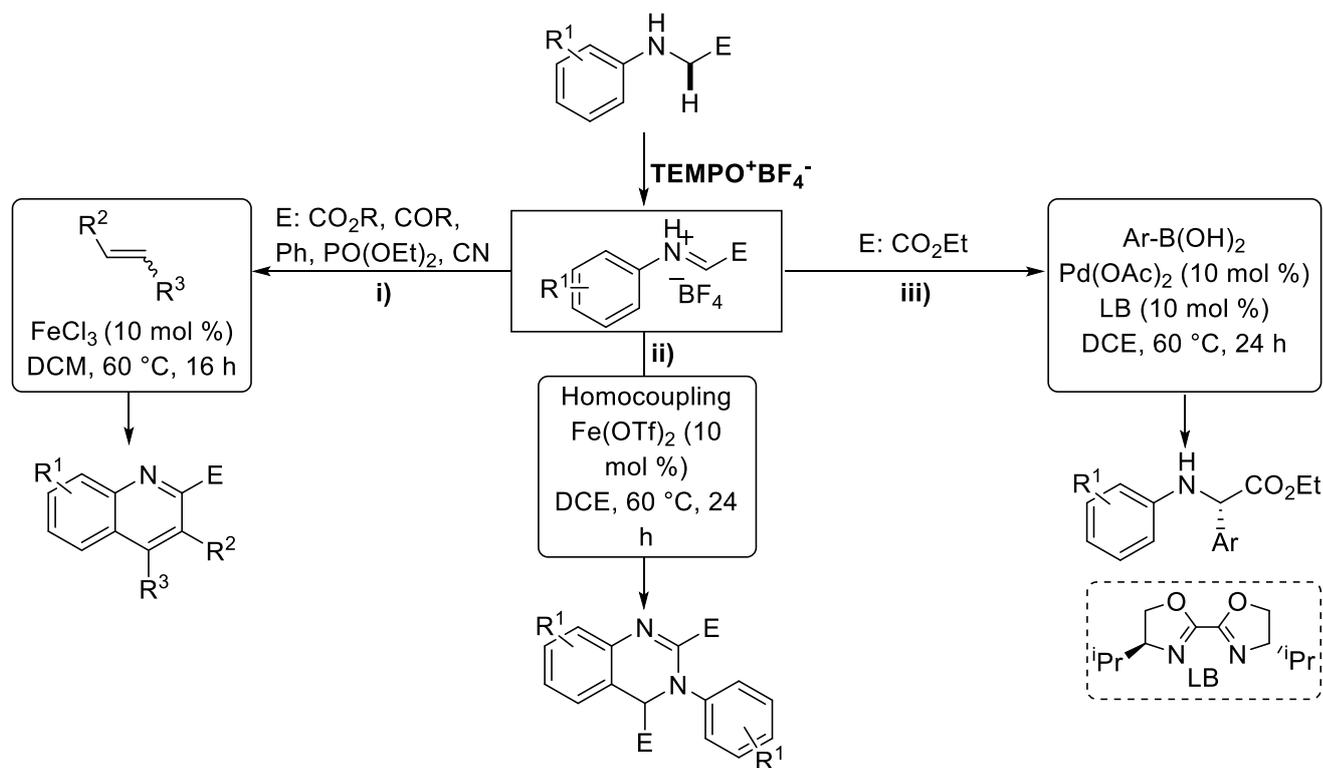
In the second example, a direct C-H allylation with allyltetramethylsilane of N-acyl/sulfonyl tetrahydroisoquinolines was developed.<sup>38</sup> It is worth to notice that various less reactive analogues of tetrahydroisoquinoline could also be applied, leading to moderate to good yields on the corresponding allyl derivatives. Another interesting nucleophile has been recently employed by Xie and co-workers in the Csp<sup>3</sup>-H functionalization of THQs mediated by oxoammonium salts (Scheme 18).<sup>39</sup> 2-Methylquinoline is in equilibrium with its enamine form **X**, which could act as a nucleophile. Thus, various substituted 2-methylquinolines were involved in this functionalization, providing good to excellent yields. It is relevant to mention that water resulted the best solvent, giving attractiveness to this greener procedure. However, the scope is quite limited from the substrate side: only aromatic N-protecting groups could be employed.



**Scheme 18.** 2-Methylquinolines as nucleophiles.

In the past few years, glycine and peptide-like derivatives have proved as an interesting target in Csp<sup>3</sup>-H functionalization. However, the literature lacks of robust methodologies where milder oxidants are employed. Indeed, just few relevant steps have been done to extend the application of mild oxidants to such substrates, in particular TEMPO salts. The García's group reported two different pioneer works between 2011 and 2013 enrolling TEMPO salt as oxidant (Scheme 19, eq. i and ii). Various N-aryl glycine esters were then involved in Csp<sup>3</sup>-H functionalization/cyclization reactions using olefins to give multi-substituted quinolines. Moreover, the homo-coupling of the glycine substrates to dihydroquinazolines under iron catalysis was also developed.<sup>40,41</sup> Olefins were initially chosen as nucleophile because, after the first addition, they lead to a carbocation intermediate that resulted essential for the cyclization through an aromatic electrophilic substitution step.

Furthermore, the presence of a Lewis acid catalyst was crucial for the success of such methodology, since it facilitated both the nucleophilic addition and the cyclization. Indeed, the absence of a Lewis acid led to lower yields when olefins are involved or no reaction in the case of the annulation between two glycine ester moieties. The oxidation to a more stable aromatic system (when it was possible) was achieved by the oxidant in excess. However, it was also possible to isolate the tetrahydroquinoline intermediate performing the reaction at room temperature. It is interesting to notice that this procedure could be performed in a multicomponent approach, adding aniline and  $\alpha$ -ester aldehyde to form *in situ* the desired target.



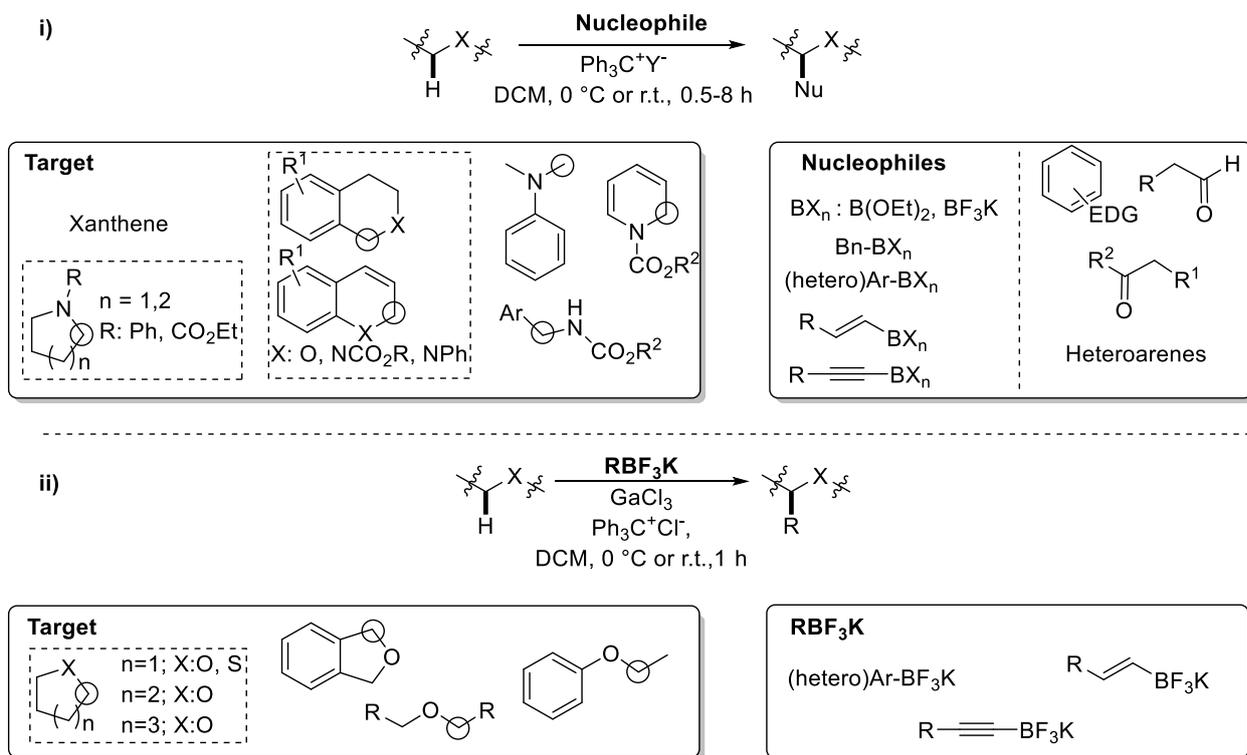
**Scheme 19.** TEMPO<sup>+</sup>BF<sub>4</sub><sup>-</sup> mediated derivatization of glycine esters.

Recently, S. D. Yang and co-workers have reported another example of C-H functionalization on glycine ester (Scheme 19, eq. iii).<sup>42</sup> This paper described a way to achieve chiral  $\alpha$ -amino esters by asymmetric addition of aryl boronic acids under palladium catalysis. A TEMPO salt was used as oxidant to achieve the reactive iminium species, which takes part as electrophile in the coupling reaction mediated by the *in situ* formed chiral catalyst. Different chiral ligands were tested, resulting (4*R*,4'*S*)-4,4'-diisopropyl-4,4',5,5'-tetrahydro-2,2'-bioxazole the best in terms of both yield and enantio-selectivity. Although the yields are strongly influenced by substituents, the enantiomeric excesses are high in almost of the cases (around 80-90% ee).

#### *Trityl salts.*

In the last 5 years, L. Liu and co-workers have obtained important results using trityl salts as oxidants with tetrahydroisoquinolines as substrates. In 2014, they proposed the first example of Csp<sup>3</sup>-H functionalization of tetrahydroisoquinolines using trityl perchlorate salt as hydrogen abstractor (Scheme 20, eq. i).<sup>43</sup> Several different benzyl, alkynyl, allyl and vinyl trifluoroborate salts were applied as nucleophiles, leading to the desired coupling products with good to excellent yields under metal-free conditions. In addition, other benzyl amines-like molecules could be effectively engaged. Noteworthy, in the same year such procedure was extended to benzopyranes<sup>44</sup>

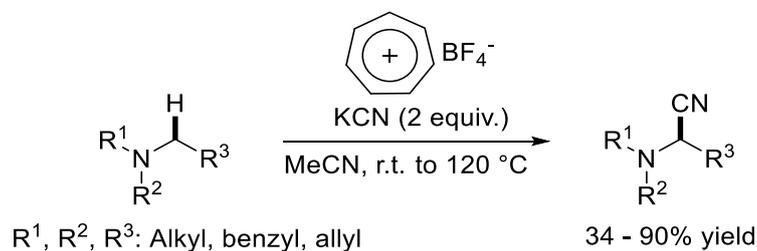
(Scheme 20, eq. i) and unactivated ethers (Scheme 20, eq. ii).<sup>45</sup> Despite the excellent results achieved with both classes of substrates, unactivated ethers required a stoichiometric amount of gallium chloride as Lewis acid and trityl chloride as oxidant to efficiently promote the reaction.<sup>45</sup>



**Scheme 20.** Trityl salt-mediated Csp<sup>3</sup>-H functionalization.

#### *Tropylium salts.*

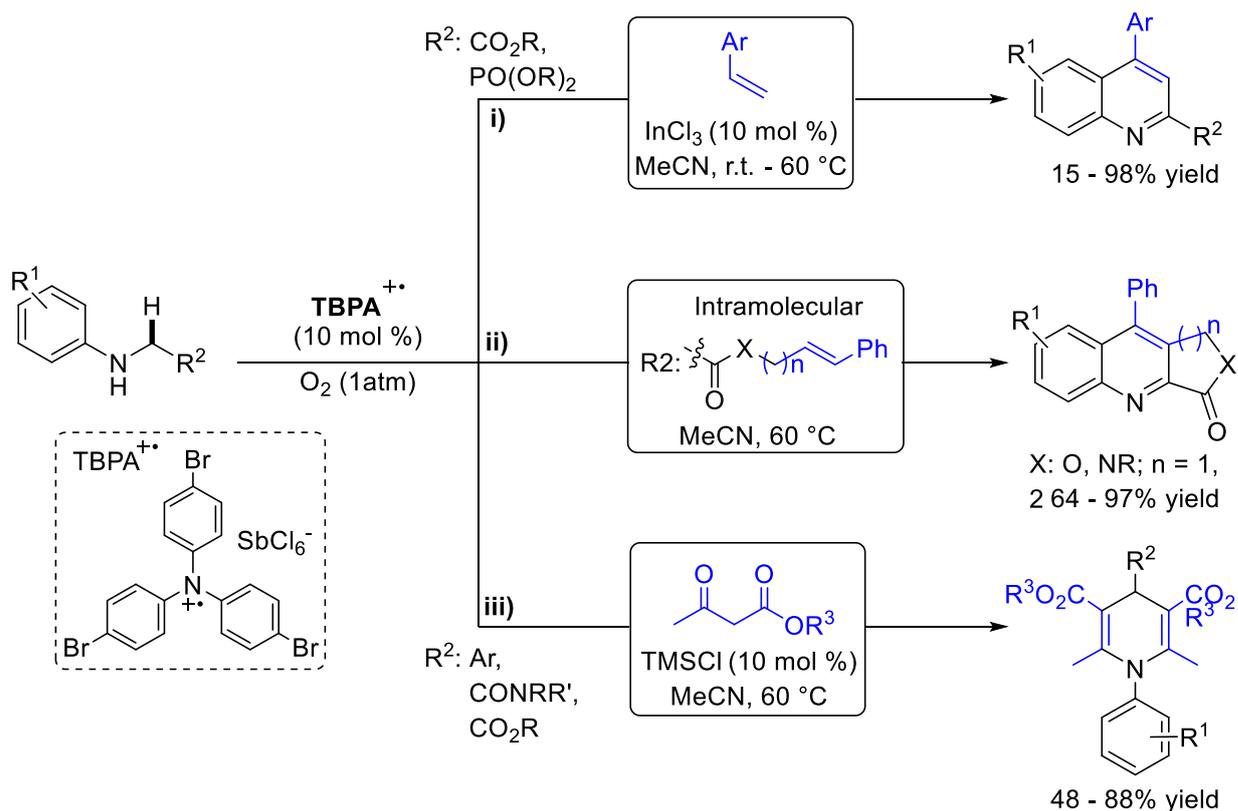
Tropylium ion represents another type of interesting mild ionic oxidant. Though less reactive than the corresponding trityl salt, it is capable of oxidizing the alpha C-H bond of various amines. Taking this into account, in 2011 T. H. Lambert reported the use of such mild oxidant for the  $\alpha$ -cyanation of a variety of differently substituted amines to generate  $\alpha$ -aminonitriles (Scheme 21).<sup>46</sup> Besides the simplicity of this transformation, the by-products produced are only water-soluble potassium tetrafluoroborate and volatile cycloheptatriene, which can easily be removed from the desired product.



**Scheme 21.**  $\alpha$ -Cyanation of amines with tropylium ion as oxidant.

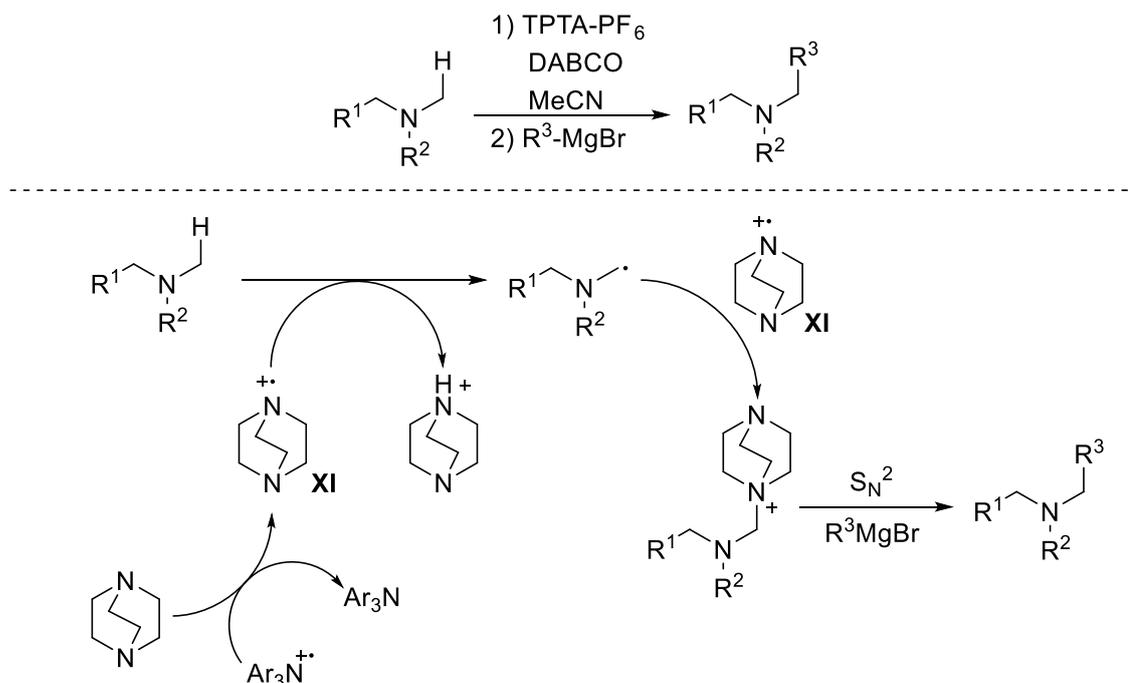
## 1.5.2 Radical-Cations as Oxidants

In this section, the applications of a different type of oxidants such as radical cations will be discussed. The dual nature of these species provides the potential of tuning the generation of a radical or an ionic intermediate in C-H functionalization reactions.<sup>47</sup> In this regard, triaryl aminium salts, such as the commercially available tris(4-bromophenyl)aminium hexachloroantimonate (TBPA<sup>+</sup>,  $E^0 = 1.15\text{V}$ ), have recently been identified as mild oxidants for such transformations. Consequently, the group of X. Jia has intensively been working towards the application of aminium salts in Csp<sup>3</sup>-H bond functionalization. Thus, their successful implementation in several Povarov-type reactions with various glycine ester derivatives and N-benzyl substituted anilines has recently been proven (Scheme 22, eq. i and ii).<sup>48</sup> In these cases, catalytic amounts of TBPA<sup>+</sup> (10 mol %) were employed under oxygen atmosphere (1 atm) in the presence or absence of InCl<sub>3</sub> as catalyst to produce the corresponding quinolines. Alternatively, the same In-catalyzed Povarov reactions of glycine derivatives could be performed by generating in situ the active radical cation from the amine precursor TBPA (20 mol %) by treatment with ceric ammonium nitrate (CAN) (20 mol %).<sup>48</sup> Moreover, in 2014 X. Jia and co-workers further extended the use of TBPA<sup>+</sup> for the formation of dihydropyridines from glycine ester derivatives and  $\alpha$ -ketoesters in the presence of catalytic amounts of TMSCl (Scheme 22, iii).<sup>49</sup>



**Scheme 22.** Aminium salts as radical-cation oxidants.

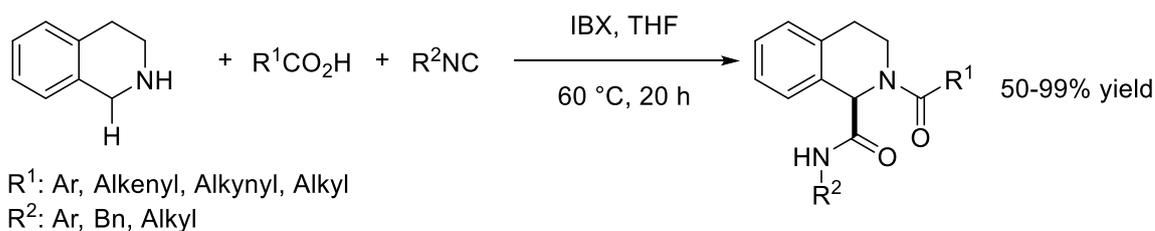
Recently, Murphy and co-workers have developed another interesting two-step approach that permits the high selective functionalization of a N-CH<sub>3</sub> group in the presence of a more thermodynamically favored N-CH<sub>2</sub>-R moiety (Scheme 23).<sup>50</sup> To achieve such high chemoselectivity with N-methyl N-dialkyl amines, a DABCO/TBPA-PF<sub>6</sub> oxidative-system was proposed. The effective bulky oxidant ammonium radical cation DABCO<sup>•+</sup> (XI), which acts as both hydrogen abstractor and radical trap, was fast oxidized by the more common reagent TBPA-PF<sub>6</sub>. The successive addition of phenyl magnesium bromide led to the substituted products in moderate to high yields.



**Scheme 23.** Selective functionalization of methyl dialkyl amines.

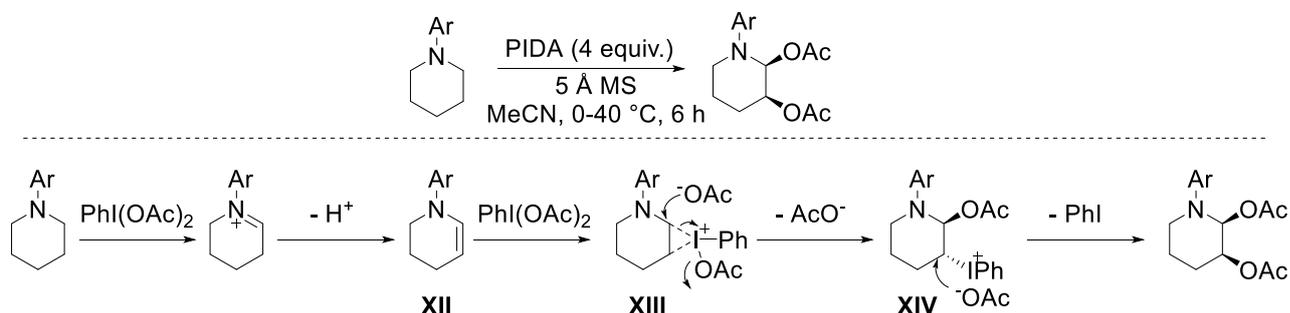
### 1.6 Iodine-based Oxidants

Since the discovery of hypervalent iodine reagents by D. B. Dess and J. C. Martin, this chemistry has received an increased attention due to the diverse chemical transformations successfully mediated by such type of oxidants.<sup>51</sup> Among others, hypervalent iodine reagents have shown interesting and wide applications in amine oxidations.<sup>52</sup> In 2007, T. Ngouansavanh and J. Zhu reported the first example of C-H functionalization/Ugi-type multicomponent reaction of tetrahydroisoquinolines mediated by 2-iodoxybenzoic acid (IBX) (Scheme 24).<sup>53</sup>



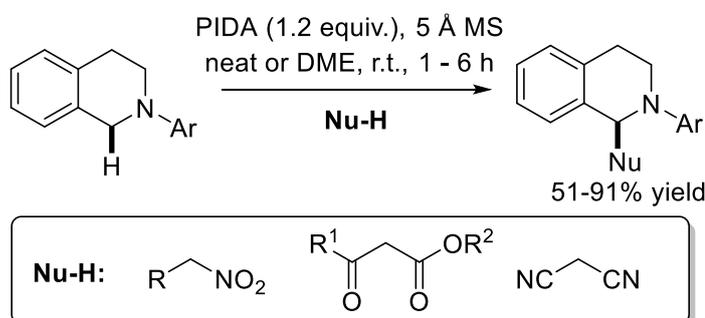
**Scheme 24.** IBX-mediated Ugi-type reaction.

Different carboxylic acids and isocyanides were tested at 60 °C in DMSO/THF mixture. Additionally, 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indoles and di-benzyl amines could also react under those conditions. In 2009, Y. M. Liang and co-workers reported the first example of Csp<sup>3</sup>-H functionalization of aliphatic amines with (diacetoxyiodo)benzene (PIDA) (Scheme 25).<sup>54</sup>



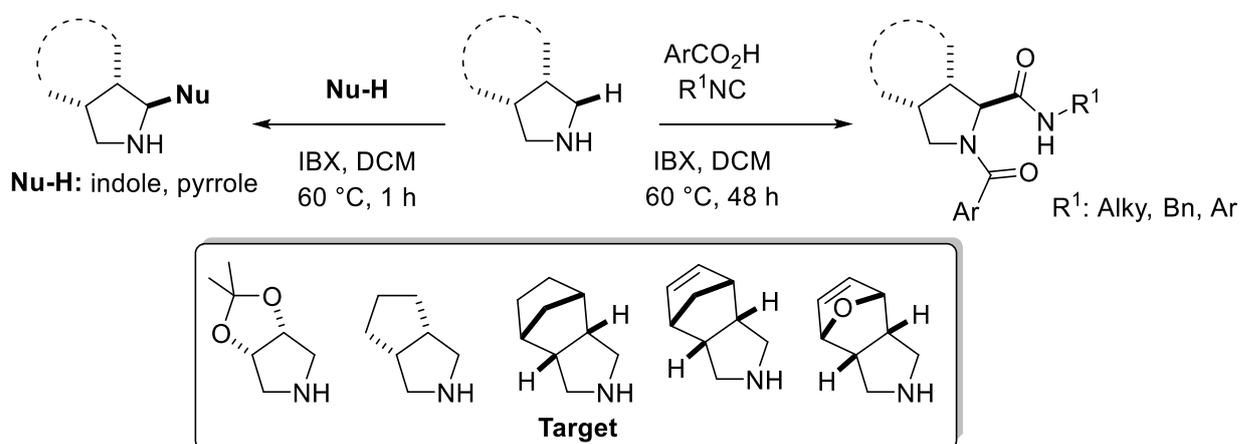
**Scheme 25.** PIDA as oxidant and nucleophile source.

In this work, various N-aryl piperidines were successfully oxidized to the corresponding enamine, moiety not stable in the reaction condition. Hence, a following functionalization to a diester took place. The authors proposed that the PIDA activates the double bond of the in-situ generated enamine **XII**, making it susceptible to the addition of a first molecule of acetate through an intermediate of type **XIII**. Then, a S<sub>N</sub><sup>2</sup> occurs on the hypervalent iodine unit **XIV**, giving the final diester along with iodobenzene as by-product. It is important to observe that substituted piperidines were not tested and the reaction is moisture sensitive. Moreover, tetrahydroisoquinolines could also be enrolled under these conditions, but using considerably less amount of oxidant (1.2 vs. 4 equivalents) and strong carbonyl nucleophiles (Scheme 26).



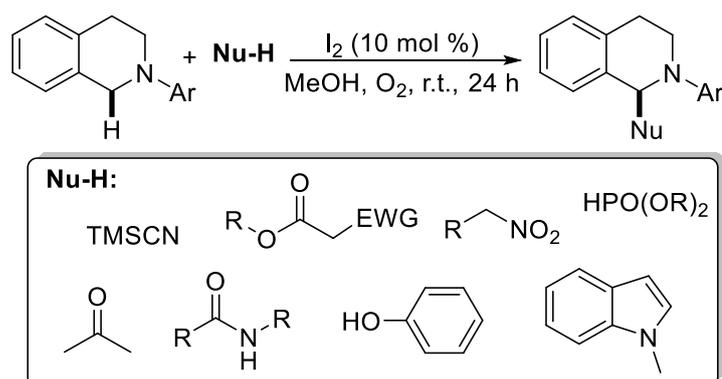
**Scheme 26.** PIDA-mediated Csp<sup>3</sup>-H functionalization of THIQs.

On the other hand, in 2015 R. V. A. Orru and co-worker reported a novel example of IBX-mediated formation of enamine from unactivated aliphatic amines, which were subsequently involved in an Ugi-type multicomponent reaction (Scheme 27).<sup>55</sup> Several bicyclic and tricyclic pyrrolidines were tested at 60 °C with various carboxylic acids and isocyanides. The obtained yields after prolonged reaction times (2 days) were good considering the difficult substrate-type employed. Moreover, it is interesting to notice that this methodology can be applied on oxidative aza-Friedel-Crafts reaction with the same aliphatic amine in moderated yields.



**Scheme 27.** Csp<sup>3</sup>-H functionalization of unactivated polycyclic aminoalkanes.

As illustrated in the previous sections, tetrahydroisoquinoline is a sort of privileged substrate, and in the area of iodine-based oxidations several applications have also been reported with this type of compounds. Therefore, it is important to notice that THIQs can be considered benchmark test substrates for the development of novel strategies in oxidative Csp<sup>3</sup>-H bond functionalization. In fact, in 2013 a metal-free iodine catalyzed Csp<sup>3</sup>-H activation of tetrahydroisoquinolined under oxygen atmosphere was reported by Prabhu and co-workers (Scheme 28).<sup>56</sup>



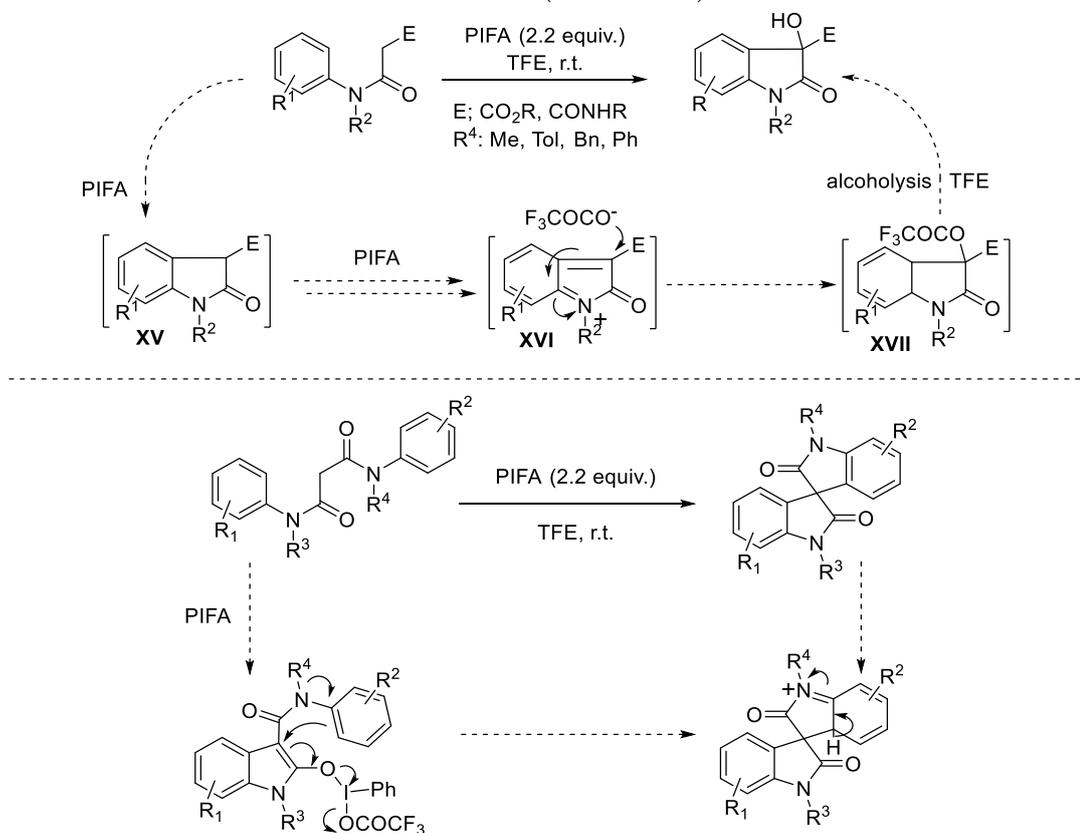
**Scheme 28.** I<sub>2</sub>-catalyzed cross-dehydrogenative coupling of THIQs

A broad spectrum of nucleophiles was extensively tested at room temperature: cumarines, nitroalkanes, phosphites, trimethylsilyl cyanides, imides, amides, as well as electron rich aromatic rings. Even though the procedure is limited to N-aryl substituted THIQs, moderate to high yields were obtained. It is worth to notice that during the screening of the optimal reaction conditions, different catalytic systems were tested and both potassium iodide and N-iodosuccinimide resulted high efficient under oxygen atmosphere. Returning back to more standard hypervalent iodine oxidants, in 2014 C. J. Li and co-workers proved the robustness of [bis(trifluoroacetoxy)iodo]benzene (PIFA) in the Csp<sup>3</sup>-H functionalization of THIQs in the presence of Grignard reagents (Scheme 29).<sup>57</sup>



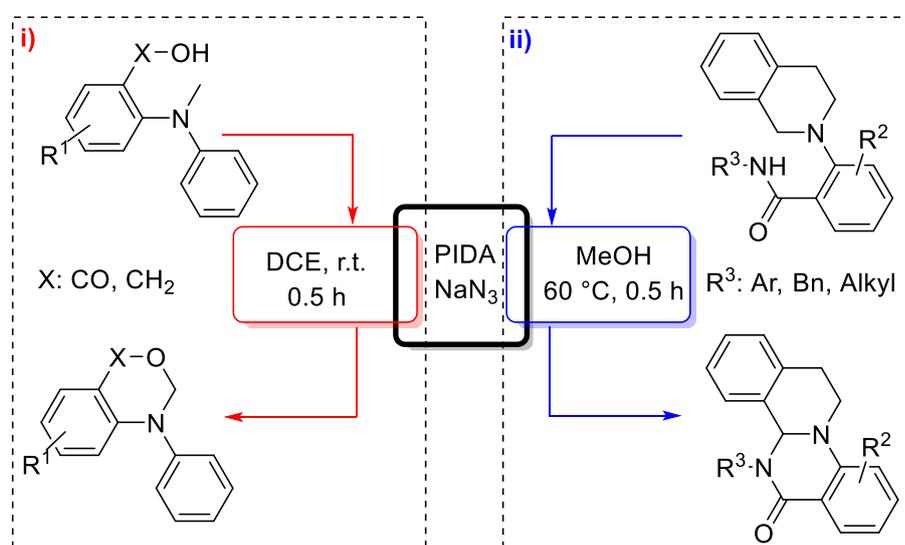
**Scheme 29.** PIFA in the Csp<sup>3</sup>-H functionalization of THIQs with Grignard reagents.

The biggest issue of this reaction was the incompatibility between the strong Grignard nucleophile and the electrophilic iodine reagent. Therefore, a sequential addition procedure was employed. The oxidation step was carried out for 10 minutes at r.t. prior the addition of the Grignard reagent at 0 °C. Nevertheless, owing to the strong class of nucleophilic reagents involved in the reaction, both the alkylation and the arylation proceeded in excellent yields. Alternatively, Z. Du and co-workers developed a simple and potent procedure to obtain 3-hydroxy-2-oxindoles and spirooxindoles from the corresponding anilides, using phenyliodine(III) bis(trifluoroacetate) (PIFA) as oxidant in trifluoroethanol as solvent (Scheme 30).<sup>58</sup>



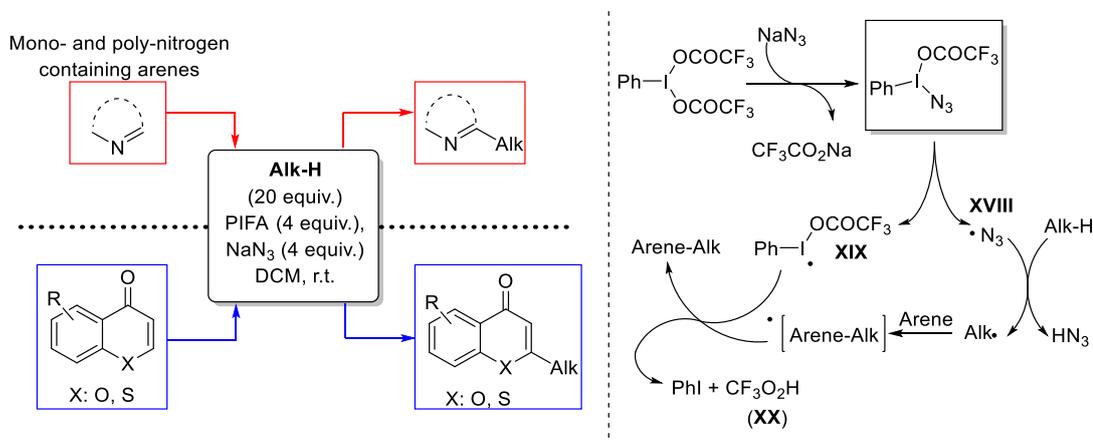
**Scheme 30.** PIFA-mediated Csp<sup>3</sup>-H functionalization/internal cyclization of anilides.

Firstly, the iodine-based oxidant induced the ring-closing reaction to **XV**. Thus, a further oxidation (**XVI**) and consecutive addition of a trifluoroacetate moiety led to an unstable diester **XVII**. This intermediate could then undergo an alcoholysis (path A) to the corresponding alcohol or, in the case of diphenylmalonamides, another cyclization to the spiro-structures (path B). In 2014, Z. Du also reported an intramolecular C-H bond functionalization of N-alkyl-N-aryl anthranilic acids mediated by the in situ formed (azidoacetoxyiodo)benzene, giving the corresponding benzoxazine in good yield (Scheme 31, i).<sup>59</sup> The in situ azide/acetate ligand exchange on the hypervalent iodine is fundamental to reach the corresponding stronger intermediate oxidant I(III)-N<sub>3</sub>, which resulted an efficient reagent with less reactive substrates, without important changes on regioselectivity. In the 2016, the same group showed the potential of this special oxidative system in the intramolecular annulation of tetrahydroisoquinolines to form high-value quinazolinone derivatives (Scheme 31, eq. ii).<sup>60</sup> This methodology worked efficiently with amides, carboxylic acids and, in moderated yields, also with ketones.



**Scheme 31.** PIDA/NaN<sub>3</sub> promoted C-N and C-O bond formation.

It should be noticed that this azide dependent oxidative system was for the first time employed in Csp<sup>3</sup>-H bond functionalization reactions by P. Antonchick and co-workers (Scheme 26).<sup>61,62</sup>



**Scheme 32.** Alkyl insertion into heteroarenes using PIFA/NaN<sub>3</sub> and proposed mechanism.

The functionalization of unactivated alkanes with various nitrogen-containing heteroarenes<sup>61</sup> and (thio)chromones<sup>62</sup> was efficiently achieved using PIFA, sodium azide as additive and a large excess of alkane at room temperature in 4 hours. The formed azide radical **XVIII** ( $E_0 \approx 1.33\text{V}$ )<sup>11b</sup> from the hypervalent iodine- $\text{N}_3$  species activates the alkane by radical abstraction of a hydrogen generating a radical alkane and **XIX** (Scheme 26). Moreover, the resulting acid by-product from the oxidant **XX** may facilitate the insertion step via protonation of the basic heteroarene nitrogen. Lastly, it has to be mentioned that the group of P. Antonchick has efficiently further exploited this azide-hypervalent iodine approach for additional applications in C-H bond functionalization.<sup>63</sup>

## 1.7 Conclusion and Outlooks

Despite some current limitations, especially on the class of substrate that is enrolled, the most significant recent advances in the area of oxidative Csp<sup>3</sup>-H bond functionalization rely on the introduction of specific, selective and, in last instance, more benign oxidative systems. This has already been translated not only in an improvement of previous methodologies, but it has also already led to the discovery of new transformations. Furthermore, the right choice of a mild oxidant-system will permit to circumvent incompatibility issues and allow the broadening of the list of suitable substrate classes and reagents. Thus, it can be easily envisioned the original design and development of more practical, highly inspiring and unconventional transformations embracing this technology based on mild oxidative Csp<sup>3</sup>-H bond functionalization.

Following this perspective, it is clear the potential of envisioning new methodologies by following such oxidative based approach, looking for unexplored reactivities or targets. In this context, this dissertation focuses on my results on the Csp<sup>3</sup>-H bond activation concerning the synthesis and the functionalization of (poli)heterocyclic moieties. Several strategies and unusual targets have been explored, aiming at obtaining the most easy, safe and selective system.

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# 2

## C-H functionalization leading to unstable intermediates: Trapping by dipolar cycloaddition

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### Chapter 2.1

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[2] Contents of table 1 and the chapter 2.1.5 “Reactivity and Mechanistic Studies” were performed by M. Segler

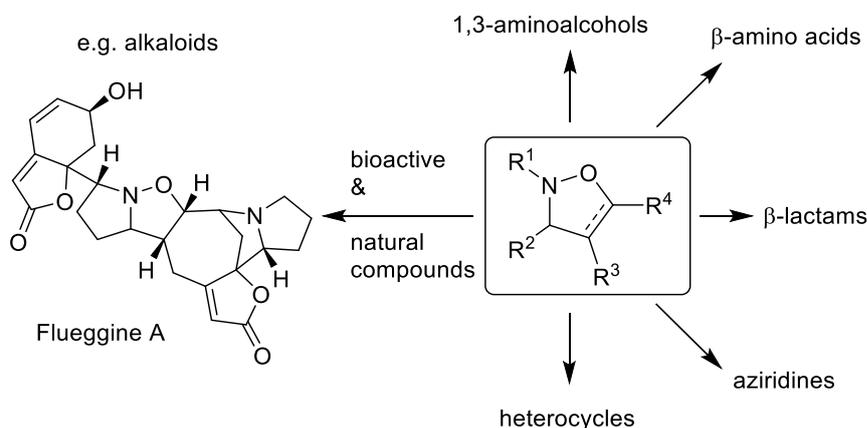
### Chapter 2.2

[1] Contents of the table 2, entries **4d**, **4e**, **4g** and **4h**, and table 3, entries **4k** and **4l** were performed by T. Brandhofer.

## 2.1 Trapping unstable nitrones to form Isoxazolines

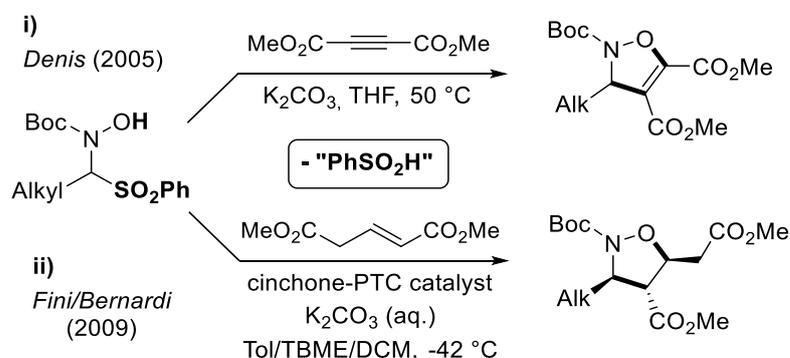
### 2.1.1 Introduction

4-Isoxazolines are valuable 5-membered heterocycles<sup>1</sup> with interesting biological activities, including anti-inflammatory or miotic kinesin inhibition properties among others.<sup>2</sup> In addition, they are also used as versatile building blocks for the preparation of numerous biological active compounds such as 1,3-aminoalcohols and -carbonyls,<sup>3</sup>  $\beta$ -lactams,<sup>4</sup> a variety of N-heterocycles<sup>5</sup> or natural products such as alkaloids (Figure 1).<sup>6</sup>



**Figure 1.** Versatility of isoxazolines as building blocks and bioactive units.

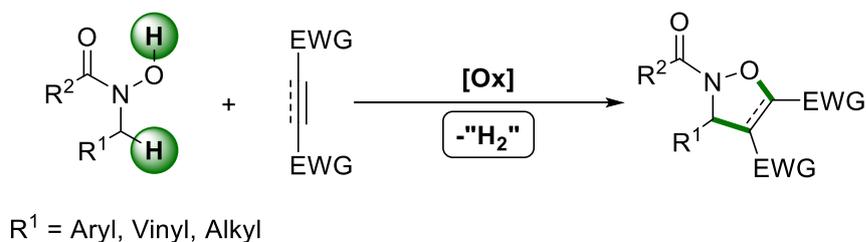
Several methods for the preparation of isoxazolines and isoxazolidines have been described, including both metal-catalyzed and metal-free approaches.<sup>7</sup> These procedures are mainly based on the 1,3-dipolar cycloaddition reaction (1,3-DC) between isolated stable nitrones<sup>8</sup> with alkynes and olefins as dipolarophiles. Despite the various powerful available methods, they are basically restricted to the use of N-alkyl and N-aryl substituted nitrones. This leads to isoxazolines with groups at the nitrogen that are difficult to cleave or even unremovable, which significantly limits the scope of this methodology for further synthetic applications.<sup>9</sup> Therefore, the use of nitrones bearing removable electron-withdrawing groups such as acyl or carbamoyl units is highly desirable. These dipole species are however difficult to isolate and manipulate due to their intrinsic instability. Thus, only few examples have been reported in the literature,<sup>10,11</sup> in which such nitrones have been generated *in situ* from N-acyl protected precursors. A prominent example is the base-mediated elimination of the sulfonyl group of N-carbamoyl N-hydroxy- $\beta$ -amido sulfones (Scheme 1).<sup>10</sup>



**Scheme 1.** Previously reported approaches for the *in situ* generation and trapping of N-carbamoyl protected nitrones.

### 2.1.2 Objectives

The employment of unstable N-acyl and carbamoyl nitrones in dipolar cycloaddition is still an ongoing challenge, since there are several limitations regarding the nature of the substrate. Indeed, the presence of necessary sacrificial functional groups on the target hydroxylamines is highly unwanted, especially considering the several synthetic steps needed for the insertion of such moieties.<sup>12</sup> Thus, the development of novel strategies in which the nitrones are formed by activation of simple N-acyl and N-carbamoyl hydroxylamines is still demanding. In this context, we aimed at a more direct and metal free approach which involves the oxidative activation of the target hydroxylamine through a formal dehydrogenative process. However, the instability of the involved intermediates may lead to undesired decomposition products under standard oxidative condition, and the choice of the reagents is crucial for a successful formation and trapping of the unstable nitron. Indeed, the oxidant and its side-products may have a major role in the decomposition of the active intermediates, and the cycloaddition needs to be faster than the other possible degradation routes. Thus, based on our experiences in oxidative coupling reactions of Csp<sup>3</sup>-H bonds using mild oxidants,<sup>13</sup> several oxidative systems would be tested for the development of a more general and metal-free synthesis of N-carbamoyl and N-Acyl isoxazolines by dipolar cycloaddition involving *in situ* formed nitrones (Scheme 2).



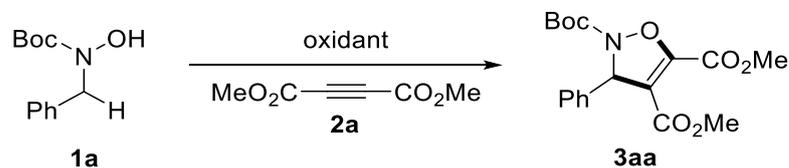
- Acyl and Carbomoyl protecting group.
- general R<sup>1</sup> substitution pattern.
- no need of prefunctionalization.
- dehydrogenative approach (H<sub>2</sub> as formal waste).

**Scheme 2.** Our proposal for the *in situ* formation/trapping of unstable nitrones.

### 2.1.3 Results and Discussion

Initially, N-Boc protected benzylhydroxylamine (**1a**) was chosen as model substrate for the one-pot *in situ* oxidative nitron formation and cycloaddition trapping reaction with dimethyl acetylenedicarboxylate (**2a**, DMAD) (Table 1).

**Table 1.** Optimization of the model reaction<sup>[a]</sup>



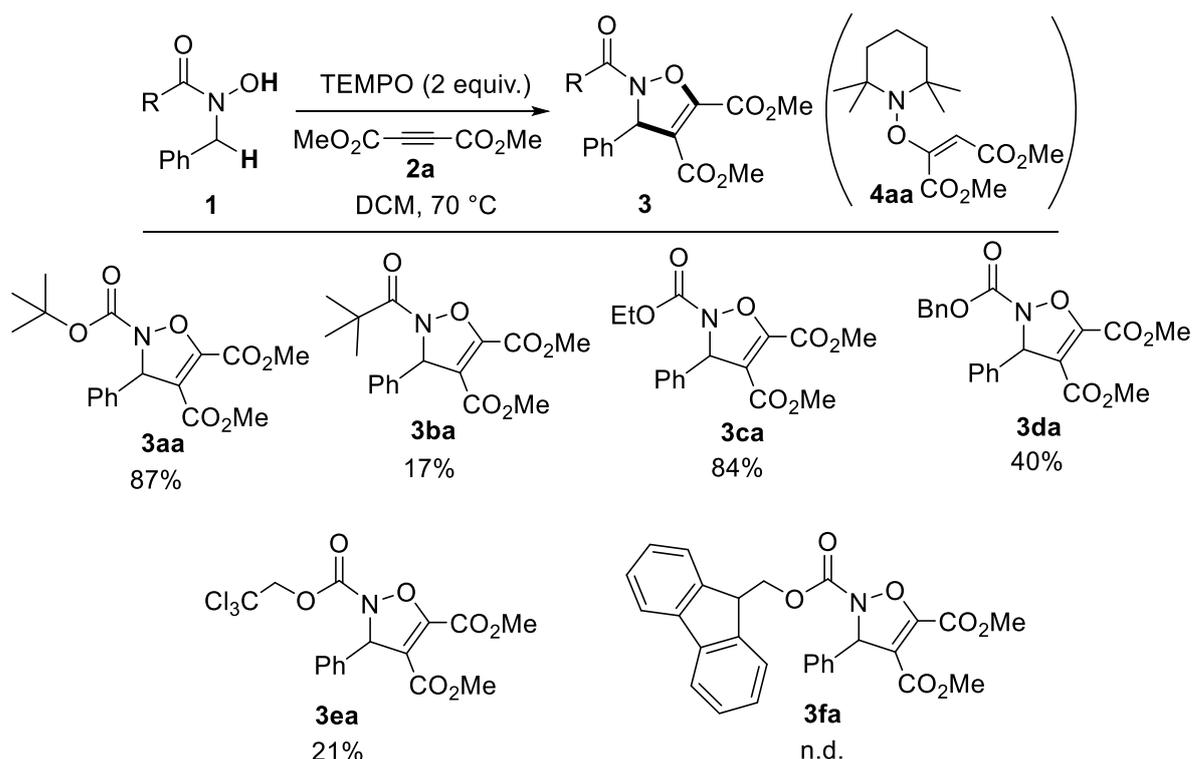
Entry	oxidant (equiv.)	solvent	Temp. (°C)	yield (%) <sup>[b]</sup>
1	<i>t</i> BuOOH (2)	neat	rt	--
2	DDQ (2)	DCM	rt	<5
3	TEMPO <sup>+</sup> BF <sub>4</sub> <sup>-</sup>	DCM	rt	<5
4	TEMPO (2)	DCM	rt	25
5	TEMPO (2)	DCM	50	75
6	4-NHAc-TEMPO (2)	DCM	50	64
7	4-OH-TEMPO (2)	DCM	50	60
8	TEMPO (2)	DCM	70	87
9	TEMPO (2)	BTF <sup>c</sup>	70	63
10	TEMPO (2.5)	DCM	70	80
11	--	DCM	70	--
12	TEMPO (0.1)/O <sub>2</sub> <sup>[c]</sup>	DCM	50	25
13	TEMPO (2)	DCE	70	80

[a] **1a** (0.25 mmol, 1 equiv.), **2a** (4 equiv.) and oxidant in DCM (0.125 M) at the corresponding temperature for 24 h. [b] Isolated yields. [c] 1 atm of O<sub>2</sub> was used. BTF = Benzotrifluoride (or trifluorotoluene).

Various oxidants were tested under neat conditions or in dichloromethane as solvent at room temperature to minimize the possible decomposition of the generated *N*-carbamoyl nitron. Whereas the typical reagents for dehydrogenative cross-coupling (CDC) reactions or Csp<sup>3</sup>-H bond functionalization<sup>14</sup> such as organic peroxides, DDQ or TEMPO oxoammonium salts did not lead to the desired product (Table 1, entries 1-3), the use of TEMPO radical<sup>15,16</sup> provided isoxazoline **3aa** in a promising 25% yield (Table 1, entry 4). A complete conversion of the hydroxylamine **1a** was observed with all the oxidants explored. However, except for the reaction with TEMPO, a complex reaction mixture was obtained in which only traces of the desired product were present. This indicates that the *in situ* formed *N*-carbamoyl nitron and/or the product decompose readily in the presence of a strong oxidant. Conversely, when using TEMPO radical the low conversion into **3aa** and observation of certain decomposition by-products at room temperature could be attributed to

a not effective next cycloaddition step. The increase of the temperature to 50 °C favored the overall transformation, most probably by increasing the efficiency of the second 1,3-cycloaddition trapping reaction. Thus, **3aa** was obtained in a good 75% yield (Table 1, entry 5). Other TEMPO radical derivatives were also suitable oxidants (Table 1, entries 6-7), leading to slightly lower yields (60-64%). Taking TEMPO as the oxidant of choice, the temperature, solvent and amount of oxidant was finally optimized. Consequently, the use of 2 equivalents of TEMPO at 70 °C in DCM in a pressure schlenk tube led to an improved yield of 87% (Table 1, entry 8). 1,2 dichloroethane (DCE) was also tested as solvent at the optimized condition due to its higher boiling point (70 °C *vs* 40 °C), but with slightly lower performance (Table 1, entry 13). With these excellent results in hand, the scope of the reaction was explored. Various N-acyl and N-carbamoyl protected benzylhydroxylamines were evaluated in the reaction with **2a** (Table 2). The carbamoyl group Boc proved to be superior to its corresponding acyl group pivaloyl (Piv) (87% *vs.* 17%). Other carbamate substitution (R = EtO and BnO) was well tolerated, leading to isoxazolines **3** in moderate to good yields. However, a low yield (21%) and a significant decomposition of the starting material **1** were observed when using sterically hindered protecting groups such as Troc, or in the case of Fmoc (**3fa**), no product was detected. In addition, it was observed that in the reaction a by-product **4aa**, derived from the addition of TEMPO to the dipolarophile **2a**, was also formed in high yields. This explains the need of employing an excess of **2a** to achieve high conversions into **3**.

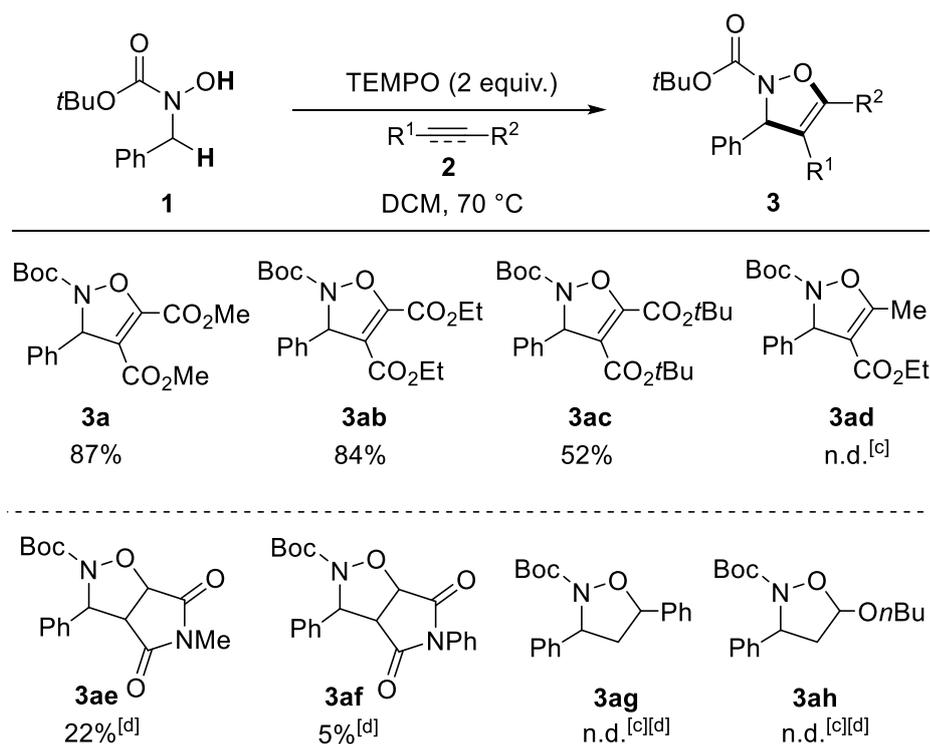
**Table 2.** Scope of the reaction: N-Carbamoyl/Acyl group variation<sup>[a][b]</sup>



[a] **1** (0.25 mmol, 1 equiv.), **2** (4 equiv.) and TEMPO (2 equiv.) in DCM (0.125 M) at 70 °C for 24 h. [b] Isolated yields.

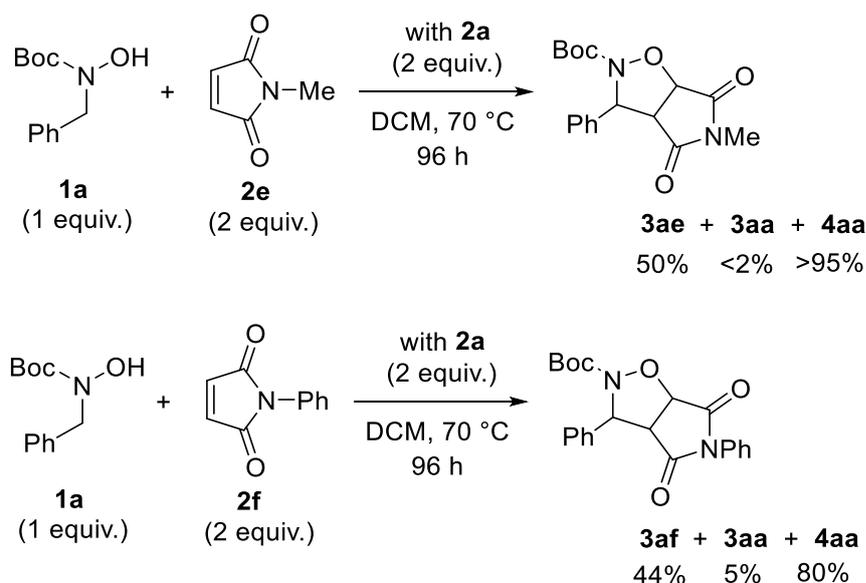
The reaction of hydroxylamine **1a** with different dipolarophiles **2** was then investigated (Table 3). The diethylester derivative **2b** reacted in a similar way to **2a** (84% vs. 87%). Furthermore, the bulkier *tert*-butyl acetylenedicarboxylate (**2c**) provided **3g** in a good 52% yield, whereas the use of the mono-ethylester **2d** led to no desired reaction. In these last cases a substantial decomposition of the *in situ* formed nitrone was observed. Unexpectedly, other typical cyclic dipolarophiles such as N-methyl (**2e**) and N-phenyl maleimide (**2f**) showed a low reactivity, providing the corresponding isoxazolidines **3ae** and **3af** in only 22% and 5% yield. Finally, unactivated dipolarophiles such as styrene and butyl vinyl ether did not participate in the reaction under our standard conditions.

**Table 3.** Scope of the reaction: Dipolarophile variation<sup>[a][b]</sup>



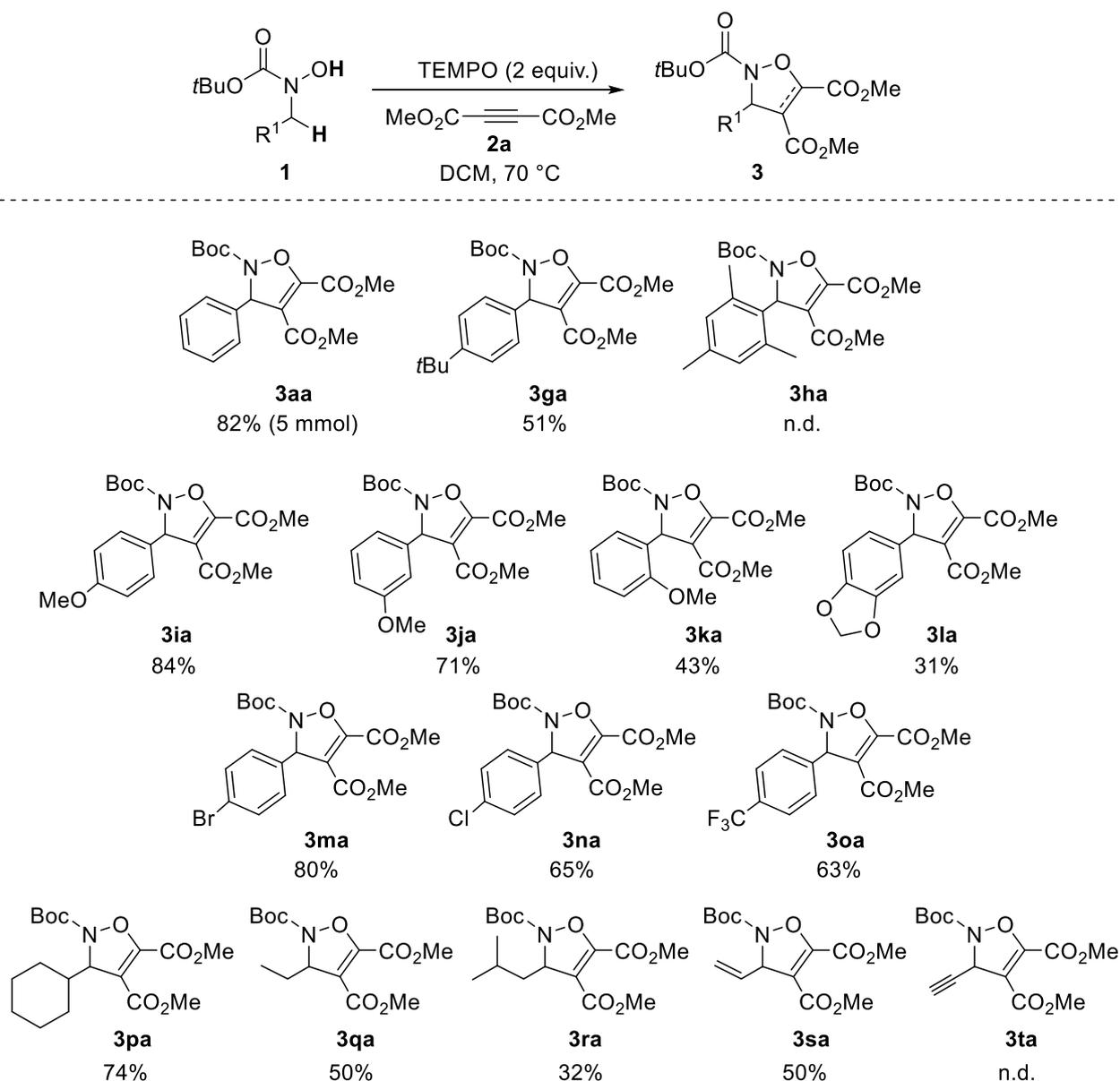
[a] **1** (0.25 mmol, 1 equiv.), **2** (4 equiv.) and TEMPO (2 equiv.) in DCM (0.125 M) at 70 °C for 24 h. [b] Isolated yields. [c] n.d. = Not detected. [d] 96 h reaction.

In order to enroll more effectively the less reactive dipolarophiles such as maleimides in the cycloaddition step, the reaction was carried out in the presence of **2a** as a cheap sacrificial reagent (Scheme 3). Considering the higher performance of DMAD as dipolarophile and the formation of **4a**, we envisioned that **2a** might be involved in an important mechanistic step of the process and therefore it may facilitate the reaction of other dipolarophiles (see below for further discussion). Satisfactorily, the desired products **3ae** and **3af** were then obtained in 50% and 44% yields after 96 h, and only traces of the product derived from **2a** were formed (**3a**, <5%).



**Scheme 3.** DMAD as cheap sacrificial reagent: Enrollment of less reactive dipolarophiles.

Next, a variety of different N-substituted N-Boc hydroxylamines was studied (Table 4). In first instance, it is worthy to mention that the reaction could be scaled up to 5 mmol without detriment on the reactivity (**3aa**, 82% yield, 24 h). Moreover, electron-donating groups such as *p*-*t*Bu, *p*-OMe and *m*-OMe at the aromatic unit led to similar good results (51, 84 and 71% yield, respectively). However, the introduction of substituents at the *ortho* position, such as an *o*-MeO group, was not well tolerated and translated to a significant drop on the yield to 43%. In addition, only decomposition products were detected when high steric hindered target such as **1n** were enrolled in the reaction. Halogen-containing (*p*-Br and *p*-ClC<sub>6</sub>H<sub>4</sub>-) and electron-deficient (*p*-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>-) substrates **1m-o** also reacted satisfactorily, providing **3** in good yields (63-80%). This methodology showed a remarkable broad structural scope since not only benzylic but also the more demanding allylic (**1s**) and alkylic (**1p-r**) substituted N-Boc hydroxylamines could be successfully enrolled in this transformation. Consequently, allyl isoxazoline **3sa** was obtained in a good 50% yield and alkyl derivatives **3pa-ra** in moderate to excellent yields (up to 74%), although propargyl derivative (**1t**) did not participate in the desire reaction under the proposed condition, leading to full conversion of decomposition products.

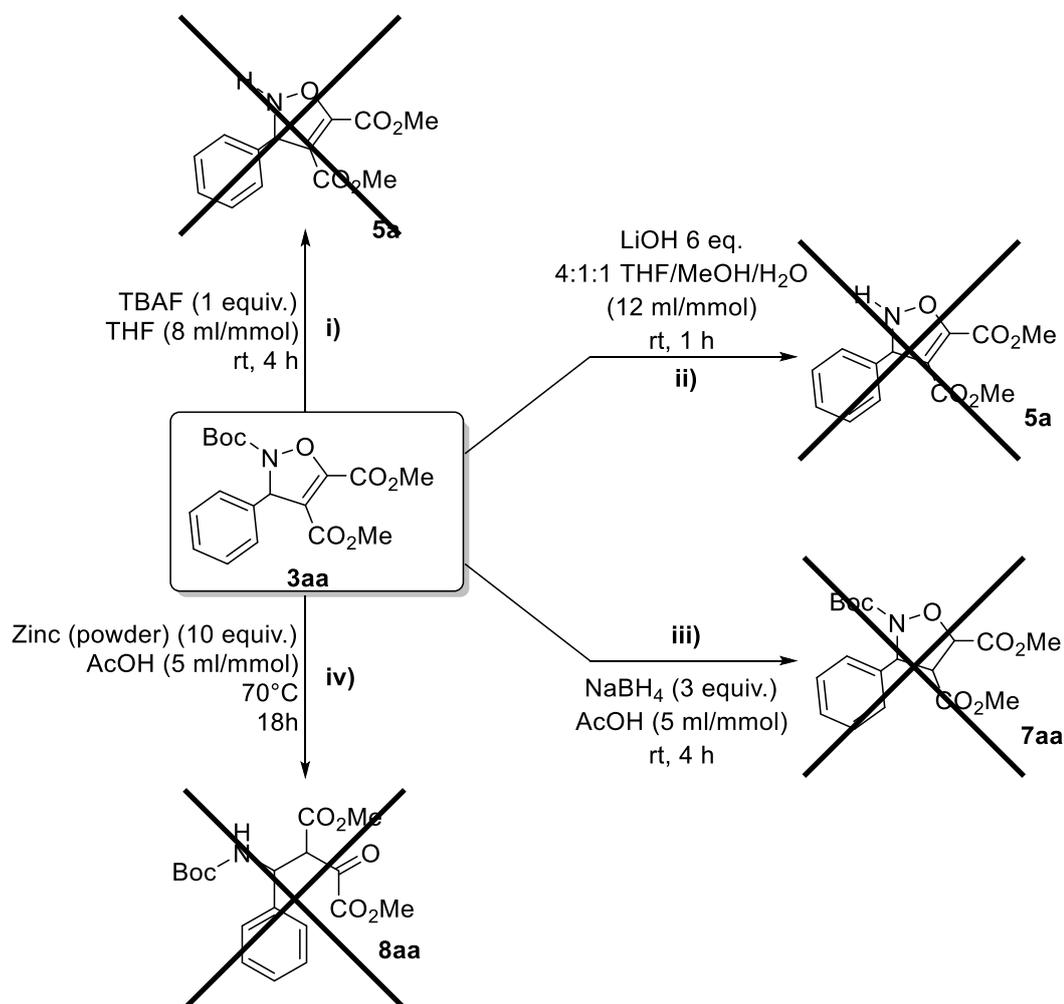
**Table 4.** Scope of the reaction: Substitution of the N-Boc hydroxylamine **1**<sup>[a][b]</sup>

[a] **1** (0.25 mmol, 1 equiv.), **2a** (4 equiv.) and TEMPO (2 equiv.) in DCM (0.125 M) at 70 °C for 24 h. [b] Isolated yields.

### 2.1.4 Attempts for the functionalization and deprotection of **3a**

Several attempts to further functionalize the obtained isooxazoline **3** were tested. In first instance, various experiments were carried to achieve the deprotection of the Boc group, but in all the cases the desired product was not observed (Scheme 4, eq. i and ii). Tetrabutyl ammonium fluoride (TBAF) resulted an inefficient reagent for the the deprotection of **3aa**, recovering almost all the unreacted starting material. Furthermore, strong basic conditions are not suitable with such electron-poor isooxazoline as **3aa**, leading to a complex mixture of by-product (Scheme 3, eq. ii). Noteworthy, from NMR analysis the signal of the Boc group, as well as the signal of the benzylic hydrogen, were missing. Thus, we supposed that in first instance a deprotection/aromatization reaction occurs. Then, other uncontrolled rearrangement reactions lead to a multitude of decomposition products. The re-aromatization of electron-poor N-H free isoxazolines was also observed by A. Tomelli and co-workers.<sup>17</sup> Two different procedure for the site-selective reduction

were carry out, but with poor results (Scheme 3, eq. iii and iv). Although the low electron-density of the double bond moiety in **3a**, sodium boron hydride (NaBH<sub>4</sub>) revealed itself as an ineffective reagent for the reduction of **3a** to form **7a**. Furthermore, all the attempts to break the N-O bond were unsuccessful, and only an undefined mixture of products was observed.<sup>18</sup>



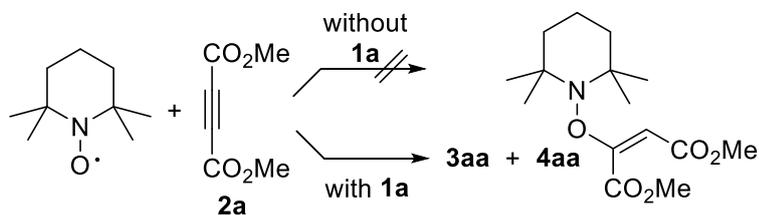
**Scheme 4.** A summary of tested functionalization/deprotection procedures

### 2.1.5 Reactivity and Mechanistic Studies

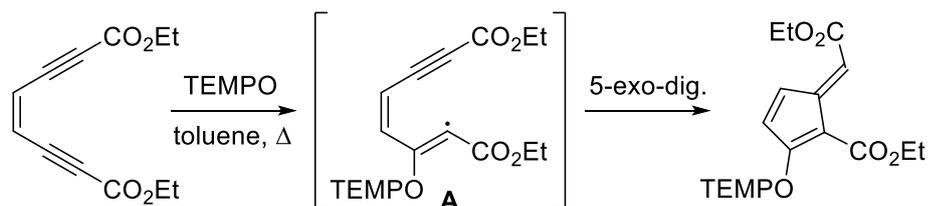
In order to better understand the formation of **4aa**, DMAD (**2a**) was reacted with stoichiometric amounts of the oxidant TEMPO (Scheme 5, i). While no reaction was observed in the absence of **1a**, the by-product **4aa** was obtained quantitatively in the presence of the substrate hydroxylamine. These results indicate, as we initially anticipated, a certain interaction or prior reaction with the substrate, which might suggest an active participation of the dipolarophile in the *in situ* generation of the required nitron species. Moreover, the formation of **4a** by a radical addition of TEMPO to **2a** to form a more reactive carbon-centered radical can be envisioned. In this regard, a similar reaction between TEMPO and electron-poor endiynes has been postulated by B. König and P. R. Schreiner as intermediate step (radical *A*) for a radical 5-exo-dig cyclization (Scheme 5, ii).<sup>19</sup> The course of the model reaction between **1a** and DMAD (**2a**) was next followed by GC-FID in the first 7 hours (Scheme 5, iii). We could observe that the hydroxylamine was

rapidly consumed (<10% left after 60 min). At the same time almost two equivalents of DMAD have reacted and the formation of the TEMPO addition by-product **4aa** was observed. However, the final cycloaddition product **3aa** was built up comparably slowly.

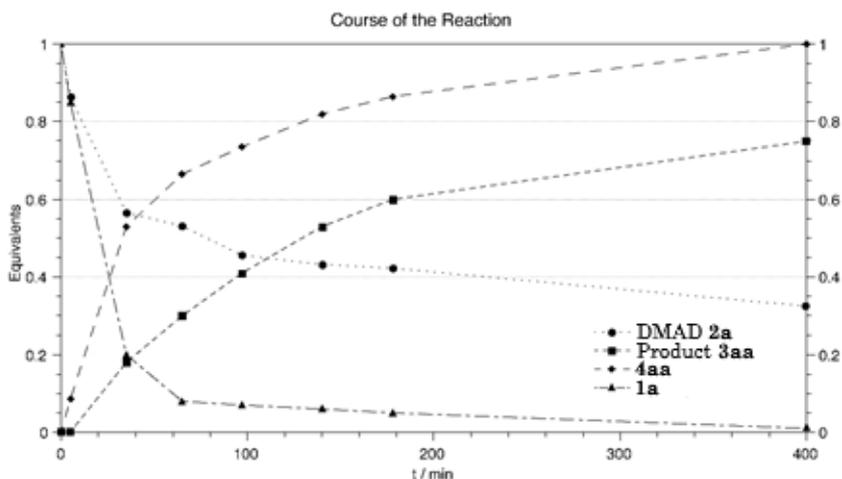
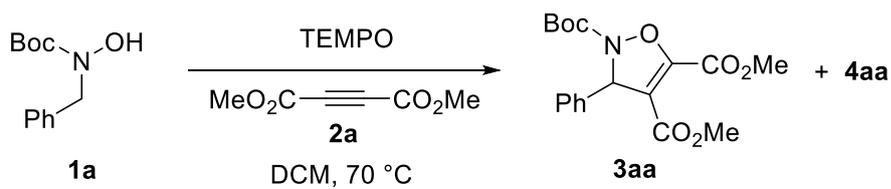
i) Formation of nitroxide-addition by-products



ii) Proposed similar TEMPO-addition intermediate by König & Schreiner



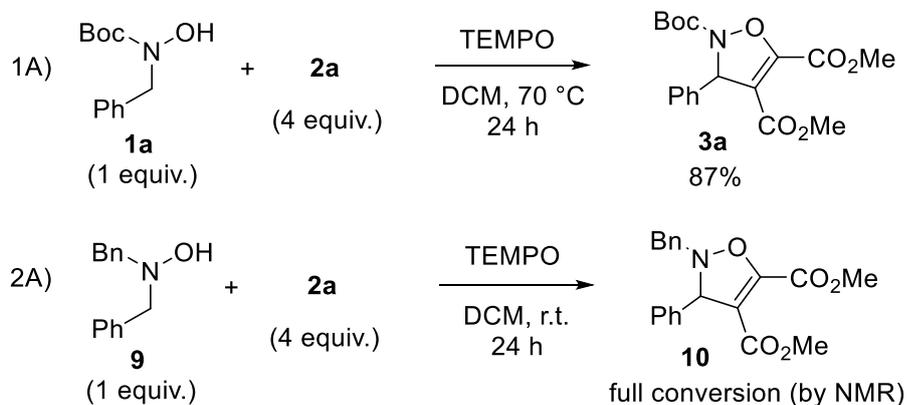
iii) Reaction course



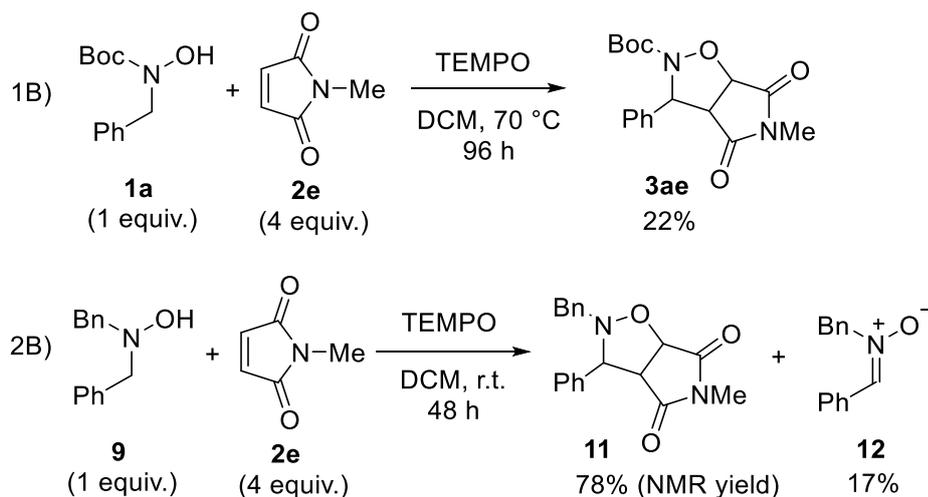
Scheme 5. Reactivity insights.

Furthermore, the dipolar cycloaddition reaction with the electron-deficient N-carbamoyl nitrones is generally less favored than the classical with N-aryl or alkyl derivatives (Scheme 5).<sup>20</sup> The reaction with N-benzyl hydroxylamine **9**, which leads to a stable and isolable nitrone **12**,<sup>21</sup> proceeded more readily than the one with the N-Boc derivative **1a**. Thus, milder conditions (r.t. vs. 70°C) were required. Additionally, the unstable N-carbamoyl nitrone may readily decompose under the employed temperature and long reaction times.

**A) Reaction of N-Boc vs. N-Bn hydroxylamines with DMAD:**

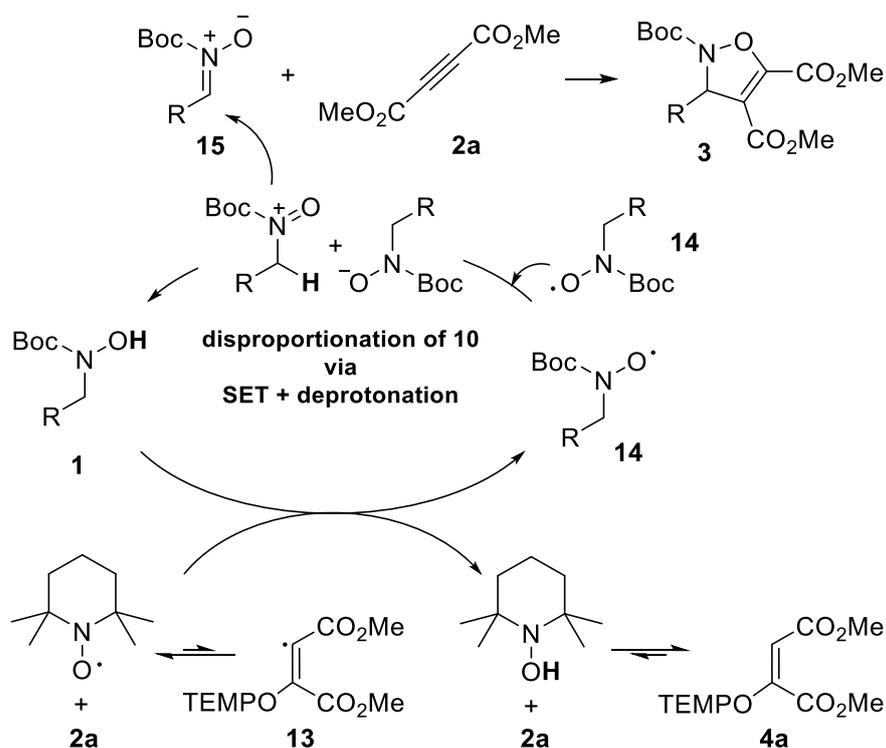


**B) Reaction of N-Boc vs. N-Bn hydroxylamines with N-methyl maleimide:**



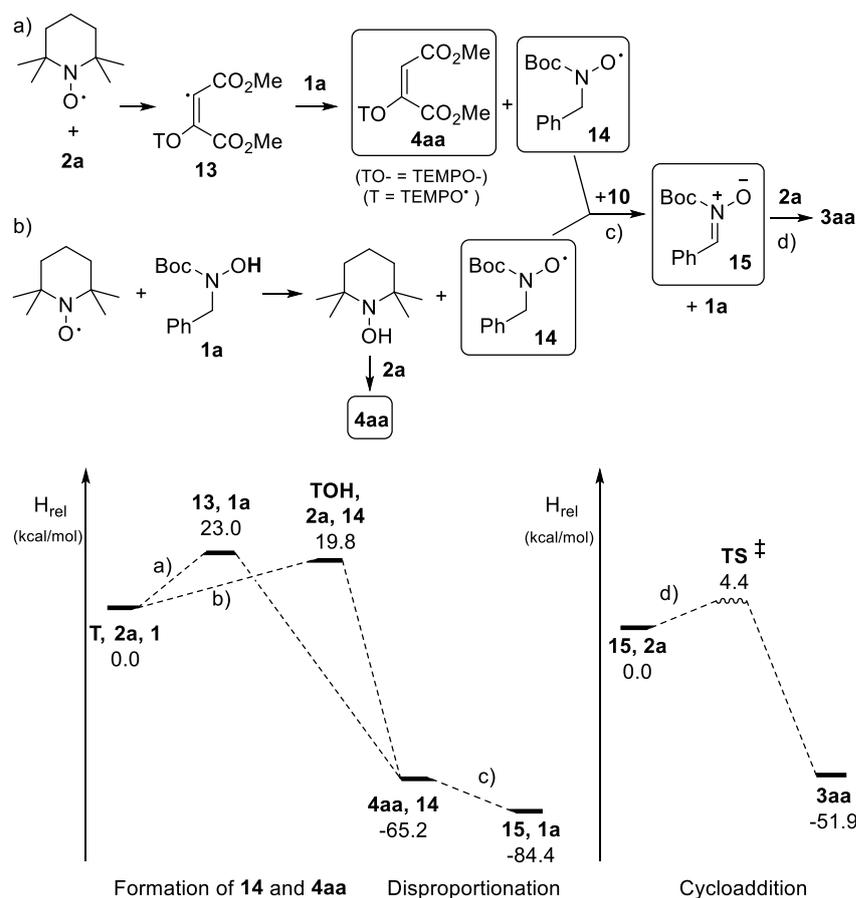
**Scheme 6.** Reactivity comparison between *in situ* formed unstable N-Boc and stable N-Bn nitrones.

Therefore, the nitrone might not be present in high concentrations, suggesting the participation of a different intermediate. With all this information, a plausible mechanism is depicted in Scheme 6. First, a hydrogen atom abstraction from the hydroxylamine **1** occurs. This hydrogen can be abstracted directly by TEMPO<sup>15</sup> or by the carbon-centered radical **13** obtained upon reversible radical addition of TEMPO to **2a** (Path a). The nitroxide **14** is then formed together with **4** or TEMPOH, which can also react with **2a** in a conjugate addition way to form the same by-product (Path b). Next, two molecules of nitroxide **14** disproportionate via a SET process followed by deprotonation to form nitrone **15** and hydroxylamine **1**,<sup>22</sup> the later entering again in the oxidation-cycle. Lastly, the cycloaddition between the generated nitrone **15** and **2a** takes place to form the final isoxazoline product **3**.



**Scheme 7.** Mechanistic proposal

Finally, to obtain more mechanistic insights into the two proposed possible pathways a) and b) for the formation of the nitroxide intermediate **14**, the generation of the by-product **4a** and nitronium **15**, and the subsequent 1,3-DC step, DFT-calculations were performed (Scheme 6).<sup>23</sup> Consequently, in order to complete the formation of nitroxide **10**, one of the two possible endothermic intermediate steps has to take place. However, pathways a) and b) are similar in energy, not allowing the exclusion of one of them since no transition state (TS) could be found for the formation of the radicals **13** and **14**, respectively. The calculations also indicate that the following disproportionation of **14** is an exothermic process. Additionally, the subsequent cycloaddition has an activation barrier of just 4.4 kcal/mol. Nitronium **15** should then react fast in the 1,3-DC step and thus, as previously postulated, only be present in low concentrations in the reaction media. This explains why nitronium **11** could not be detected by NMR, GC or MS during the mechanistic studies. Furthermore, all this implies that the final cycloaddition step is not likely to be the rate determining, but instead one involved in the formation of the intermediate nitroxide **14** or nitronium **15**.



**Scheme 7.** DFT gas-phase (B2PLYP-D3/def2-TZVP//BP86-D3/def2-TZVP) calculated relative enthalpy profiles for the formation of nitroxide **14**, nitrone **15** and by-product **4aa**, as well as for the 1,3-DC reaction.

### 2.1.6 Conclusions and Outlooks

In summary, we have developed a novel and potent methodology for the synthesis of N-carbamoyl/-acyl 4-isoxazolines by a TEMPO-mediated *in situ* formation and trapping via 1,3-dipolar cycloaddition of unstable N-protected nitrones. Carbamates were superior to simple acyl protecting groups, leading to good yields on the corresponding aryl, allyl and alkyl substituted isoxazolines (up to 87%). However, the approach resulted restricted to strongly electron-poor dipolarophile, which rapidly undergoes the cycloaddition reaction with the nitrone, limiting the formation of undesired side-product. Even though we could not achieve to date any functionalization or deprotection of **3**, the intrinsic reactivity of such substrate may lead to interesting application or rearrangement. Moreover, the employed dipolarophile showed an important assistant role on the slowly generation of the active, unstable N-protected nitrone.

### 2.1.7 References

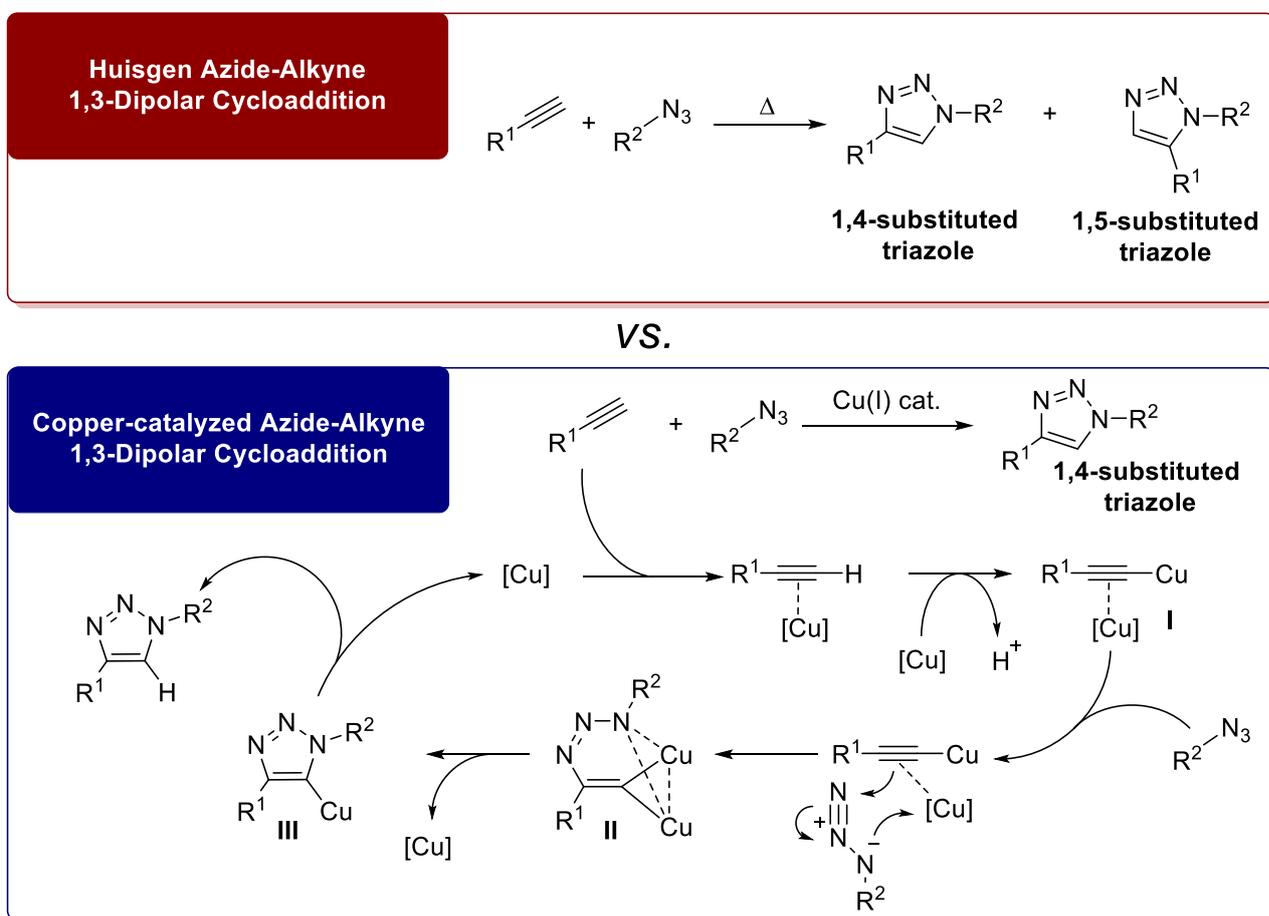
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## 2.2 Two-steps one-pot azidonation/CuAAC reaction studies

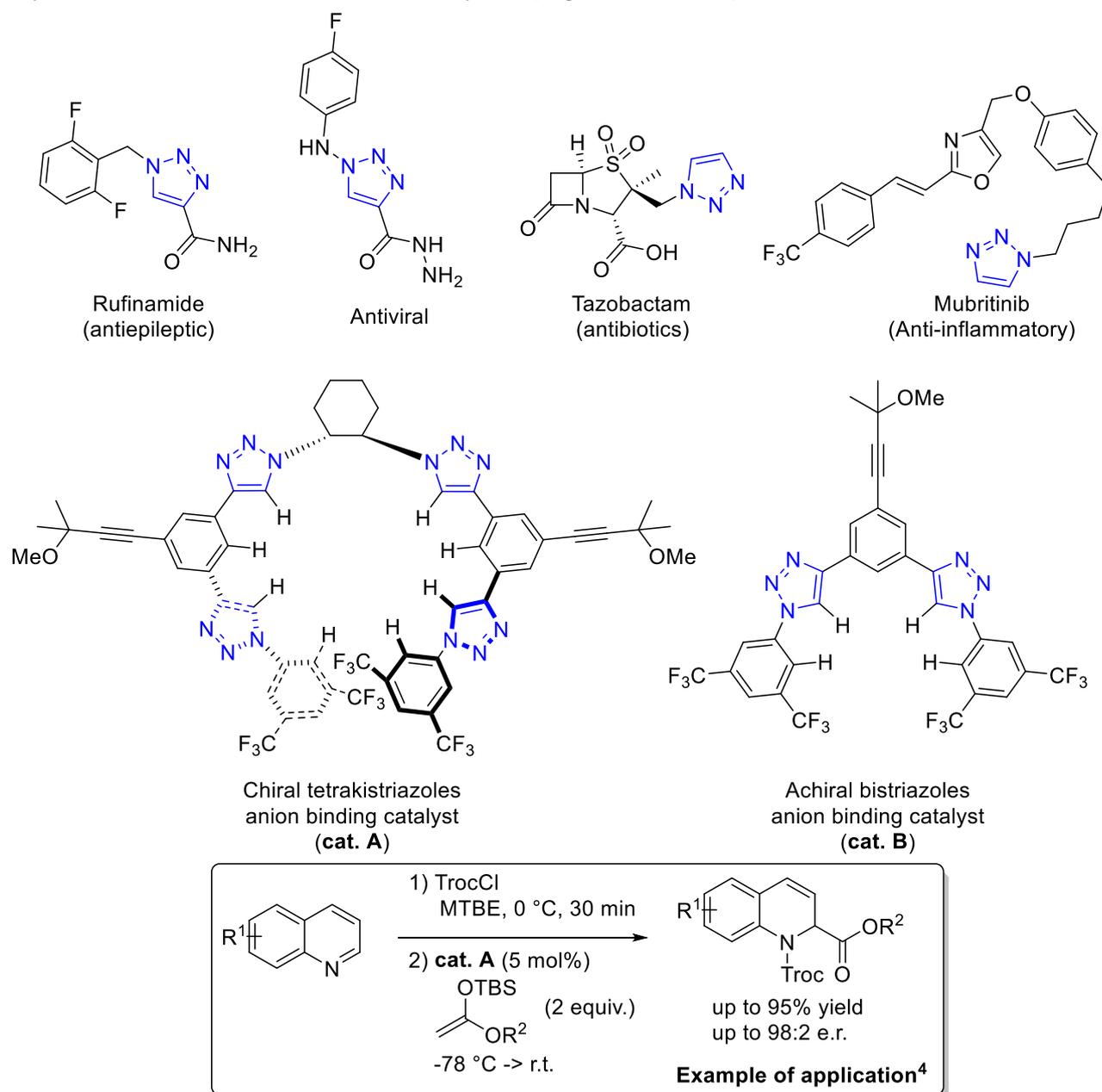
### 2.2.1 Introduction

“Click chemistry” is a term introduced by K. B. Sharpless in 2001<sup>1</sup> to describe reactions which are simple to make, wide in scope, high yielding and carried out with an overall optimal atom economy. Indeed, the “click chemistry” approach might be called the research of perfect reactions. Following this purpose, the copper catalyzed azide-alkyne cycloaddition (CuAAC) reaction (Scheme 1), a regioselective version of the thermal Huisgen azide-alkyne 1,3-dipolar cycloaddition, was elevated to be one of the most prominent example on this field, and its application was extended to a broad variety of synthetic strategies, conditions and substrates.<sup>2</sup> The 1,4-substituted triazole is obtained as only product, and the achievement of such selectivity in the CuAAC process is driven by the copper acetylide intermediate (Scheme 1, bottom). It is interesting to note that two atoms of copper are involved in the activation of the system, leading to a concerned di-nuclear copper intermediate (II).



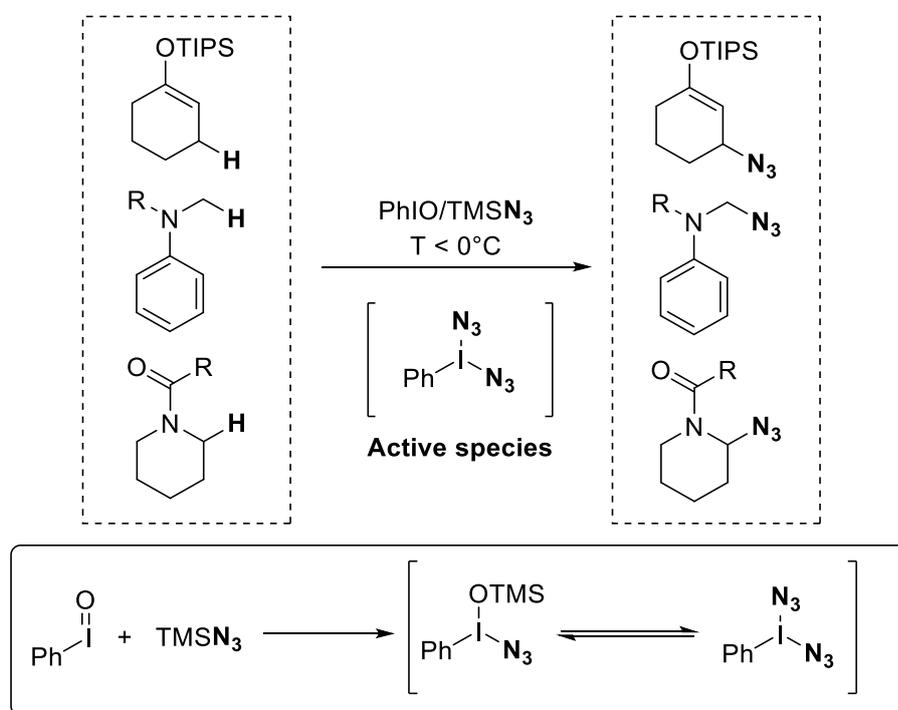
**Scheme 1.** Huisgen Azide-Alkyne 1,3-dipolar cycloaddition vs. CuAAC.<sup>2b</sup>

The CuAAC approach has shown an incredible potential to cover the non-reactivity gap of standard methods used in molecule discovery, especially when soft or aqueous conditions are needed, as well as when complicated or harsh purification processes are not suitable with the desired product. In addition, it gives to chemists a practical tool for the design and synthesis of a multitude of new 1,2,3-triazole-based core structures, with relevant properties in several fields, such as medicinal (figure 1, top) or material chemistry.<sup>3</sup> 1,2,3-Triazole has also demonstrated promising properties in asymmetric and supramolecular-based catalysis, such as in the asymmetric dearomatization of heterocycles (Figure 1, bottom).<sup>4</sup>



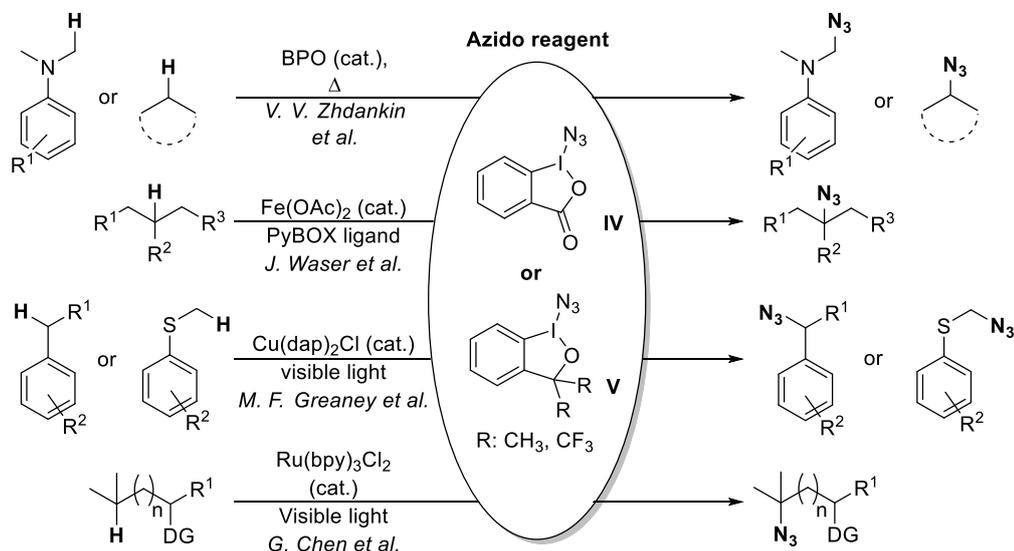
**Figure 1.** Examples of triazole applications in medicinal chemistry and catalysis.

Another important aspect to consider following a “click chemistry” point of view is the accessibility of all the reaction partners. Indeed, even if the alkyne and azide are generally easily available, in some cases the preparation of the starting materials, in particular regarding the azide-containing substrates, might become a real limitation. Although the chemistry beyond the insertion of azide moieties is well-established,<sup>5</sup> most procedures are still based on nucleophilic substitutions or diazo transfers when the target is a Csp<sup>3</sup> atom. Consequently, most standard azido-functionalization are limited to substrates in which a pre-installed leaving group is present, limiting the application in late stage reactions or in systems presenting regioselective issues. This was translated in a large number of target-specific strategies, and only in the last 30 years new methodologies on the direct Csp<sup>3</sup>-H bond azido-functionalization have been established.<sup>5</sup> From the pioneering works reported by P. Magnus on the direct azido-derivatization mediated by *in situ* formed (diazideiodo)benzene (Scheme 2),<sup>6</sup> several hypervalent iodine-azide reagents has been enrolled for the direct Csp<sup>3</sup>-H bond azidonation of a broad variety of substrate.



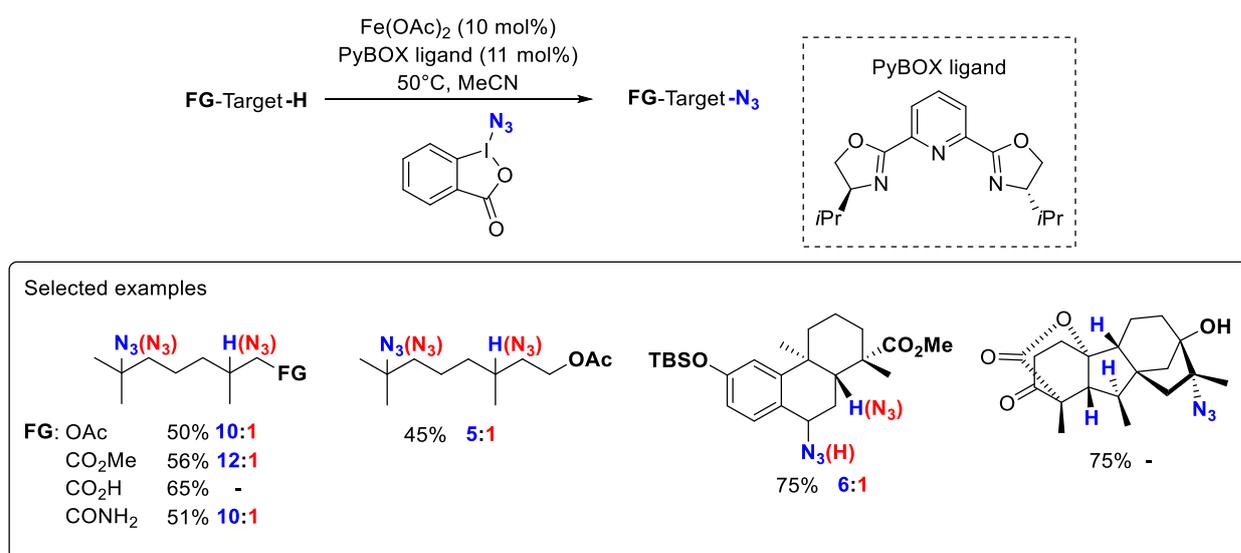
**Scheme 2.** A selection of Magnus work on azidonation.

Beside the P. Magnus contributions, in which iodosobenzene (PhIO)/trimethylazide (TMSN<sub>3</sub>) reagents combination has been employed in α-N-alkyl and β-enol ether azidonation, stable azido cyclic iodinanones, such as **IV** and **V**, have also shown a wide potential in direct azido-derivatization (Scheme 3). Among the reported works, it is interesting to notice that the azidonation of relative inert targets, such as tertiary Csp<sup>3</sup> alkyl carbon is also possible in the presence of a catalytic amount of a radical starter and/or a metal catalyst.<sup>7</sup>



**Scheme 3.** Azido cyclic iodinanones mediated azidonation of various Csp<sup>3</sup> targets.

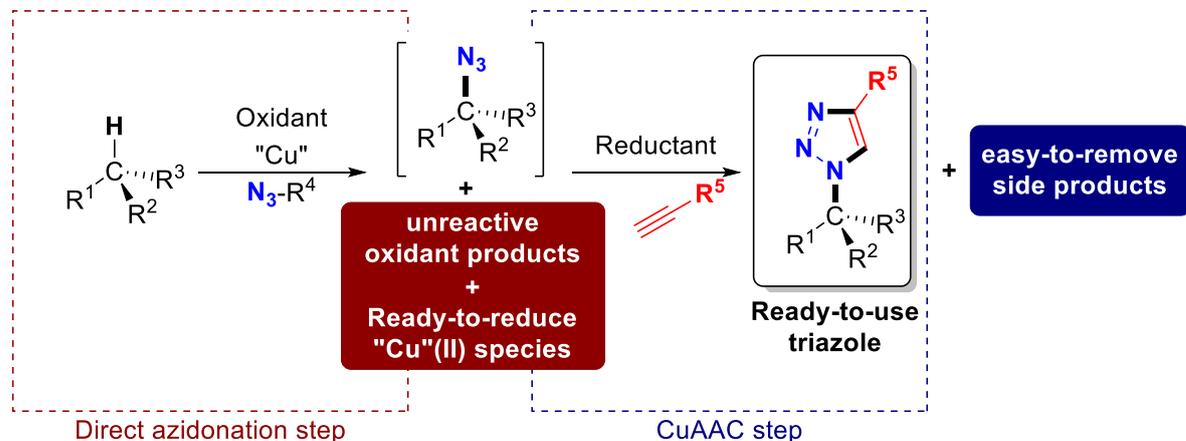
In this context, in 2015 J. F. Hartwig and coworker displayed the effectiveness of 2 azido 1,2-benziodoxol-3(1H)-one as regioselective azidonation agent under iron catalysis on complex alkylic scaffold, as well as in late stage functionalization (Scheme 4).<sup>8</sup> Several functional groups were well tolerated, even acid and free-hydroxy group. Surprisingly, the presence of such groups leads to only one isomer, and the obtained yields resulted higher respect with standard substrate. Thus, -OH free moieties are efficient directing groups in this strategy.



**Scheme 4.** A summary of the work reported by J. F. Hartwig.

### 2.2.2 Objectives

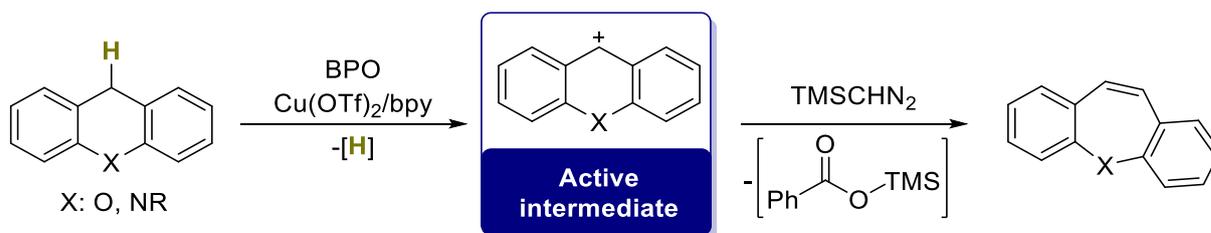
After this short overview, it is evident the potential of azido-iodine reagents in organic synthesis. However, there are some limitation when a “click-chemistry” approach is aimed towards a combined direct azidation/CuAAC process for the creation of an even more efficient procedure. Indeed, to the best of our knowledge, no procedure of one-pot direct azidation of Csp<sup>3</sup>-H bond/copper catalysed alkyne azide cycloaddition, even performed in a 2-step 1-pot strategy, has been reported so far in the literature. This restraint hailed from the interaction within the copper catalyst and the iodine-containing reagents and by-products of the azidation step, which deactivate the copper for the CuAAC catalytic cycle. From this point of view, considering also the probable formation of unwanted azide-isomers, it is evident that, right now, the isolation of the desire azide is still best solution to conduct such azidation/CuAAC processes. However, azide moieties are sensitive substrates, which could undergo uncontrolled degradation reactions, even in an explosive manner. As follow, trapping the azide *in situ* could be essential when the target azide is difficult to handle in the required environment for the work-up, the purification and the cycloaddition steps. Therefore, it outcomes that a procedure for the direct Csp<sup>3</sup>-H bonds azidation/cyclization in which the reagents are compatible with the next CuAAC process, is highly demanding. In this context, our efforts focused to the extension of this “click-chemistry” approach to involve the whole process, from the azide synthesis to the triazole purification. More in detail, our main goal was the development of a 2-step 1-pot procedure for the Csp<sup>3</sup>-H oxidative functionalization/azide addition enrolling copper, coupled with common and easy-to-remove reagents suitable with the consecutive trapping of the stable or unstable azide intermediates by CuAAC process (Scheme 5). In addition, we want to develop a process that is also applicable in a late stage functionalization, as well as for the synthesis of biomarkers or biosensors.



**Scheme 5.** The main goal of this project.

### 2.2.3 Results and Discussion

To ensure the highest conversion into the desired azide avoiding unwanted side-product, the azidation step was initially investigated. Xanthene (**1a**) was chosen as model substrate for various reasons: i) the experience on Csp<sup>3</sup>-H bond functionalization of xanthene and acridane moieties acquired in our laboratory;<sup>9</sup> ii) it resulted an unexplored target in direct azidation reaction; iii) it facilitated the first screening of the reaction, since the product **2a** is a known molecule prepared following other multi-step procedures.<sup>10</sup> As mentioned above, our research group have already developed a direct Csp<sup>3</sup>-H bond functionalization of xanthene and acridane with TMSCHN<sub>2</sub> under oxidative condition to conduct a ring expansion reaction (Scheme 6).<sup>9</sup>



**Scheme 6.** Summary of our previous work on C-H functionalization of xanthene and acridane.

Based on this previous work, **1a** was enrolled in the reaction using TMSN<sub>3</sub> under the same oxidative system (BPO/Cu(OTf)<sub>2</sub>/bpy).<sup>9</sup> Unfortunately, the conversion into desired product was unsatisfying after 18 h (Table 1, entry 1).

**Table 1.** Optimization of the first step<sup>[a]</sup>

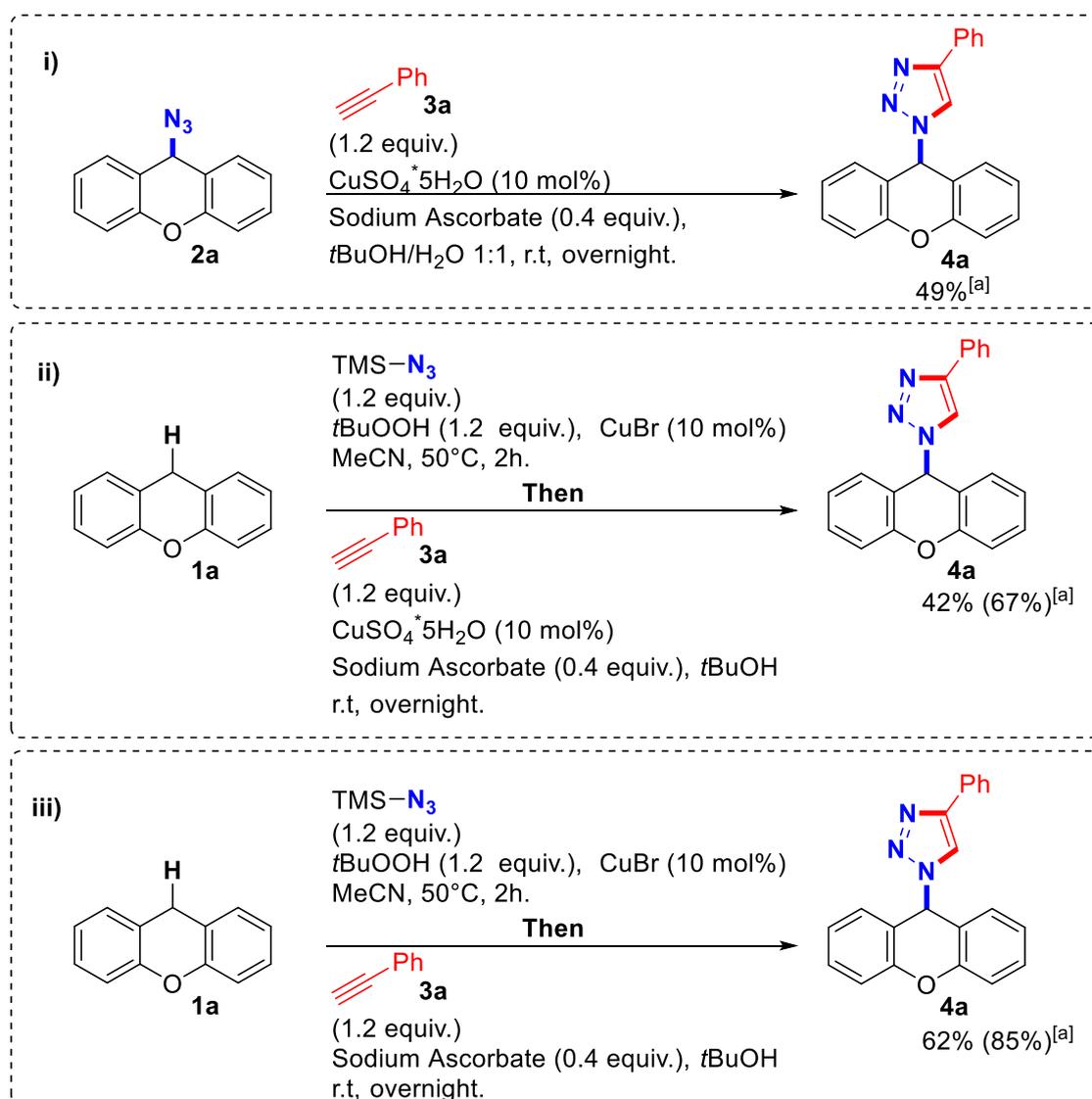


Entry	oxidant (equiv.)	"Cu" cat. (10 mol%)	Temp. (°C)	Time (h)	Conversion (%) <sup>[b]</sup>
1	BPO (1.2)	Cu(OTf) <sub>2</sub> <sup>[c]</sup>	rt	18	33%
2	BPO (1.2)	CuBr	50 °C	18	>99%
3	<i>t</i> BuOOH (1.2) <sup>[d]</sup>	CuBr	50 °C	2	>99%
4	<i>t</i> BuOOH (1.2) <sup>[e]</sup>	CuBr <sup>[f]</sup>	50 °C	24	51%
5	<i>t</i> BuOOH (1.2) <sup>[d]</sup>	CuSO <sub>4</sub> ·5H <sub>2</sub> O	50 °C	24	92%
6 <sup>[g]</sup>	<i>t</i> BuOOH (1.2) <sup>[d]</sup>	CuBr	50 °C	24	20%
7 <sup>[h]</sup>	<i>t</i> BuOOH (1.2) <sup>[d]</sup>	CuBr	50 °C	2	>99%
8 <sup>[h]</sup>	<i>t</i> BuOOH (1.2) <sup>[e]</sup>	CuBr	50 °C	2	>99%

[a] **1a** (0.4 mmol, 1 equiv.), TMSN<sub>3</sub> (2 equiv.), oxidant and catalyst (10 mol%) in MeCN (0.4 M) at the corresponding temperature until disappearance of **1a**. [b] Conversion evaluated by NMR analysis. [c] Bipyridyl (30 mol%) was used as ligand. [d] *t*BuOOH 70% in water. [e] dry *t*BuOOH 5.5 M in decane. [f] FeCl<sub>3</sub> (20 mol%) was used as co-catalyst. [g] NaN<sub>3</sub> (2 equiv.) was used instead of TMSN<sub>3</sub>. [h] 1.2 equiv. of N<sub>3</sub>TMS was used.

Increasing the temperature to 50 °C and changing the oxidative system to *t*BuOOH under CuBr catalysis, full conversion was achieved in 2 hours (Table 1, entry 3). Interestingly, the performance did not change when the amount of TMSN<sub>3</sub> was decreased to 1.2 equivalent or when water free *t*BuOOH was used (Table 1, entries 7 and 8). The addition of FeCl<sub>3</sub> as co-catalys, as well as switching the azidonation agent to more nucleophilic species such as NaN<sub>3</sub>, led to low conversion even after 24 h (Table 1, entries 4 and 6). It is important to noticed that the crude product resulted almost pure when full conversion was achieved.

Having in hand the accomplishment of the first step, the cyclization step was next investigated (Scheme 7).



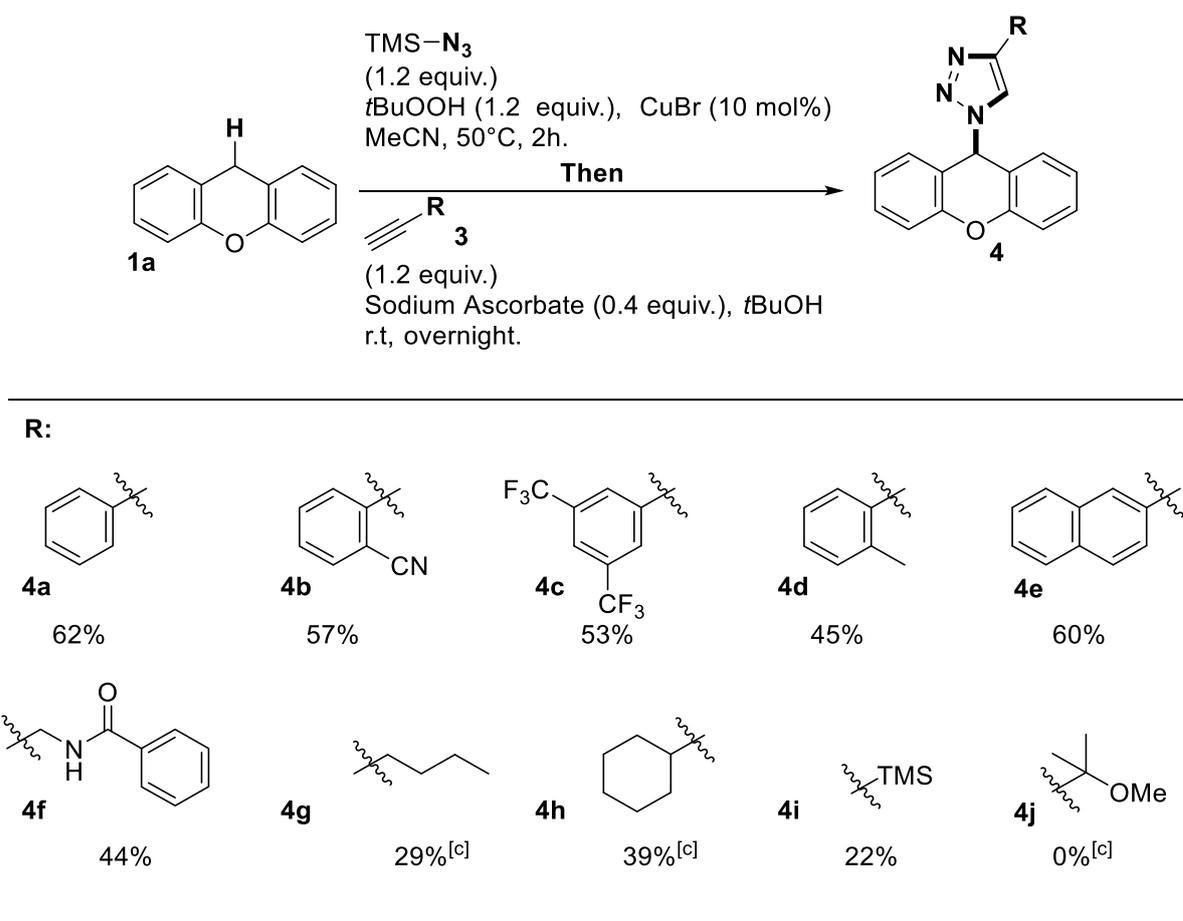
[a] Isolated yield. The yield in brackets was extrapolated from the crude product

**Scheme 7.** Exploration of the 2-step 1-pot azidonation/CuAAC reaction.

Thus, the CuAAC was performed with the isolated azide **2a** under standard click condition using  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  as catalyst in the presence of sodium ascorbate, providing the desired triazole product in 49% isolate yield (Scheme 7, eq. i). Then, the 2-step 1-pot approach was examined. Initially, after the oxidative azidonation step, the addition of a second species of copper ( $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ ) was explored (Scheme 7, eq. ii). The CuAAC reaction was carried out adding all the required reagents and an auxiliary solvent without any additional work-up. However, this 2-copper system led to significantly lower yield of the product. Then, the reaction was enrolled only with the initial CuBr catalyst, without charging any other copper species during the second step (Scheme 7, eq. iii). To our delight, this 2-step 1-pot version worked very efficiently (62% yield), avoiding the need of additional metal species, and therefore, generating less waste.

The reaction of xanthene with different dipolarophile partners was then investigated (Table 2). The yields were good with all the aromatic substituted alkynes (up to 62%), and steric hindrance was well tolerated as well (es. **4d**, 45%). Instead, the employment of alkylic substituted alkynes led to lower performance and longer reaction times (29-39%, 48h). Interestingly, the trimethylsilylacetylene product (**4i**) resulted very unstable, being difficult to discriminate the reason for the obtained low 22% yield.

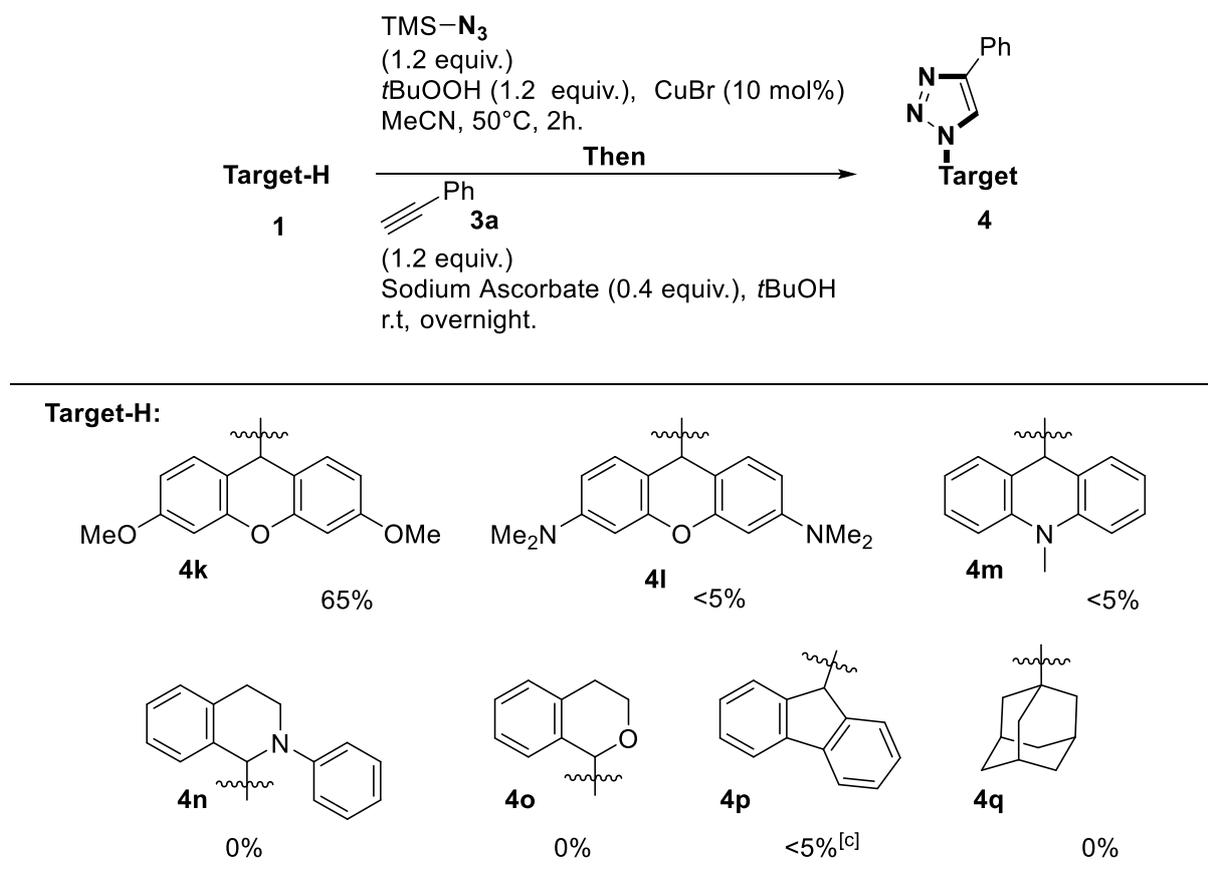
**Table 2.** Scope of the reaction: Alkyne partner variation.<sup>[a],[b]</sup>



[a] **1a** (0.4 mmol, 1 equiv.),  $\text{TMSN}_3$  (1.2 equiv.),  $t\text{BuOOH}$  70% in water (1.2 equiv.) and  $\text{CuBr}$  (10 mol%) in  $\text{MeCN}$  (0.4 M) at  $50^\circ\text{C}$  for 2 h, then **3** (1.2 equiv.), sodium ascorbate (0.4 equiv.) and  $t\text{BuOH}$  (0.4 M) at  $\text{rt}$  for 18 h. [b] Isolated yields. [c] CuAAC step was performed for 48 h.

Next, several different classes of substrate were explored in the reaction, involving phenylacetylene (**3a**) as alkynyl partner (Table 3). While dimethoxy xanthene **1k** provided the triazole in **4k** in high 65% yield, amine containing electron rich xanthene like **4l** and **4m** appear not suitable for reaction. In one hand, both azido intermediate **2l** and triazole **4l** are not stable under poor oxidative condition. In the other hand, 9-azido N-methyl acridane intermediate **2m**, obtained almost quantitative, but presented a poor participation in the cycloaddition step. In addition, **4m** resulted unstable and impossible to isolate, decomposing rapidly to give the corresponding acridone. Interestingly, even though tetrahydroisoquinoline **1n** gave the azido-intermediate **2n**, after the second step it was observed just the addition product of the alkyne **3a** to **1n**. Finally, fluorene, isochromane and adamantane needed harsher conditions to achieve a significant amount of azide to enroll in the CuAAC step.

**Table 3.** Substrates scope.



[a] **1** (0.4 mmol, 1 equiv.), TMSN<sub>3</sub> (1.2 equiv.), tBuOOH 70% in water or 5.5M in decane (1.2 equiv.) and CuBr (10 mol%) in MeCN (0.4 M) at 50°C for 2 h then **3a** (1.2 equiv.), sodium ascorbate (0.4 equiv.) and tBuOH (0.4 M) at rt for 18h. [b] Isolated yields. [c] Azidonation step was performed for 24h.

## 2.2.4 Conclusion and Outlooks

In summary, in this early study, important advances for the development of an efficient and easy procedure to extend a classical “click-chemistry” process were carried out. Thus, the CuAAC approach was extended to a 2-step 1-pot procedure, from the synthesis of the starting material (azide) to the effective target (triazole), involving a direct Csp<sup>3</sup>-H bond functionalization. Furthermore, as far as we know, the easy and direct synthesis of several triazole-substituted heterocycles, such as **4n** and xanthene-based triazoles **4a-l**, we efficiently achieved for the first time. However, taking into account the moderate yields and some limitation in the scope, especially concerning the CuAAC step, it is evident that further studies on the optimization are needed. In this regard, we are already testing other copper species, as well as different auxiliary solvents.

## 2.2.5 References

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## 2.3 Experimental Part.

### 2.3.1 Trapping Unstable Nitrones to form Isoxazolines

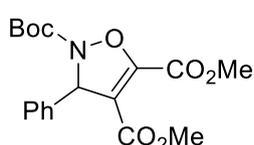
#### *General Information and Materials:*

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded in  $\text{CDCl}_3$ , (reference signal:  $^1\text{H}$  = 7.26 ppm,  $^{13}\text{C}$  = 77.16 ppm,  $\text{CDCl}_3$ ) on *Brucker Avance* 300 MHz spectrometer. Chemical shifts ( $\delta$ ) are given in ppm and spin-spin coupling constants ( $J$ ) are given in Hz. Analytical thin layer chromatography was performed using silica gel 60 F<sub>254</sub> and a solution of  $\text{KMnO}_4$  or a Iodine camera served as staining agent. Column chromatography was performed on silica gel 60 (0.040-0.063 mm). Exact masses (**HRMS (ES)**) were recorded on an *Agilent Q-TOF 6540 UHD* spectrometer (samples in  $\text{CH}_3\text{OH}$  as solvent).  $\text{CH}_2\text{Cl}_2$  and  $\text{Et}_3\text{N}$  were dried over molecular sieves; THF was distilled and dried over Na. TEMPO was purified by sublimation under reduced pressure. Other solvents and commercially available reagents were used without further purification. All the flasks were dried under vacuum using a heating gun.

#### *General Procedure:*

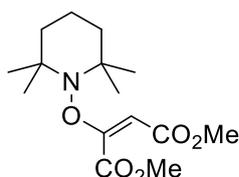
In a screw-cap schlenk tube, the corresponding *N*-protected *N*-benzylhydroxyamine derivative **1** (1.00 equiv.) was dissolved in dry  $\text{CH}_2\text{Cl}_2$  (2.00 mL). Acetylenedicarboxylate (**2**) (4.00 equiv.) and TEMPO (2.00 equiv.) were added and the reaction mixture was stirred at 70 °C for 24 h. The solvent was removed under reduced pressure and the obtained crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt to give the corresponding *N*-protected isoxazoline **3**.

#### **2-tert-Butyl 4,5-dimethyl 3-phenylisoxazole-2,4,5-tricarboxylate (3aa)**



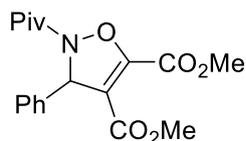
According to the general procedure, *N*-Boc *N*-benzyl hydroxylamine (**1a**) (0.25 mmol, 63.3 mg, 1.00 equiv.), dry  $\text{CH}_2\text{Cl}_2$  (2 mL), **2a** (122  $\mu\text{L}$ , 1.00 mmol, 4.00 equiv.) and TEMPO (78.8 mg, 0.50 mmol, 2.00 equiv.) were reacted. The crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt [(%AcOEt): 1% (30 mL); 5% (50 mL); 15% (300 mL) 25% (200 mL)] to give **3aa** as a viscous solid (0.22 mmol, 79.3 mg, 84%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm 7.34 – 7.20 (m, 5H), 6.06 (s, 1H), 3.87 (s, 3H), 3.57 (s, 3H), 1.39 (s, 9H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm: 161.4, 158.1, 155.2, 149.9, 138.7, 128.81, 127.3, 111.0, 84.3, 68.9 53.6, 52.2, 28.1. **MS-ESI:**  $m/z$  calculated for  $[\text{C}_{18}\text{H}_{21}\text{NO}_7\text{Na}]^+ = 386.1210$ ; found  $m/z = 386.1207$

#### **Dimethyl 2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)maleate (4aa)**



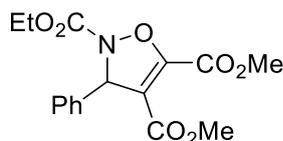
$^1\text{H}$ -NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm: 5.94 (s, 1H), 6.43 (s, 1H), 3.91 (s, 3H), 3.68 (s, 3H), 1.60-1.52 (m, 6H), 1.17 (s, 6H), 1.12 (s, 6H).  $^{13}\text{C}$ -NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm: 167.4, 165.6, 95.6, 61.4, 52.9, 51.4, 39.7, 31.9, 20.5, 16.8. **GC-MS (T<sub>0</sub> 50°C\_20°C/min\_T<sub>max</sub> 280°C):** for  $[\text{C}_{15}\text{H}_{25}\text{NO}_5]$ ;  $t_{\text{R}}$  10.4 min =  $m/z$  300 ( $\text{MH}^+$ , 23), 269 ( $\text{M}^+ - \text{C}_2\text{H}_6$ , 100).

### 2-Pivaloyl 4,5-dimethyl 3-phenylisoxazole-4,5-dicarboxylate (**3ba**)



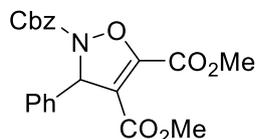
According to the general procedure, hydroxylamine **1b** (0.50 mmol, 104.0 mg, 1.00 equiv.), dry CH<sub>2</sub>Cl<sub>2</sub> (4 mL), **2a** (245 μL, 2.00 mmol, 4.00 equiv.) and TEMPO (157.6 mg, 1.00 mmol, 2.00 equiv.) were reacted. The crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt [(%AcOEt): 1% (30 mL); 5% (50 mL); 20% (200 mL)] to give **3ba** as a viscous solid (0.090 mmol, 31.3 mg, 17%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ/ppm: 7.40 – 7.31 (m, 5H), 6.43 (s, 1H), 3.98 (s, 3H), 3.65 (s, 3H), 1.27 (s, 9H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ/ppm: 178.6, 161.1, 157.8, 148.4, 138.1, 128.7, 128.7, 127.3, 111.9, 67.28, 53.6, 52.2, 39.6, 26.3. MS-ESI: m/z calculated for [C<sub>18</sub>H<sub>21</sub>NO<sub>6</sub>Na]<sup>+</sup> = 370.1261; found m/z = 370.1257.

### 2-Ethyl 4,5-dimethyl 3-phenylisoxazole-2,4,5-tricarboxylate (**3ca**)



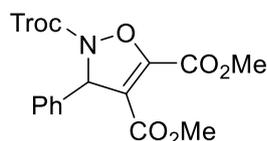
According to the general procedure, hydroxylamine **1c** (0.25 mmol, 63.3 mg, 1.00 equiv.), dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL), **2a** (122 μL, 1.00 mmol, 4.00 equiv.) and TEMPO (78.8 mg, 0.50 mmol, 2.00 equiv.) were reacted. The crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt [(%AcOEt): 1% (30 mL); 5% (50 mL); 15% (300 mL) 25% (200 mL)] to give **3ca** as a white viscous solid (0.21 mmol, 69.9 mg, 84%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.46 – 7.28 (m, 5H), 6.22 (s, 1H), 4.28 (qq, J = 10.6, 7.1 Hz, 2H), 3.95 (s, 3H), 3.65 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 161.1, 157.9, 155.0, 150.0, 137.8, 131.9, 129.0, 122.8, 110.3, 84.6, 68.3, 53.6, 52.2, 28.0. MS-ESI: m/z calculated for [C<sub>16</sub>H<sub>17</sub>NO<sub>7</sub>Na]<sup>+</sup> = 358.0897; found m/z = 358.0903.

### 2-Benzyl 4,5-dimethyl 3-phenylisoxazole-2,4,5-tricarboxylate (**3da**)



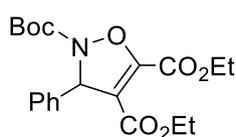
According to the general procedure, hydroxylamine **1d** (0.25 mmol, 064.2 mg, 1.00 equiv.), dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL), **2a** (122 μL, 1.00 mmol, 4.00 equiv.) and TEMPO (78.8 mg, 0.50 mmol, 2.00 equiv.) were reacted. The crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt [(%AcOEt): 1% (30 mL); 5% (50 mL); 15% (300 mL) 25% (200 mL)] to give **3da** as viscous solid (0.10 mmol, 39.7 mg, 40%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ/ppm: 7.35 – 7.16 (m, 10H), 6.15 (s, 1H), 5.19 (d, J = 12.2 Hz, 1H), 5.12 (d, J = 12.2 Hz, 1H), 3.87 (s, 3H), 3.56 (s, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ/ppm: 161.0, 157.8, 156.3, 149.65, 138.0, 134.8, 128.9, 128.8, 128.6, 128.3, 127.3, 111.1, 110.0, 69.0, 68.9, 53.6, 52.2, 29.7. MS-ESI: m/z calculated for [C<sub>21</sub>H<sub>19</sub>NO<sub>7</sub>Na]<sup>+</sup> = 420.1054; found m/z = 420.1058

### 2-(2,2,2-Trichloroethyl) 4,5-dimethyl 3-phenylisoxazole-4,5-tricarboxylate (**3ea**)



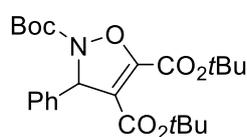
According to the general procedure, hydroxylamine **1e** (0.25 mmol, 74.7 mg, 1.00 equiv.), dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL), **2a** (122 μL, 1.00 mmol, 4.00 equiv.) and TEMPO (78.8 mg, 0.50 mmol, 2.00 equiv.) were reacted. The crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt [(%AcOEt): 1% (50 mL), 5% (50 mL), 10% (200 mL), 15% (300 mL)] to give **3ea** as a white viscous solid (0.05 mmol, 22.9 mg, 21%). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ/ppm: 7.42 – 7.36 (m, 5H), 6.27 (s, 1H), 4.88 (d, J = 11.8 Hz, 1H), 4.72 (d, J = 4.6 Hz, 1H), 3.97 (s, 3H), 3.66 (s, 3H). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ/ppm: 160.8, 157.5, 149.4, 137.3, 128.9, 128.2, 127.4, 111.3, 94.2, 75.7, 69.1, 53.7, 52.4. MS-ESI: m/z calculated for [C<sub>21</sub>H<sub>19</sub> Cl<sub>3</sub>NO<sub>7</sub>Na]<sup>+</sup> = 459.9728; found m/z = 459.9729.

### 2-*tert*-Butyl 4,5-diethyl 3-phenylisoxazole-2,4,5-tricarboxylate (**3ab**)



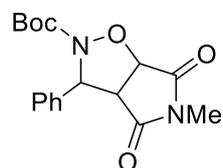
According to the general procedure, hydroxylamine **1a** (0.25 mmol, 55.8 mg, 1.00 equiv.), dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL), **2b** (160 μL, 1.00 mmol, 4.00 equiv.) and TEMPO (78.8 mg, 0.50 mmol, 2.00 equiv.) were reacted. The crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt [(%AcOEt): 1% (50 mL), 5% (50 mL), 10% (100 mL), 15% (400 mL)] to give **3ab** as light yellow oil (0.21 mmol, 82.2 mg, 84%). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ/ppm: 7.42 – 7.29 (m, 5H), 6.11 (s, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 4.15 – 4.02 (m, 2H), 1.46 (s, 9H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ/ppm: 161.0, 157.9, 155.3, 150.1, 138.9, 128.8, 127.5, 110.7, 84.3, 69.0, 63.2, 61.2, 28.2. MS-ESI: *m/z* calculated for [C<sub>20</sub>H<sub>26</sub>NO<sub>7</sub>]<sup>+</sup> = 392.1704; found *m/z* = 392.1710.

### 2,4,5-tri-*tert*-Butyl 3-phenylisoxazole-2,4,5-tricarboxylate (**3ac**)



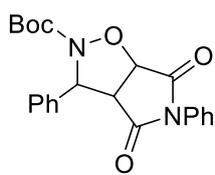
According to the general procedure, hydroxylamine **1a** (0.25 mmol, 55.8 mg, 1.00 equiv.), dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL), **2c** (226.3 mg, 1.00 mmol, 4.00 equiv.) and TEMPO (78.8 mg, 0.50 mmol, 2.00 equiv.) were reacted. The crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt [(%AcOEt): 1% (100 mL), 5% (100 mL), 10% (200 mL), 15% (200 mL), 20% (200 mL)] to give **3ac** as light yellow oil (0.13 mmol, 58.1 mg, 52%). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ/ppm: 7.42 – 7.33 (m, 5H), 6.05 (s, 1H), 1.62 (s, 9H), 1.49 (s, 9H), 1.32 (s, 9H). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ/ppm: 160.1, 156.6, 155.3, 149.9, 139.3, 128.5, 128.5, 127.6, 111.5, 85.0, 83.8, 81.9, 69.2, 28.1, 28.0, 27.9. MS-ESI: *m/z* calculated for [C<sub>24</sub>H<sub>33</sub>NO<sub>7</sub>Na]<sup>+</sup> = 470.2149; found *m/z* = 470.2152.

### 2-*tert*-Butyl-4,6-dioxo-3-phenyl-5-methylhexahydro-2H-pyrrolo[3,4-*d*]isoxazole-2-carboxylate (**3ae**)



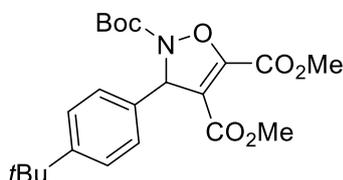
In a screw cap schlenk tube, hydroxylamine **1a** (0.50 mmol, 112.0 mg, 1.00 equiv.), *N*-methylmaleimide (**2e**) (1.00 mmol, 173.0 mg, 2.00 equiv.), **2a** (1.00 mmol, 122 μL, 2.00 equiv.) and TEMPO (1.00 mmol, 142.2 mg, 2.00 equiv.) were dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (4 mL), and the reaction mixture was stirred at 70 °C for 4 days. The solvent was removed under reduced pressure and the obtained crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt [(%AcOEt): 0% (200 mL), 5% (200 mL), 10% (200 mL), 15% (200 mL), 20% (200 mL)] to give **3ae** as light yellow oil (0.25 mmol, 83.0 mg, 50%). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ/ppm: 7.44 – 7.31 (m, 5H), 5.74 (s, 1H), 4.94 (d, *J* = 7.3 Hz, 1H), 3.76 (d, *J* = 7.3 Hz, 1H), 3.01 (s, 3H), 1.41 (s, 9H). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ/ppm: 174.3, 172.1, 156.7, 138.1, 129.0, 128.2, 126.0, 83.7, 78.2, 65.9, 56.2, 27.8, 25.5. MS-ESI: *m/z* calculated for [C<sub>16</sub>H<sub>25</sub>NO<sub>7</sub>Na]<sup>+</sup> = 366.1523; found *m/z* = 366.1527.

### 2-*tert*-Butyl-4,6-dioxo-3,5-diphenylhexahydro-2H-pyrrolo[3,4-d] isoxazole-2 carboxylate (**3af**)



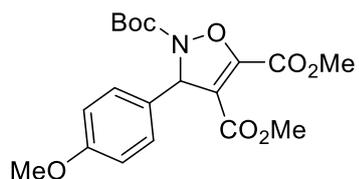
In a screw cap schlenk tube, hydroxylamine **1a** (0.50 mmol, 112.0 mg, 1.00 equiv.), **2a** (1.00 mmol, 122  $\mu$ L, 2.00 equiv.), *N*-phenylmaleimide (**2f**) (1.00 mmol, 173.0 mg, 2.00 equiv.) and TEMPO (1.00 mmol, 142.2 mg, 2.00 equiv.) were dissolved in dry  $\text{CH}_2\text{Cl}_2$  (4 mL), and the reaction mixture was stirred at 70  $^\circ\text{C}$  for 4 days. The solvent was removed under reduced pressure and the obtained crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt [(%AcOEt): 5% (100 mL), 5% (100 mL), 15% (200 mL), 20% (500 mL)] to give **3af** as a 1:7 mixture of diastereoisomers (0.22 mmol, 86.3 mg, 44%). *Major diastereoisomer*:  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm: 7.53 – 7.26 (m, 10H), 5.90 (s, 1H), 5.09 (d,  $J = 7.4$  Hz, 1H), 3.93 (d,  $J = 7.4$  Hz, 1H), 1.34 (s, 9H).  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm: 173.5, 171.1, 157.0, 138.2, 134.3, 129.2, 129.2, 129.0, 126.3, 126.1, 126.1, 125.9, 84.1, 78.4, 66.34, 56.4, 27.9. **MS-ESI**:  $m/z$  calculated for  $[\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_5\text{Na}]^+$  = 417.1421; found  $m/z$  = 417.1419.

### 2-*tert*-Butyl 4,5-dimethyl 3-(4-*tert*-butylphenyl)isoxazole-2,4,5-tricarboxylate (**3ga**)



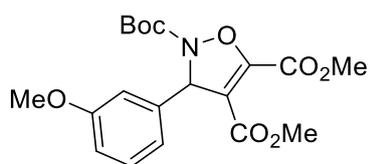
According to the general procedure, hydroxylamine **1g** (0.25 mmol, 72.8 mg, 1.00 equiv.), dry  $\text{CH}_2\text{Cl}_2$  (2 mL), **2a** (122  $\mu$ L, 1.00 mmol, 4.00 equiv.) and TEMPO (78.8 mg, 0.50 mmol, 2.00 equiv.) were reacted. The crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt [(%AcOEt): 1% (50 mL), 5% (50 mL), 10% (200 mL), 25% (200 mL)] to give **3ga** as pale yellow viscous oil (0.16 mmol, 53.3 mg, 51%).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm: 7.40 – 7.29 (m, 4H), 6.12 (s, 1H), 3.95 (s, 3H), 3.66 (s, 3H), 1.46 (s, 9H), 1.30 (s, 9H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm: 161.4, 158.1, 155.4, 151.6, 149.8, 135.5, 126.8, 125.7, 125.5, 111.0, 84.2, 68.6, 53.5, 52.1, 34.6, 31.4, 31.3, 28.0. **MS-ESI**:  $m/z$  calculated for  $[\text{C}_{22}\text{H}_{30}\text{NO}_7]^+$  = 420.2018; found  $m/z$  = 420.2017.

### 2-*tert*-Butyl 4,5-dimethyl 3-(4-methoxyphenyl)isoxazole-2,4,5-tricarboxylate (**3ia**)



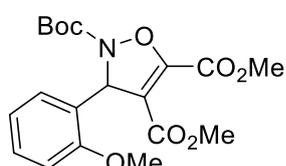
According to the general procedure, hydroxylamine **1i** (0.25 mmol, 63.3 mg, 1.00 equiv.), dry  $\text{CH}_2\text{Cl}_2$  (2 mL), **2a** (122  $\mu$ L, 1.00 mmol, 4.00 equiv.) and TEMPO (78.8 mg, 0.50 mmol, 2.00 equiv.) were reacted. The crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt [(%AcOEt): 1% (50 mL), 5% (50 mL), 10% (200 mL), 15% (300 mL), 25% (200.00 mL)] to give **3ia** as a white viscous solid (0.21 mmol, 82.5 mg, 84%).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm: 7.33 – 7.26 (m, 2H), 6.91 – 6.83 (m, 2H), 6.08 (s, 1H), 3.94 (s, 3H), 3.79 (s, 3H), 3.64 (s, 3H), 1.46 (s, 8H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm: 161.4, 159.9, 158.1, 155.2, 149.6, 130.79, 128.6, 114.1, 110.9, 84.17, 68.5, 55.3, 53.5, 52.1, 28.0. **MS-ESI**:  $m/z$  calculated for  $[\text{C}_{19}\text{H}_{23}\text{NO}_8\text{Na}]^+$  = 416.1316; found  $m/z$  = 416.1315

### 2-*tert*-Butyl 4,5-dimethyl 3-(3-methoxyphenyl)isoxazole-2,4,5-tricarboxylate (**3ja**)



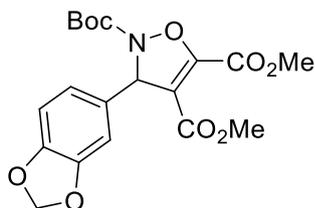
According to the general procedure, hydroxylamine **1j** (0.25 mmol, 63.3 mg, 1.00 equiv.), dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL), **2a** (122 μL, 1.00 mmol, 4.00 equiv.) and TEMPO (78.8 mg, 0.50 mmol, 2.00 equiv.) were reacted. The crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt [(%AcOEt): 1% (50 mL), 5% (50 mL), 10% (200 mL), 15% (300 mL)] to give **3ja** as a pale yellow viscous oil (0.18 mmol, 69.8 mg, 71%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ/ppm: 7.26 – 7.20 (m, 1H), 7.02 – 6.70 (m, 3H), 6.06 (s, 1H), 3.91 (s, 3H), 3.76 (s, 3H), 3.61 (s, 3H), 1.43 (s, 9H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ/ppm: 161.3, 159.9, 158.0, 155.2, 149.8, 140.1, 129.8, 119.5, 114.3, 112.8, 110.9, 84.3, 68.8, 55.3, 53.5, 52.2, 28.1. MS-ESI: m/z calculated for [C<sub>19</sub>H<sub>23</sub>NO<sub>8</sub>Na]<sup>+</sup> = 416.1316; found m/z = 416.1314.

### 2-*tert*-Butyl 4,5-dimethyl 3-(2-methoxyphenyl)isoxazole-2,4,5-tricarboxylate (**3ka**)



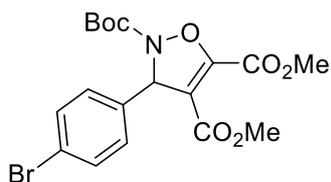
According to the general procedure, hydroxylamine **1k** (0.25 mmol, 63.3 mg, 1.00 equiv.), dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL), **2a** (122 μL, 1.00 mmol, 4.00 equiv.) and TEMPO (78.8 mg, 0.50 mmol, 2.00 equiv.) were reacted. The crude product was purified by flash column chromatography on silica eluting with pentane/AcOEt [(%AcOEt): 1% (50 mL), 5% (50 mL), 15% (200 mL), 20% (300 mL)] to give **3ka** as light yellow oil (0.11 mmol, 42.4 mg, 43%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ/ppm: 7.33 – 7.27 (m, 2H), 6.99 – 6.86 (m, 2H), 6.51 (s, 1H), 3.94 (s, 3H), 3.85 (s, 3H), 3.63 (s, 3H), 1.43 (s, 9H). <sup>13</sup>C NMR 161.6, 158.4, 157.4, 155.4, 149.7, 130.1, 129.1, 126.5, 120.9, 111.2, 111.1, 83.9, 64.4, 55.8, 53.5, 52.1, 28.1. MS-ESI: m/z calculated for [C<sub>19</sub>H<sub>23</sub>NO<sub>8</sub>Na]<sup>+</sup> = 416.1316; found m/z = 416.1317.

### 2-*tert*-butyl 4,5-dimethyl 3-(benzo[d][1,3]dioxol-5-yl)isoxazole-2,4,5-tricarboxylate (**3la**)



According to the general procedure, hydroxylamine **1l** (0.25 mmol, 66.8 mg, 1.00 equiv.), dry CH<sub>2</sub>Cl<sub>2</sub> (2.00 mL), **2a** (122 μL, 1.00 mmol, 4.00 equiv.) and TEMPO (78.8 mg, 0.50 mmol, 2.00 equiv.) were reacted. The crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt [(%AcOEt): 1% (50 mL), 5% (50 mL), 15% (300 mL), 20% (500 mL)] to give **3la** as a yellow low melting point solid (0.08 mmol, 31.6 mg, 31%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ/ppm: 6.89 – 6.74 (m, 3H), 6.05 (s, 1H), 5.95 (s, 2H), 3.94 (s, 3H), 3.66 (s, 3H), 1.48 (s, 9H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ/ppm: 161.3, 158.0, 155.2, 149.7, 148.03, 148.0, 132.5, 121.1, 110.7, 108.3, 107.7, 101.3, 84.3, 68.7, 53.5, 52.18, 28.1. MS-ESI: m/z calculated for [C<sub>19</sub>H<sub>21</sub>NO<sub>9</sub>Na]<sup>+</sup> = 430.1109; found m/z = 430.1113

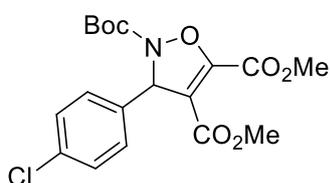
### 2-*tert*-Butyl 4,5-dimethyl 3-(4-bromophenyl)isoxazole-2,4,5-tricarboxylate (**3ma**)



According to the general procedure, hydroxylamine **1m** (0.25 mmol, 75.5 mg, 1.00 equiv.), dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL), **2a** (122 μL, 1.00 mmol, 4.00 equiv.) and TEMPO (78.8 mg, 0.50 mmol, 2.00 equiv.) were reacted. The crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt [(%AcOEt): 1% (50 mL), 5% (50 mL), 10% (200 mL), 15% (300 mL)] to give **3ma** as light yellow oil (0.16 mmol, 70.6 mg, 80%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ/ppm: 7.52 – 7.45 (m, 2H), 7.30 – 7.24 (m, 2H), 6.09 (s, 1H), 3.95 (s, 3H), 3.65 (s, 3H), 1.47 (s, 9H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ/ppm: 161.1, 157.9, 155.0, 150.0, 137.8, 131.9, 129.0, 122.8, 110.3, 84.6, 68.3, 53.6, 52.2, 28.0.

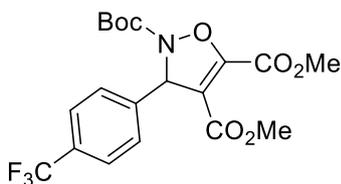
**MS-ESI:** m/z calculated for [C<sub>18</sub>H<sub>20</sub>BrNO<sub>7</sub>Na]<sup>+</sup> = 464.0315; found m/z = 464.0312.

### 2-*tert*-Butyl 4,5-dimethyl 3-(4-chlorophenyl)isoxazole-2,4,5-tricarboxylate (**3na**)



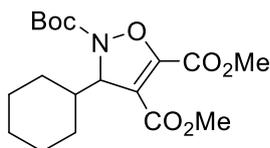
According to the general procedure, hydroxylamine **1na** (0.25 mmol, 64.4 mg, 1.00 equiv.), dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL), **2a** (122 μL, 1.00 mmol, 4.00 equiv.) and TEMPO (78.8 mg, 0.50 mmol, 2.00 equiv.) were reacted. The crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt [(%AcOEt): 1% (50 mL), 5% (50 mL), 10% (200 mL), 15% (300 mL)] to give **3na** as viscous solid (0.16 mmol, 64.6 mg, 65%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ/ppm: 7.33 (s, 4H), 6.10 (s, 1H), 3.95 (s, 3H), 3.65 (s, 3H), 1.47 (s, 9H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ/ppm: 161.3, 158.0, 155.2, 150.1, 137.4, 134.7, 129.1, 128.8, 110.5, 84.70, 68.3, 53.7, 52.3, 28.2. **MS-ESI:** m/z calculated for [C<sub>18</sub>H<sub>21</sub>ClNO<sub>7</sub>]<sup>+</sup> = 398.1001; found m/z = 398.1000

### 2-*tert*-Butyl 4,5-dimethyl 3-(4-trifluoromethylphenyl)isoxazole-2,4,5-tricarboxylate (**3oa**)



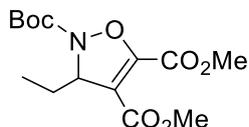
According to the general procedure, hydroxylamine **1o** (0.25 mmol, 72.8 mg, 1.00 equiv.), dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL), **2a** (122 μL, 1.00 mmol, 4.00 equiv.) and TEMPO (78.8 mg, 0.50 mmol, 2.00 equiv.) were reacted. The crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt [(%AcOEt): 1% (50 mL), 5% (50 mL), 10% (200 mL), 15% (300 mL)] to give **3oa** as viscous solid (0.16 mmol, 67.9 mg, 63%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ/ppm: 7.62 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.2 Hz, 2H), 6.18 (s, 1H), 3.95 (s, 3H), 3.65 (s, 3H), 1.47 (s, 9H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ/ppm: 161.0, 157.9, 155.0, 150.3, 142.5, 127.69, 125.8, 125.7, 125.7, 125.6, 110.0, 84.7, 68.2, 53.6, 52.2, 28.0. **MS-ESI:** m/z calculated for [C<sub>19</sub>H<sub>20</sub>F<sub>3</sub>NO<sub>7</sub>Na]<sup>+</sup> = 454.1084; found m/z = 454.1073.

### 2-*tert*-Butyl 4,5-dimethyl 3-cyclohexylisoxazole-2,4,5-tricarboxylate (**3pa**)



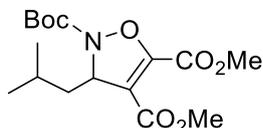
According to the general procedure, hydroxylamine **1p** (0.25 mmol, 50.8 mg, 1.00 equiv.), dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL), **2a** (122 μL, 1.00 mmol, 4.00 equiv.) and TEMPO (78.8 mg, 0.50 mmol, 2.00 equiv.) were reacted. The crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt [(%AcOEt): 1% (100 mL), 5% (50 mL), 10% (300 mL)] to give **3pa** as light yellow oil (0.19 mmol, 68.6 mg, 74%). **<sup>1</sup>H-NMR** (400 MHz, CDCl<sub>3</sub>) δ/ppm: 5.07 (d, *J* = 2.8 Hz, 1H), 3.89 (s, 3H), 3.76 (s, 3H), 1.68 (m, 5H), 1.50 (s, 9H), 1.20 – 0.84 (m, 6H). **<sup>13</sup>C-NMR** (100 MHz, CDCl<sub>3</sub>) δ/ppm: 162.1, 158.3, 157.2, 150.7, 109.3, 84.0, 70.7, 53.3, 52.2, 41.2, 30.0, 29.8, 28.1, 26.3, 26.2, 26.0, 25.8. **MS-ESI**: *m/z* calculated for [C<sub>18</sub>H<sub>28</sub>NO<sub>7</sub>]<sup>+</sup> = 370.1860; found *m/z* = 370.1855.

### 2-*tert*-Butyl 4,5-dimethyl 3-ethylisoxazole-2,4,5-tricarboxylate (**3qa**)



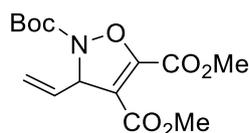
According to the general procedure, hydroxylamine **1q** (0.25 mmol, 43.8 mg, 1.00 equiv.), dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL), **2a** (122 μL, 1.00 mmol, 4.00 equiv.) and TEMPO (78.8 mg, 0.50 mmol, 2.00 equiv.) were reacted. The crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt [(%AcOEt): 1% (100 mL), 5% (100 mL), 10% (300 mL)] to give **3qa** as light yellow oil (0.13 mmol, 39.1 mg, 50%). **<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>) δ/ppm: 5.16 (dd, *J* = 6.8, 3.4 Hz, 1H), 3.91 (s, 3H), 3.77 (s, 3H), 1.86 (m, 1H), 1.70 (m, 1H), 1.52 (s, 9H), 0.96 (t, *J* = 7.4 Hz, 3H). **<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>) δ/ppm: 161.8, 158.20, 156.5, 150.6, 118.7, 110.1, 83.9, 67.2, 53.3, 52.2, 28.1, 27.0, 8.8. **MS-ESI**: *m/z* calculated for [C<sub>14</sub>H<sub>21</sub>NO<sub>7</sub>]<sup>+</sup> = 316.1391; found *m/z* = 316.1387.

### 2-*tert*-Butyl 4,5-dimethyl 3-isobutylisoxazole-2,4,5-tricarboxylate (**3ra**)



According to the general procedure, hydroxylamine **1r** (0.25 mmol, 50.8 mg, 1.00 equiv.), dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL), **2a** (122 μL, 1.00 mmol, 4.00 equiv.) and TEMPO (78.8 mg, 0.50 mmol, 2.00 equiv.) were reacted. The crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt [(%AcOEt): 1% (100 mL), 5% (50 mL), 10% (300 mL)] to give **3ra** as light yellow oil (0.08 mmol, 27.8 mg, 32%). **<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>) δ/ppm: 5.24 – 5.03 (m, 1H), 3.86 (s, 3H), 3.72 (s, 3H), 1.87 – 1.47 (m, 3H), 1.46 (s, 9H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H). **<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>) δ/ppm: 160.7, 157.2, 156.0, 149.8, 110.7, 83.0, 63.8, 52.3, 51.1, 42.3, 27.0, 23.5, 22.5, 20.3. **MS-ESI**: *m/z* calculated for [C<sub>16</sub>H<sub>25</sub>NO<sub>7</sub>Na]<sup>+</sup> = 366.1523; found *m/z* = 366.1527

### 2-*tert*-Butyl 4,5-dimethyl 3-vinylisoxazole-2,4,5-tricarboxylate (**3sa**)



According to the general procedure, hydroxylamine **1s** (0.25 mmol, 43.3 mg, 1.00 equiv.), dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL), **2a** (122 μL, 1.00 mmol, 4.00 equiv.) and TEMPO (78.8 mg, 0.50 mmol, 2.00 equiv.) were reacted. The crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt [(%AcOEt): 1% (100 mL), 5% (100 mL), 10% (300 mL)] to give **3sa** as light yellow oil (0.13 mmol, 39.1 mg, 50%). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ/ppm: 6.00 – 5.84 (m, 1H), 5.63 (d, *J* = 6.1 Hz, 1H), 5.43 (d, *J* = 17.0 Hz, 1H), 5.27 (d, *J* = 10.2 Hz, 1H), 3.92 (s, 3H), 3.77 (s, 3H), 1.52 (s, 9H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ/ppm: 161.5, 158.0, 155.7, 150.2, 133.8, 118.2, 109.8, 84.3, 67.31, 53.5, 52.2, 28.1. MS-ESI: *m/z* calculated for [C<sub>14</sub>H<sub>20</sub>NO<sub>7</sub>]<sup>+</sup> = 314.1234; found *m/z* = 314.1234.

#### *General Procedure for the Synthesis of the Hydroxylamine (1)*

##### General Experimental Procedure for the Synthesis of Benzyl Hydroxylamine (**A**):

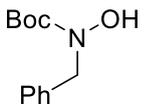
[2] The corresponding N-benzylhydroxylamine (25.04 mmol, 1.00 equiv.) was dissolved in THF-H<sub>2</sub>O (1:1 mixture, 20 mL, 1.25 M) and cooled to 0 °C. Then, K<sub>2</sub>CO<sub>3</sub> (0.50 equiv.) was slowly added, the mixture was strongly stirred and a solution (Boc)<sub>2</sub>O (1.10 equiv.) in THF (60 mL, 0.5 M) was added dropwise during 2 h. The reaction mixture was allowed to reach r.t. and was further stirred for 12 h. The crude mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (150 mL), washed with water (3 x 100 mL) and brine (250 mL). The organic layer was dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The obtained crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt mixtures.

##### General Experimental Procedure for the Synthesis of Alkyl Hydroxylamine (**B**):

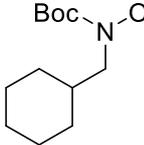
In round bottom flask, alkylaldehyd (10.00 mmol, 2.00 equiv.), *tert*-butyl N-hydroxycarbamate (5.00 mmol, 0.666 g, 1.00 equiv.), formic acid (15.00 mmol, 0.690 g, 0.566 mL, 3.00 equiv.) and a 1:2 methanol/water mixture (30 mL) were added. The obtain solution was stirred for 15 minute at room temperature, then sodium cyanoborohydride (30 mmol, 1.885 g, 6 equiv.) was added. The obtain suspension was stirred overnight still at room temperature. The crude was diluted with an aq. sat. solution of NaHCO<sub>3</sub>, and the obtain water solution was washed 3 times with ethyl acetate. The organic layers were collected and dried with MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the obtained crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt mixtures.

*Selected examples:*

***tert*-Butyl hydroxy(phenyl)carbamate (**1a**)<sup>[2]</sup>**

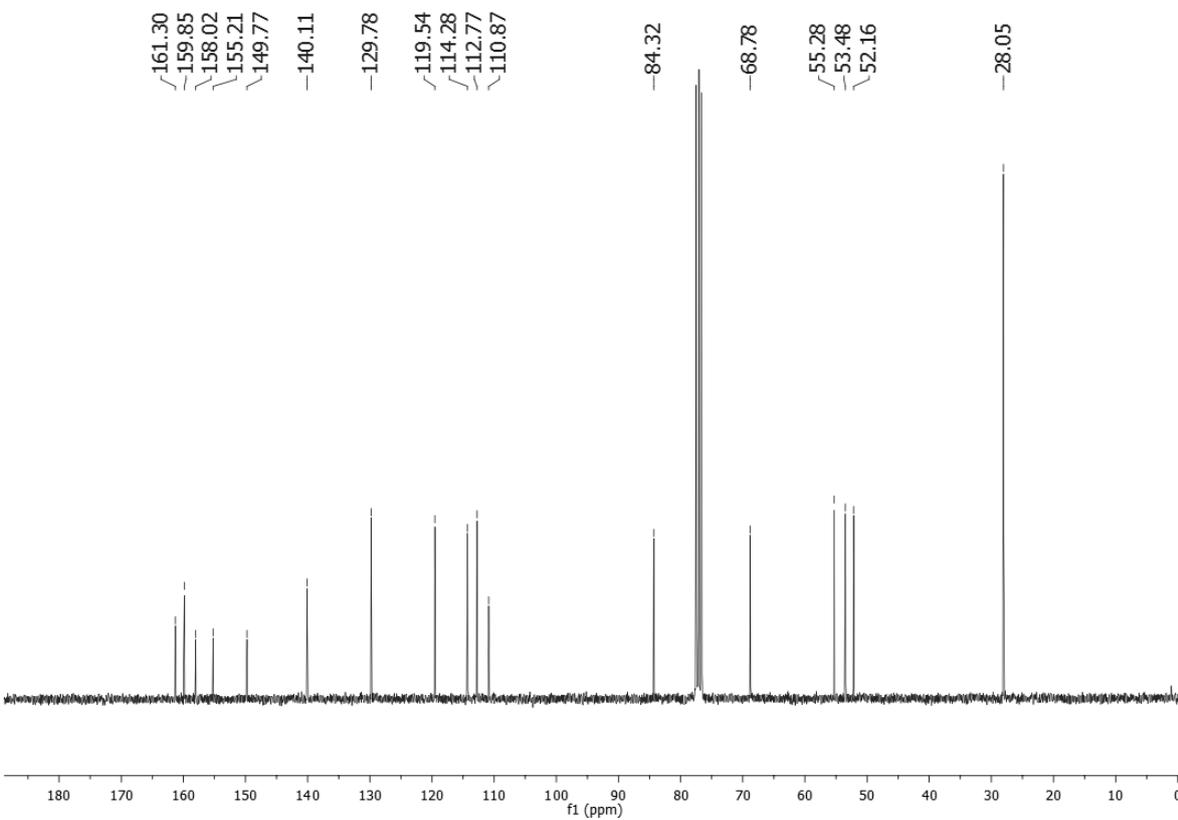
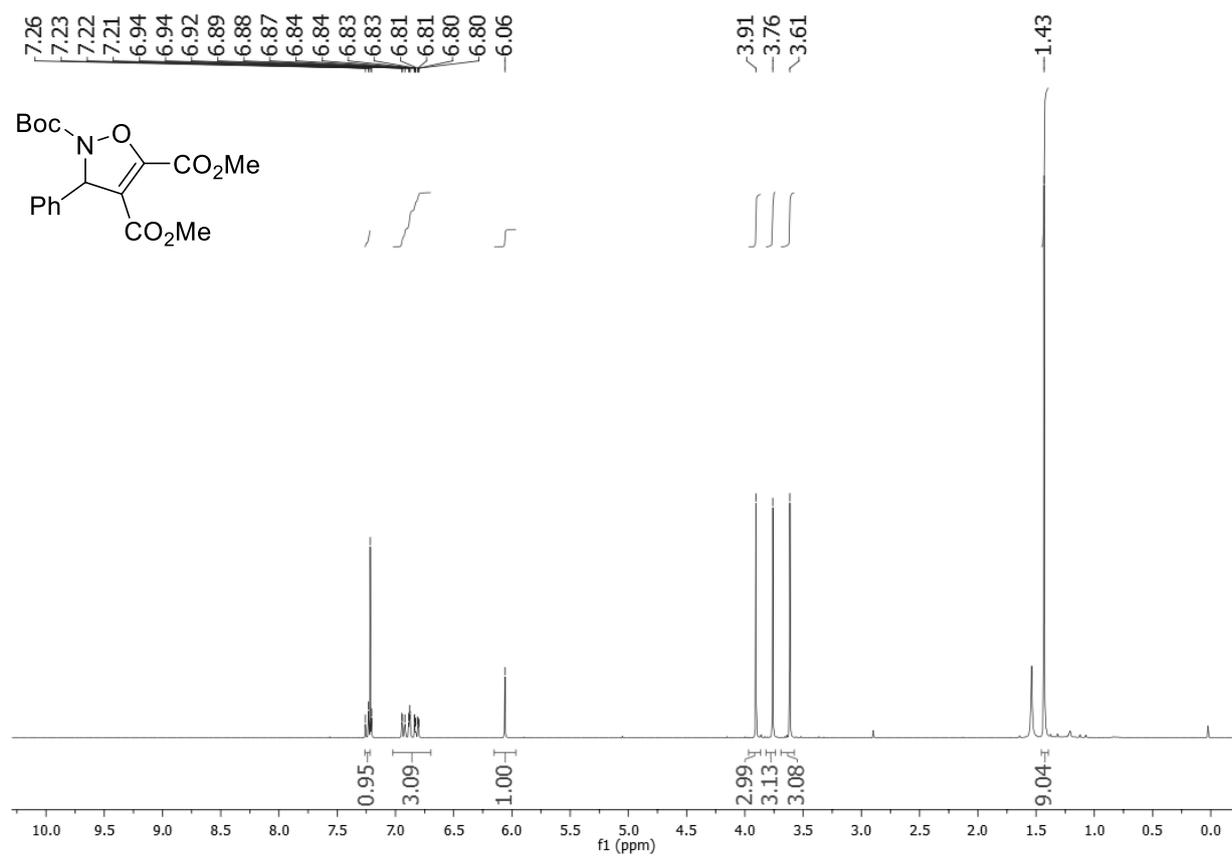
 According to the general procedure **A** for hydroxylamine, N-benzylhydroxylamine (25.04 mmol, 4.00 g, 1.00 equiv.), K<sub>2</sub>CO<sub>3</sub> (12.50 mmol, 1.73 g, 0.50 equiv.) and (Boc)<sub>2</sub>O (27.50 mmol, 6.00 g, 1.10 equiv.) were reacted. The obtained crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt [%AcOEt: 0% (500 mL); 2.5% (800 mL); 5% (400 mL); 10% (400 mL); 20% (800 mL); 40% (400 mL)] to give **1a** as a white solid (15.25 mmol, 3.43 g, 61%). **<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>) δ/ppm: 7.37 – 7.24 (m, 5H), 4.65 (s, 2H), 1.45 (s, 9H). **<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>) δ/ppm: 157.0, 136.7, 128.5, 128.1, 127.5, 82.10, 54.4, 28.3. **MS-ESI:** m/z calculated for [C<sub>12</sub>H<sub>17</sub>NO<sub>3</sub>Na]<sup>+</sup> = 246.1101; found m/z = 246.1107.

***tert*-Butyl hydroxyl(cyclohexyl)carbamate (**1p**)**

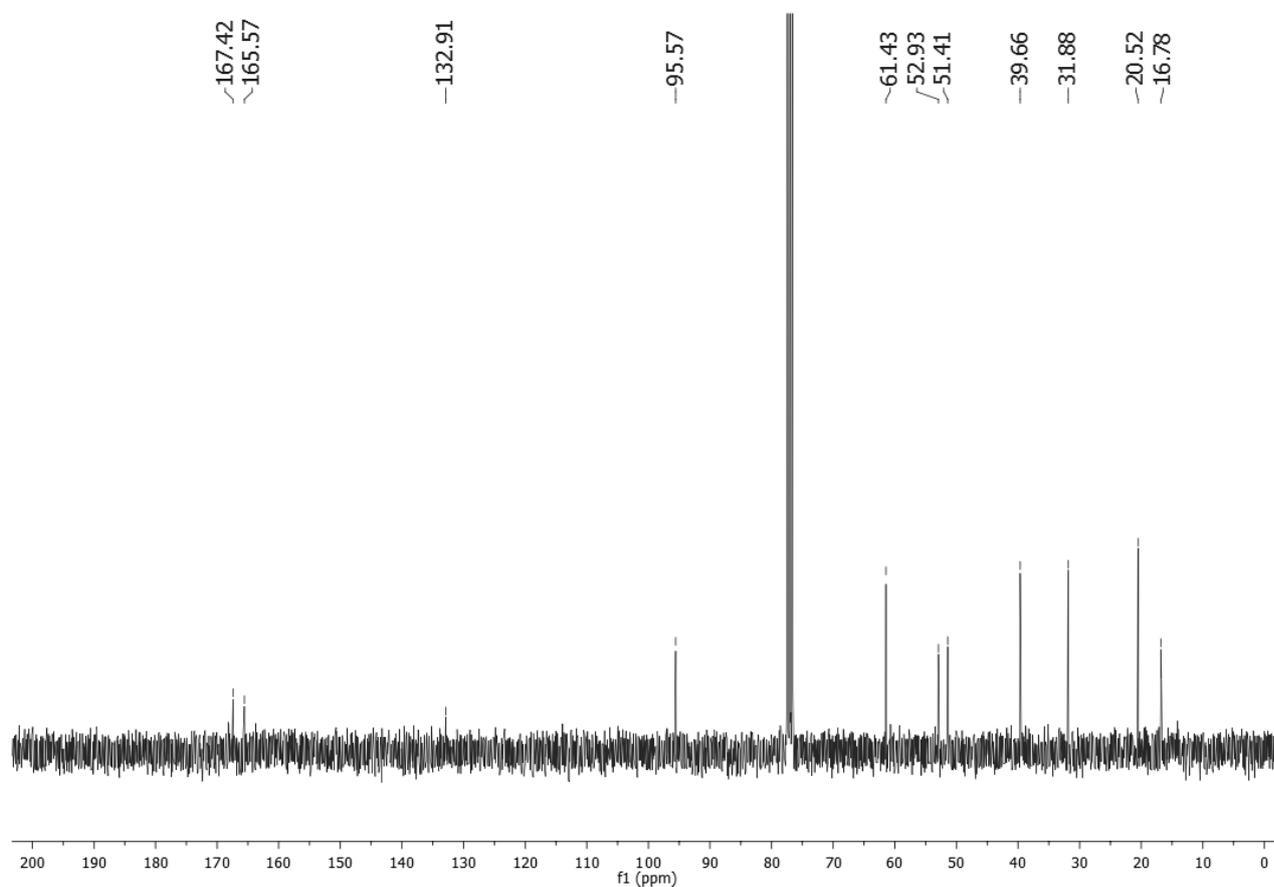
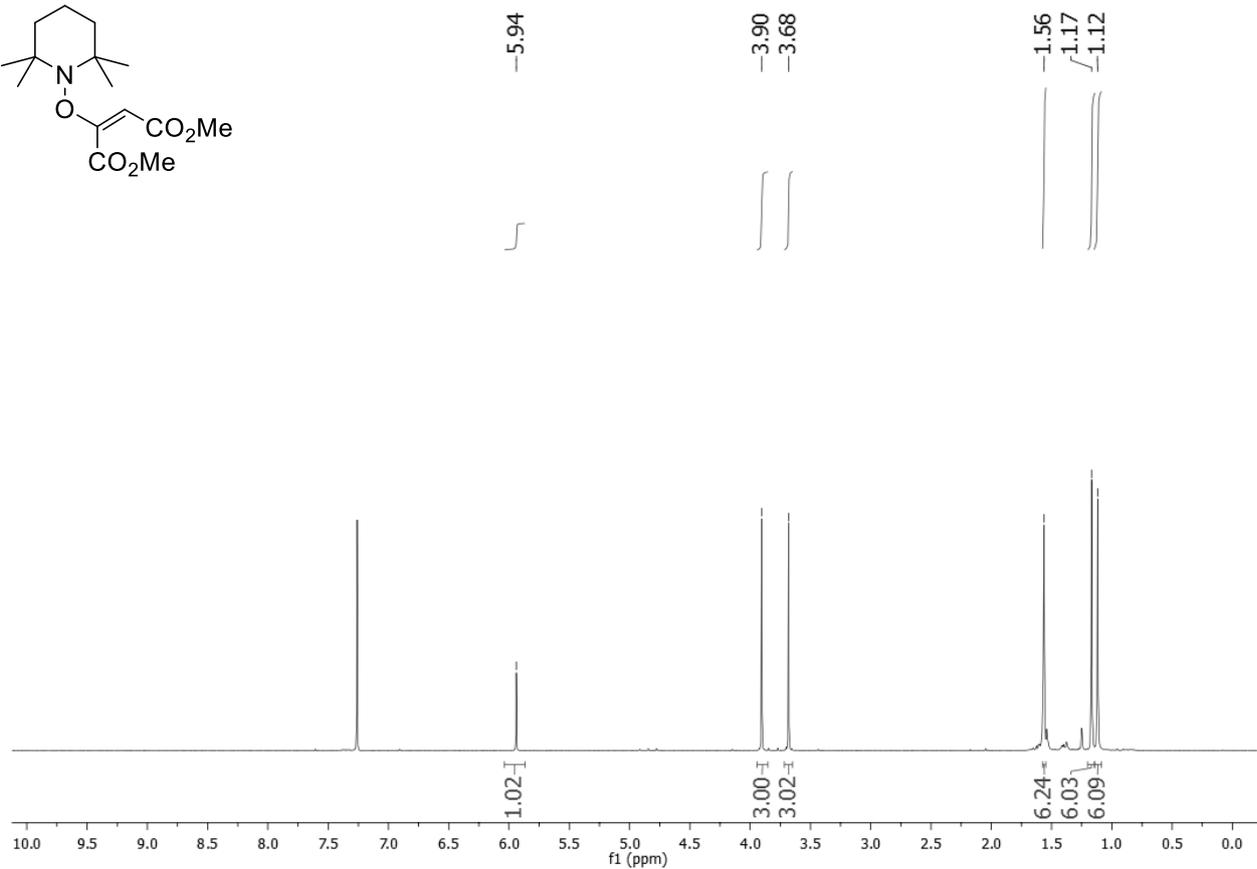
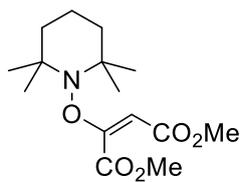
 According to the general procedure **B** for hydroxylamine, cyclohexanecarbaldehyde (10.00 mmol, 1.122 g, 1.21 mL, 2.00 equiv.) was reacted. The crude product was purified by flash column chromatography on silica gel eluting with pentane/AcOEt (20% AcOEt) to give **1p** as colorless liquid (1.18 mmol, 0.424 g, 37%). **<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>) δ/ppm: 3.32 (d, J = 6.9 Hz, 2H), 1.81 – 1.60 (m, 5H), 1.48 (s, 9H), 1.33 – 1.11 (m, 4H), 1.00 – 0.85 (m, 2H). **<sup>13</sup>C-NMR** (100 MHz, CDCl<sub>3</sub>) δ/ppm: 156.8, 81.7, 55.9, 35.8, 30.7, 28.4, 26.5, 25.9. **MS-ESI:** m/z calculated for [C<sub>12</sub>H<sub>24</sub>NO<sub>3</sub>]<sup>+</sup> = 230.1751; found m/z = 230.1751.

Selected NMR spectra

2-*tert*-Butyl 4,5-Dimethyl 3-phenylisoxazole-2,4,5-tricarboxylate (3aa)



**Dimethyl 2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)maleate (4aa)**



### 2.3.2 Two steps one-pot azidation/CuAAC reaction studies.

#### *General Information and Materials:*

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded in  $\text{CDCl}_3$ , (reference signal:  $^1\text{H} = 7.26$  ppm,  $^{13}\text{C} = 77.16$  ppm,  $\text{CDCl}_3$ ) on *Brucker Avance* 300 MHz spectrometer. Chemical shifts ( $\delta$ ) are given in ppm and spin-spin coupling constants ( $J$ ) are given in Hz. Analytical thin layer chromatography was performed using silica gel 60 F<sub>254</sub> and a solution of  $\text{KMnO}_4$  or a Iodine camera served as staining agent. Column chromatography was performed on silica gel 60 (0.040-0.063 mm). Exact masses (**HRMS (ES)**) were recorded on an *Agilent Q-TOF 6540 UHD* spectrometer (samples in  $\text{CH}_3\text{OH}$  as solvent). MeCN was distilled over  $\text{CaH}_2$ . Other solvents and commercially available reagents were used without further purification.

#### *General procedure for the formation of the azide (A):*

In a screw-cap schlenk tube, the corresponding target **1** (0.4 mmol, 1.00 equiv.), CuBr (10 mol%) were dissolved in distilled MeCN (1.00 mL).  $\text{TMSN}_3$  (1.2 equiv.) and *t*BuOOH 70% in water or 5.5M in decane (1.2 equiv.) were added and the reaction mixture was stirred at 50 °C for 2 h. DCM was added in the crude mixture and the obtained organic phase was washed 2 times with water and 1 with brine. Then the organic phase was collected, dried under  $\text{MgSO}_4$ , the solvent removed under reduced pressure to give the corresponding crude azide **2** as a colorless oil.

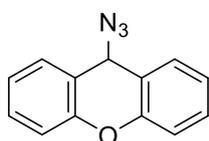
#### *General procedure for the 2-step reaction (B):*

In a screw-cap schlenk tube, the corresponding target **1** (0.4 mmol, 1.00 equiv.), CuBr (10 mol%) were dissolved in distilled MeCN (1.00 mL).  $\text{TMSN}_3$  (1.2 equiv.) and *t*BuOOH 70% in water or 5.5M in decane (1.2 equiv.) were added and the reaction mixture was stirred at 50 °C for 2 h. DCM was added in the crude mixture and the obtained organic phase was washed 2 times with water and 1 with brine. Then the organic phase was collected, dried under  $\text{MgSO}_4$ , the solvent removed under reduced pressure to give the corresponding crude azide **2** as a colorless oil. Then, without further purification, **2**, sodium ascorbate (0.4 equiv.) and the terminal alkyne **3** (1.2 equiv.) were dissolved in a mixture 1:1 water/*t*BuOH (1.2 mL) and the reaction mixture was stirred at room temperature overnight. DCM and a  $\text{NH}_3$  10% w/w in water solution and stirred for a couple of minutes, then the organic phase was separated and washed 2 times with a  $\text{NH}_3$  10% w/w in water solution, 1 time with water and 1 with brine (The crude mixture was washed 2 times with water and 1 with brine. The organic phase was collected, dried under  $\text{MgSO}_4$ , and the solvent was removed under reduced pressure. The obtained crude product, if not enough pure, was purified by re-crystallization or flash column chromatography on silica gel eluting with pentane/AcOEt or DCM/AcOEt.

### General procedure for the 2-step 1-pot reaction (C):

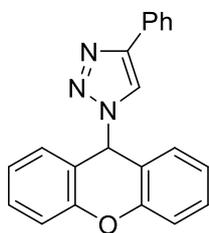
In a screw-cap schlenk tube, the corresponding target **1** (0.4 mmol, 1.00 equiv.), CuBr (10 mol%) were dissolved in distilled MeCN (1.00 mL). TMSN<sub>3</sub> (1.2 equiv.) and *t*BuOOH 70% in water or 5.5M in decane (1.2 equiv.) were added and the reaction mixture was stirred at 50 °C for 2 h. Then the reaction mixture was let cool down and *tert*-butanol (1.00 mL), sodium ascorbate (0.4 equiv.) and the terminal alkyne **3** (1.2 equiv.) and the new reaction mixture was stirred at room temperature overnight. DCM and a NH<sub>3</sub> 10% w/w in water solution and stirred for a couple of minutes, then the organic phase was separated and washed 2 times with a NH<sub>3</sub> 10% w/w in water solution, 1 time with water and 1 with brine (The crude mixture was washed 2 times with water and 1 with brine. The organic phase was collected, dried under MgSO<sub>4</sub>, and the solvent was removed under reduced pressure. The obtained crude product, if not enough pure, was purified by re-crystallization or flash column chromatography on silica gel eluting with pentane/AcOEt or DCM/AcOEt.

#### 9-Azido-xanthene (**2a**)



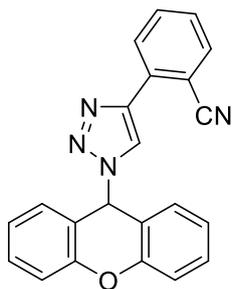
According to the general procedure (A), xanthene (**1a**) (72.9 mg, 0.40 mmol, 1.00 equiv.), CuBr (5.7 mg, 0.04 mmol, 10 mol%), TMSN<sub>3</sub> (63.1 μL, 0.48 mmol, 1.20 equiv.) and *t*BuOOH 70% in water (66.4 μL, 0.48 mmol, 1.20 equiv.) were reacted to give **2a** as a colorless oil without further purification. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ/ppm δ 7.52 – 7.47 (m, 2H), 7.43 – 7.36 (m, 2H), 7.24 – 7.17 (m, 4H), 5.58 (s, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ/ppm: 151.7, 130.3, 129.7, 123.9, 118.1, 117.2, 57.2.

#### 4-Phenyl-1-(xanthen-9-yl)-1H-1,2,3-triazole (**4a**)



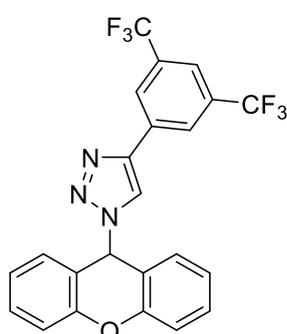
According to the general procedure (C), xanthene (**1a**) (72.9 mg, 0.40 mmol, 1.00 equiv.), CuBr (5.7 mg, 0.04 mmol, 10 mol%), TMSN<sub>3</sub> (63.1 μL, 0.48 mmol, 1.20 equiv.), *t*BuOOH 70% in water (66.4 μL, 0.48 mmol, 1.20 equiv.), sodium ascorbate (31.7 mg, 0.16 mmol, 0.4 equiv.) and phenylacetylene (**3a**) (52.7 μL, 0.48 mmol, 1.2 equiv.) were reacted. The crude product was purified by flash column chromatography on silica gel eluting with DCM/AcOEt [(%AcOEt): 0% (100 mL), 5% (300 mL)] to give **4a** as white solid (0.25 mmol, 80.7 mg, 62%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ/ppm: 7.73 – 7.69 (m, 2H), 7.44 – 7.31 (m, 8H), 7.29 – 7.27 (m, 2H), 7.16 – 7.10 (m, 2H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ/ppm: 151.0, 148.8, 130.8, 130.5, 129.7, 128.9, 128.3, 125.8, 124.9, 118.0, 117.7, 117.4, 56.3. MS-ESI: m/z calculated for [C<sub>21</sub>H<sub>15</sub>N<sub>3</sub>ONa]<sup>+</sup> = 348.1107; found m/z = 348.1107.

#### 4-(2-Cyanophenyl)-1-(xanthen-9-yl)-1H-1,2,3-triazole (4b)



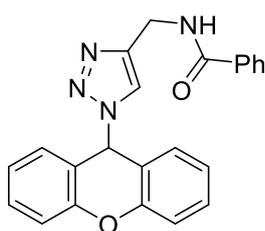
According to the general procedure (C), xanthene (**1a**) (72.9 mg, 0.40 mmol, 1.00 equiv.), CuBr (5.7 mg, 0.04 mmol, 10 mol%), TMSN<sub>3</sub> (63.1 μL, 0.48 mmol, 1.20 equiv.), *t*BuOOH 70% in water (66.4 μL, 0.48 mmol, 1.20 equiv.) sodium ascorbate (31.7 mg, 0.16 mmol, 0.4 equiv.) and (2-cyanophenyl)acetylene (**3b**) (61.0 mg, 0.48 mmol, 1.2 equiv.) were reacted. The crude product was purified by flash column chromatography on silica gel eluting with DCM/AcOEt [(%AcOEt): 0% (100 mL), 10% (100 mL), 20% (150 mL)] to give **4b** as white solid (0.21 mmol, 74.3 mg, 57%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ/ppm: 8.19 (s, 1H), 7.91 – 7.88 (m, 1H), 7.74 – 7.71 (m, 2H), 7.66 – 7.58 (m, 2H), 7.41 – 7.36 (m, 4H), 7.30 – 7.27 (m, 3H), 7.17 (s, 1H), 7.14 – 7.11 (m, 2H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ/ppm: 151.5, 144.5, 134.1, 133.7, 133.6, 133.1, 130.5, 129.4, 128.8, 128.6, 123.7, 118.7, 117.7, 117.4, 109.8, 61.1. MS-ESI: m/z calculated for [C<sub>22</sub>H<sub>14</sub>N<sub>4</sub>ONa]<sup>+</sup> = 373.1060; found m/z = 373.1063.

#### 4-(3,5-Bis(trifluoromethyl)phenyl)-1-(xanthen-9-yl)-1H-1,2,3-triazole (4c)



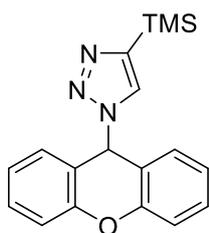
According to the general procedure (C), xanthene (**1a**) (72.9 mg, 0.40 mmol, 1.00 equiv.), CuBr (5.7 mg, 0.04 mmol, 10 mol%), TMSN<sub>3</sub> (63.1 μL, 0.48 mmol, 1.20 equiv.), *t*BuOOH 70% in water (66.4 μL, 0.48 mmol, 1.20 equiv.) sodium ascorbate (31.7 mg, 0.16 mmol, 0.4 equiv.) and (3,5-bis(trifluoromethyl)phenyl)acetylene (**3c**) (114.3 mg, 0.48 mmol, 1.2 equiv.) were reacted. The crude product was purified by flash column chromatography on silica gel eluting with hexane/AcOEt [(%AcOEt): 0% (100 mL), 10% (100 mL), 20% (150 mL)] to give **4c** as white solid (0.21 mmol, 97.8 mg, 53%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ/ppm: 8.21 – 8.13 (m, 2H), 7.90 (s, 1H), 7.82 (s, 1H), 7.43 – 7.38 (m, 2H), 7.37 – 7.33 (m, 2H), 7.31 – 7.28 (m, 2H), 7.15 (s, 1H), 7.14 – 7.09 (m, 2H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ/ppm: 151.4, 145.2, 138.5, 134.9, 133.7, 132.6, 132.5, 132.3, 132.1, 131.0, 130.5, 129.5, 129.2, 126.8, 126.1, 126.0, 126.0, 125.9, 124.4, 124.0, 123.7, 122.0, 121.9, 121.9, 121.8, 119.2, 119.1, 118.1, 117.5, 61.2. MS-ESI: m/z calculated for [C<sub>23</sub>H<sub>13</sub>F<sub>6</sub>N<sub>3</sub>ONa]<sup>+</sup> = 484.0855; found m/z = 484.0858.

#### 4-(Benzamidomethyl)-1-(xanthen-9-yl)-1H-1,2,3-triazole (4f)



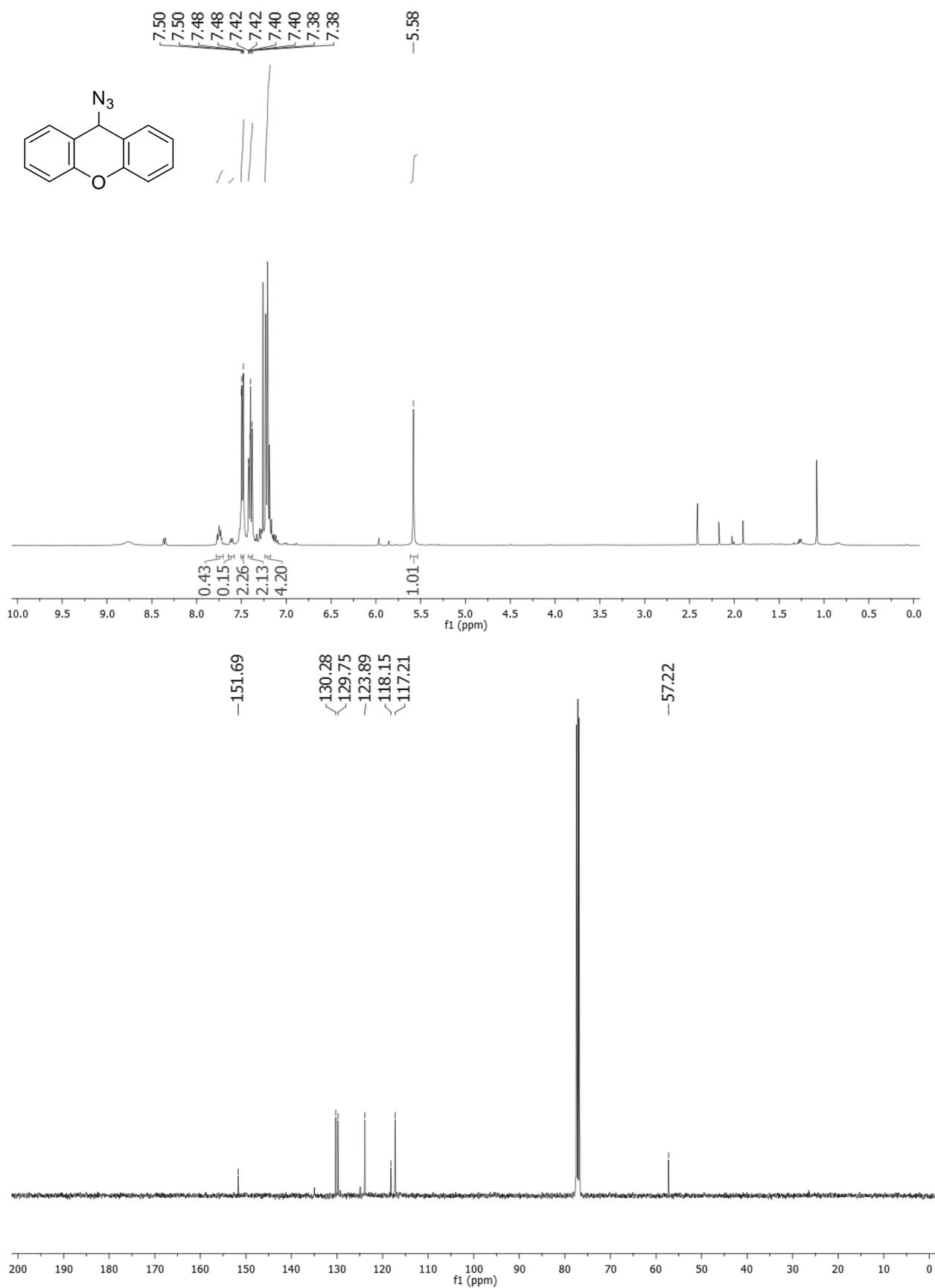
According to the general procedure (C), xanthene (**1a**) (72.9 mg, 0.40 mmol, 1.00 equiv.), CuBr (5.7 mg, 0.04 mmol, 10 mol%), TMSN<sub>3</sub> (63.1 μL, 0.48 mmol, 1.20 equiv.), *t*BuOOH 70% in water (66.4 μL, 0.48 mmol, 1.20 equiv.) sodium ascorbate (31.7 mg, 0.16 mmol, 0.4 equiv.) and N-(prop-2-yn-1-yl)benzamide (**3f**) (76.4 mg, 0.48 mmol, 1.2 equiv.) were reacted. The crude product was washed with small portion of cold AcOEt and hexane to give **4f** as white solid (0.18 mmol, 67.3 mg, 44%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ/ppm: 7.75 – 7.70 (m, 2H), 7.56 (s, 1H), 7.52 – 7.46 (m, 1H), 7.44 – 7.34 (m, 5H), 7.31 – 7.23 (m, 3H), 7.12 – 7.06 (m, 2H), 7.04 (s, 1H), 6.52 (bs, 1H), 4.63 (d, 2H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ/ppm: 167.5, 151.5, 145.7, 134.2, 133.7, 131.8, 130.3, 129.3, 128.7, 127.1, 123.7, 117.9, 117.4, 60.6, 35.5. MS-ESI: m/z calculated for [C<sub>23</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>Na]<sup>+</sup> = 405.1322; found m/z = 405.1324.

#### 4-(Benzamidomethyl)-1-(xanthen-9-yl)-1H-1,2,3-triazole (4i)

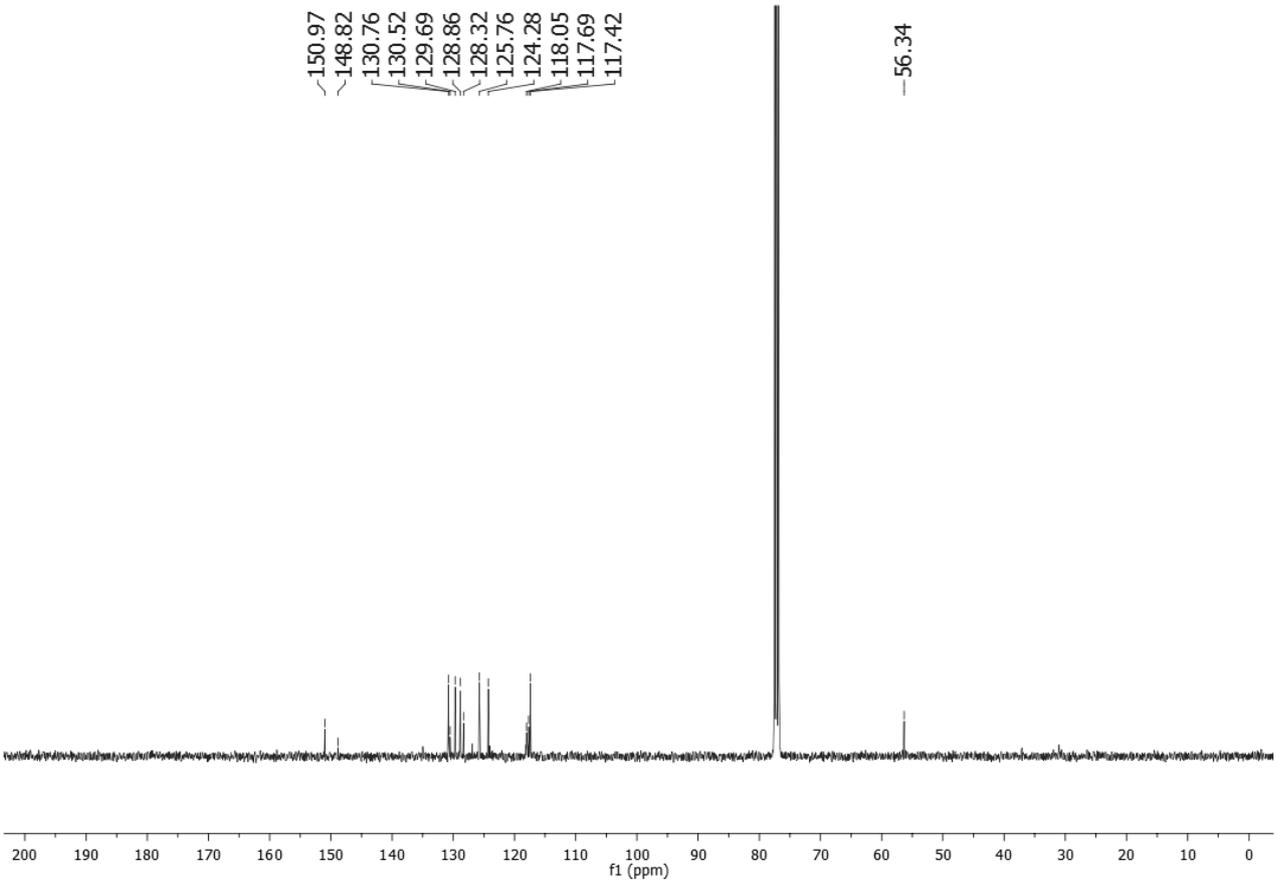
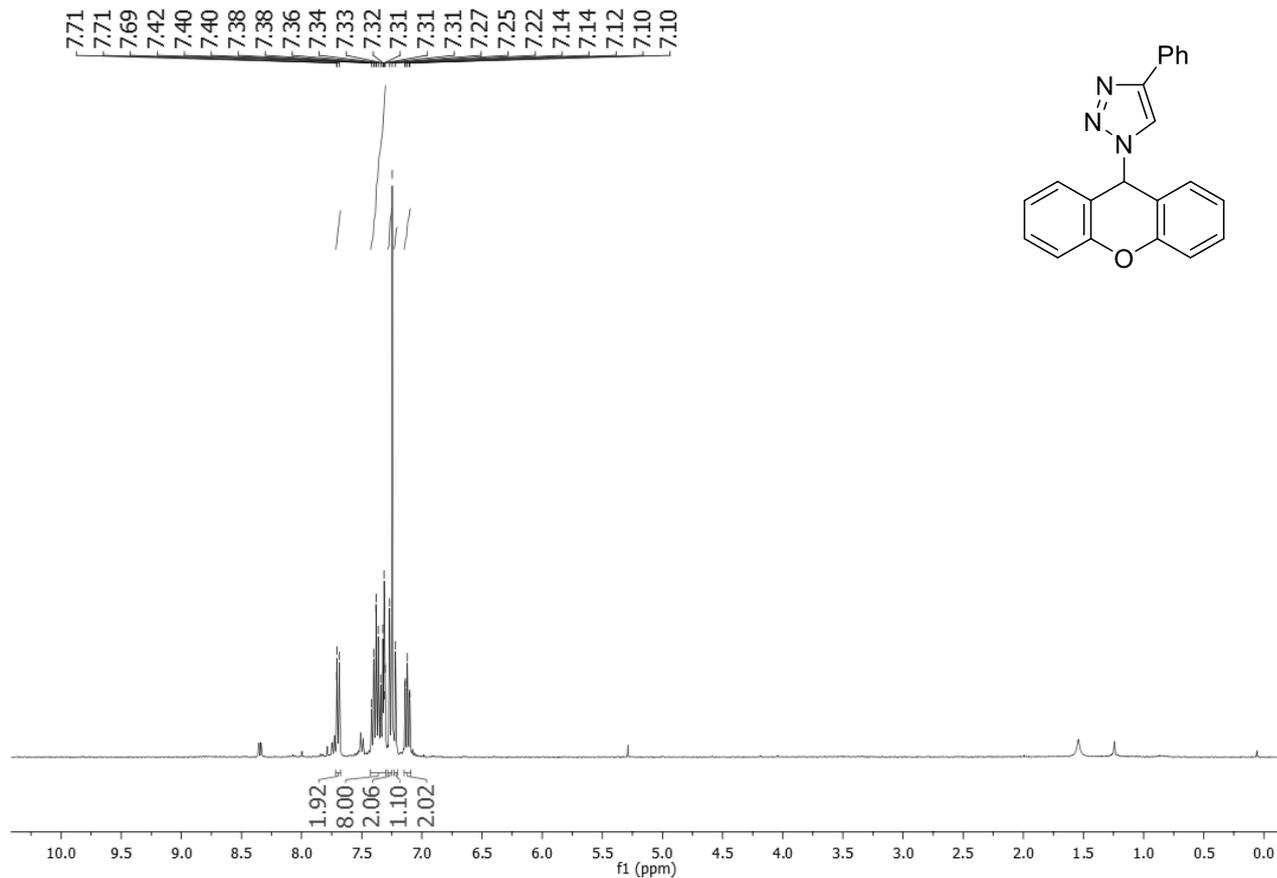


According to the general procedure (C), xanthene (**1a**) (72.9 mg, 0.40 mmol, 1.00 equiv.), CuBr (5.7 mg, 0.04 mmol, 10 mol%), TMSN<sub>3</sub> (63.1 μL, 0.48 mmol, 1.20 equiv.), *t*BuOOH 70% in water (66.4 μL, 0.48 mmol, 1.20 equiv.) sodium ascorbate (31.7 mg, 0.16 mmol, 0.4 equiv.) and ethynyltrimethylsilane (**3i**) (47.1 mg, 0.48 mmol, 1.2 equiv.) were reacted. The crude product was purified by flash column chromatography on silica gel eluting with hexane/AcOEt [(%AcOEt): 0% (100 mL), 10% (100 mL), 20% (200 mL)] to give **4i** as colorless oil (0.09 mmol, 28.3 mg, 22%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ/ppm: 7.54 (s, 1H), 7.40 – 7.31 (m, 3H), 7.25 – 7.21 (m, 3H), 7.15 (s, 1H), 7.08 – 7.04 (m, 2H), 0.29 (s, 9H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ/ppm: 151.3, 146.5, 141.27, 134.9, 130.0, 129.1, 123.5, 117.3, 60.0, -1.0. MS-ESI: m/z calculated for [C<sub>18</sub>H<sub>19</sub>N<sub>3</sub>OSiNa]<sup>+</sup> = 344.1195; found m/z = 344.1193.

*Selected NMR spectra*  
**9-Azido-xanthene (2a)**



# N-Phenyl-1-(xanthen-9-yl)-1H-1,2,3-triazole (4a)



# 3

## C-H oxidative functionalization/expansion ring tandem reactions

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### Chapter 3.1

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### Chapter 3.2

[1] Reproduced with the permission from: A. Gini, J. Bamberger, J. Luis-Barrera, M. Zurro, R. Mas-Ballesté, J. Alemán and O. García Mancheño, *Adv. Synt. Catal.*, 2016, **358**, 4049. Copyright 2015 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim; schemes, figures and text may differ from the published version.

[2] Contents of table 2, entries **3e**, **3g**, **3i**, **3j**, **3k**, **3n**, **3o** and **3p** were performed by J. Bamberger and J. Luis-Barrera.

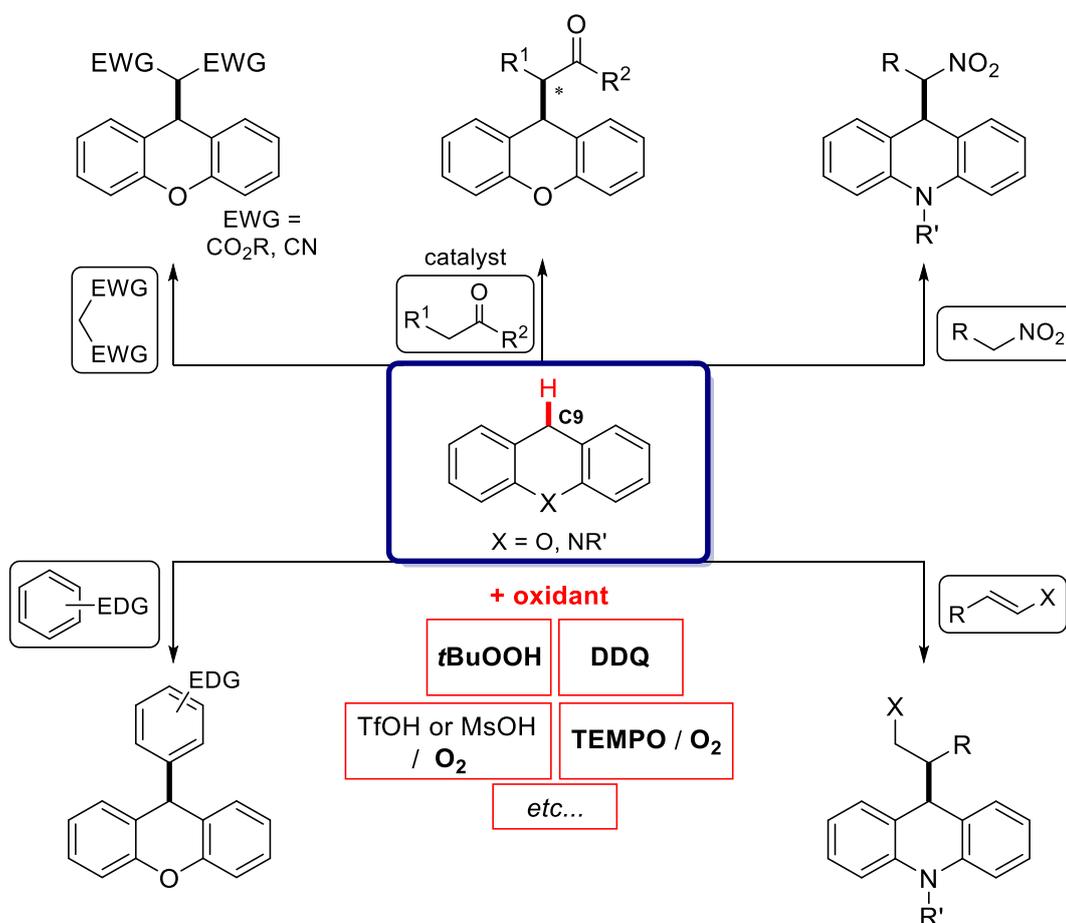
[3] Asymmetric synthesis of Lorcaserin (Scheme 4) were performed by M. Zurro.

[4] Contents of the chapter 3.2.5 “Reactivity and Mechanistic Studies” were performed by J. Luis-Barrera and Ruben Mas-Ballesté.

### 3.1 The idea beyond the expansion ring

#### 3.1.1 C-based expansion ring reaction of xanthene-like structures: An overview

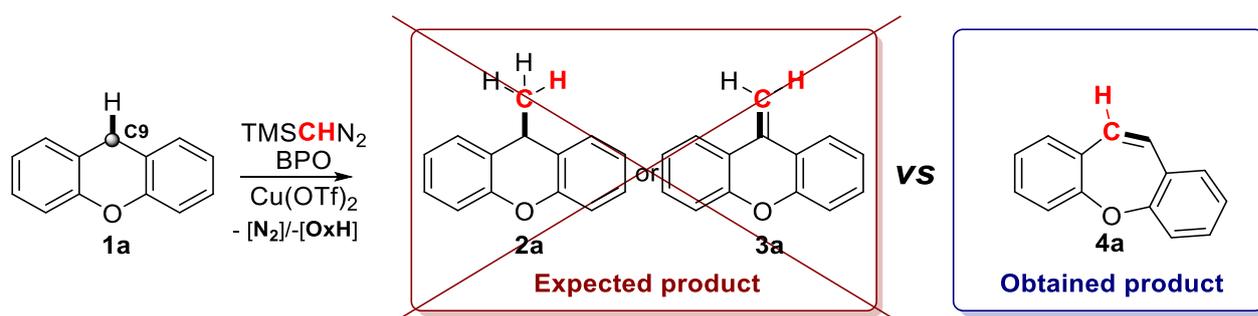
As an introduction for the last results we achieved on oxidative Csp<sup>3</sup>-H bond functionalization/expansion ring tandem reaction, it is worth to mention and shortly discuss our previously publication on expansion ring of xanthene-like structures.<sup>1</sup> As it was reported in the main introduction, the C-H bond-dissociation energy (DCE) on C-9 of xanthene and acridane is low, around 75 Kcal/mol, resulting one of the weakest Csp<sup>3</sup>-H bond energies among the common substrates enrolled in oxidative C-H bond functionalization. Despite the easy C-H bond cleavage in those substrates, the scope in the following coupling reaction is still considerably limited by the nucleophile nature (Scheme 1).<sup>2</sup>



**Scheme 1.** Oxidative C-H bond functionalization of xanthenes and acridanes.

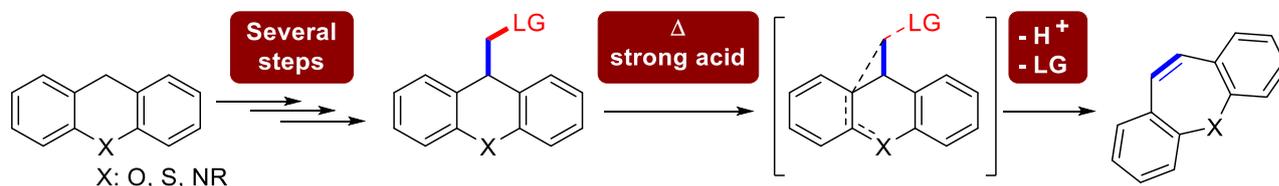
Enolizable moieties such as carbonyls and nitroalkanes are the most common classes of nucleophiles employed in the oxidative C-H functionalization of xanthenes and acridanes. However, when different transformations are desired, in most of the cases it is necessary to enroll organometallic compounds such as a Grignard or an organoboron reagent.<sup>3</sup> Thus, the potential incompatibility among classical nucleophilic alkylating agents and other involved reagents in a C-H functionalization approach may lead to twisted multi-step processes when a C9-alkyl substituted compound is required.<sup>4</sup> The Garcia's group decided to tackle this problem by investigating for the first time the less explosive and toxic version of diazomethane, trimethylsilyl-diazomethane (TMSCHN<sub>2</sub>), as methylating or methylenating reagent in the C-H functionalization of xanthenes.<sup>5,6</sup>

TMSCHN<sub>2</sub> presents various attractive advantages respect to the less benign and “explosive” diazomethane while conserving the carbene reactivity: i) a lower reactivity than diazomethane,<sup>7</sup> ii) a higher selectivity respect to the classical methylating agents,<sup>8</sup> and iii) it presents a second good leaving group, TMS, which can be eliminated or promote further transformations. Having in mind the development of a new methylation or methenylation methodology, a copper catalyst was initially explored to promote the formation of a reactive copper-carbene.<sup>9</sup> In fact, during the preliminary reactivity screening, the product resulted a completely different species, and even more interesting compare to what was searched in first instance. The xanthene underwent an expansion ring process, which gave a highly valuable dibenzoxepine product **4a** (Scheme 2). The structure of **4a** could be confirmed by X-ray.



**Scheme 2.** Our initial oxidative C-H methylation/methenylation desire product *vs* the real formed ring-expansion product.

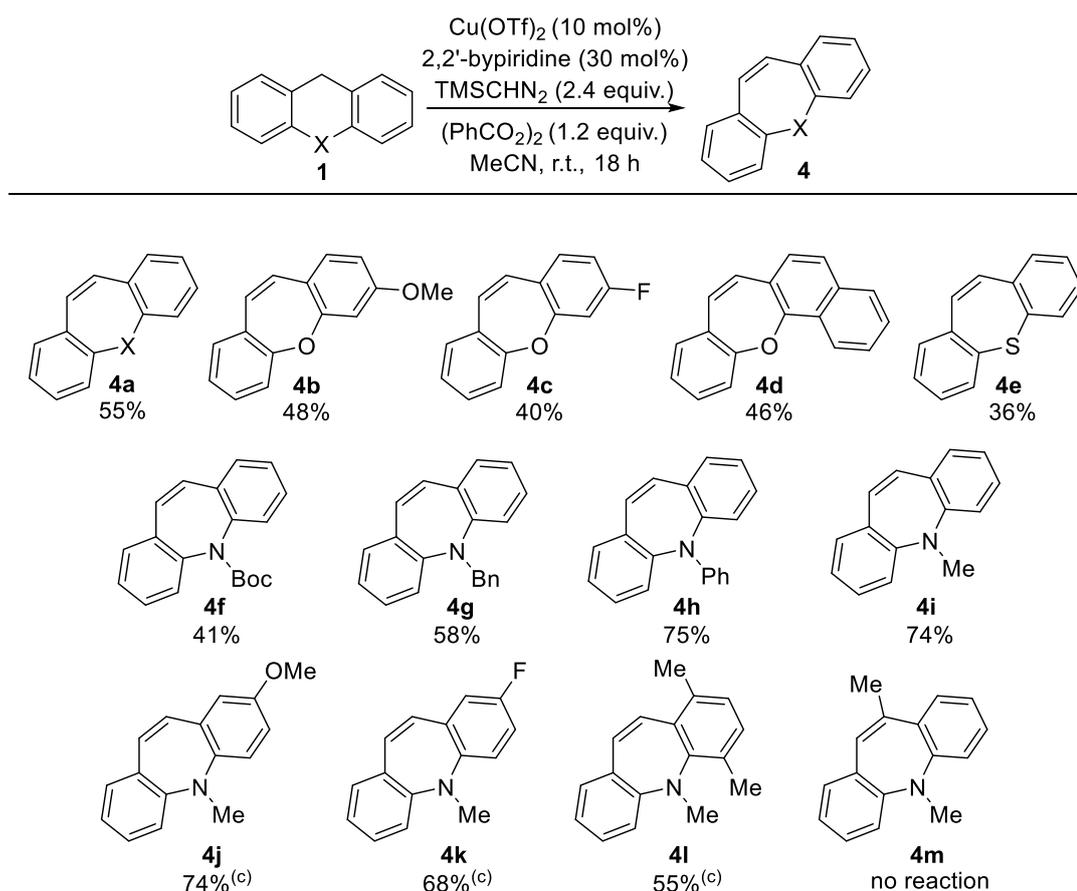
Although this result deviated from the initial targeted transformation, this synthetic approach to form dibenzoxepines that was casually found was really appealing. These molecules are an important class of bioactive compounds,<sup>10</sup> which lack of literature reported easy and fast synthetic methods for their preparation. The classical synthesis of dibenzoxepines and dibenzazepines from xanthenes and acridanes implies multistep processes to functionalize the benzylic position and introduce a CH<sub>2</sub>-LG (LG= leaving group) unit (Scheme 3).<sup>11</sup> Furthermore, harsh heating and acidic conditions are then required to promote the elimination of the incorporated LG and subsequent Wagner–Meerwein type rearrangement to obtain the desire product.<sup>11</sup>



**Scheme 3.** Dibenzoxepine/azepine synthesis by a multi-step approach implying a Wagner–Meerwein type rearrangement.

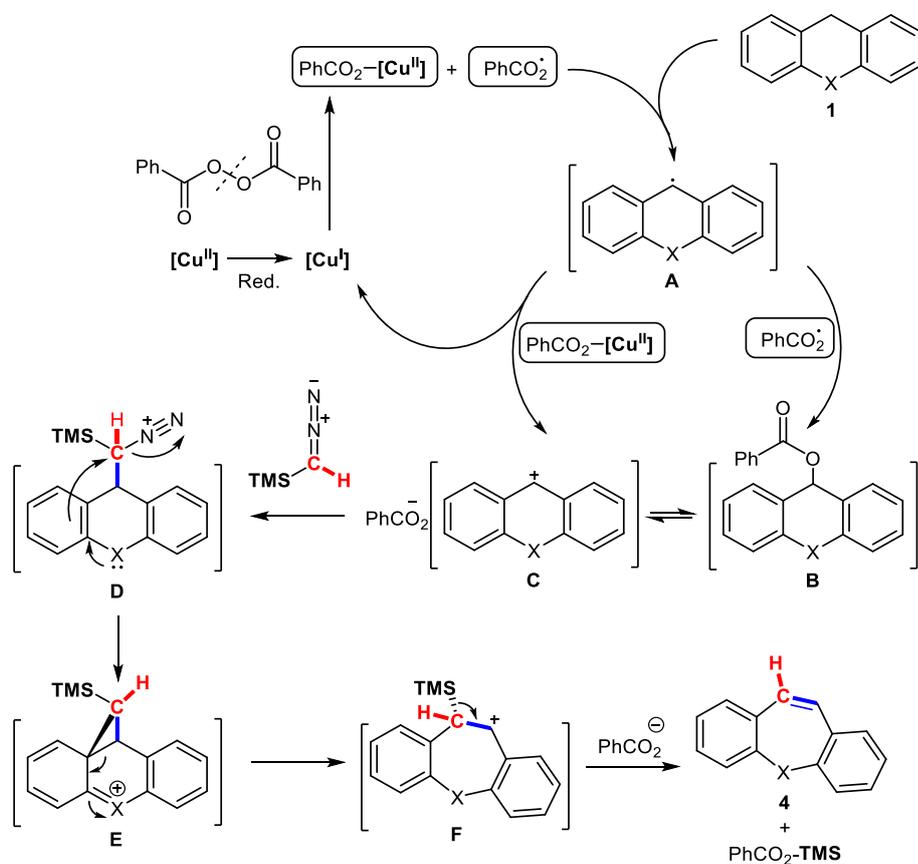
Taking into account the limitation of common procedures for the expansion ring of such O- and N-heterocycle structures, as well as the preliminary but promising outcomes, it was decided to shift the efforts into the development and optimization of this unexpected novel Csp<sup>3</sup>-H oxidative functionalization/expansion ring tandem reaction strategy. In addition, it is interesting to note that such C-H oxidative functionalization/expansion ring tandem reaction are not satisfactorily explored even on other classes of substrates. During the preliminary screening, various oxidants were tested with xanthene (**1a**) and TMSCHN<sub>2</sub> in the presence of Cu(II) triflate, which it could be involved into a reductive process mediated by the diazo compound to give the corresponding Cu(I) species.<sup>12</sup> As expected, the typical oxidants such as TBHP, TEMPO<sup>+</sup>BF<sub>4</sub><sup>-</sup> and DDQ were inefficient, most probably because they oxidize more readily the TMSCHN<sub>2</sub> than the desire target. Next, benzoyl peroxide (BPO) was tried as non-protic mild, stable organic peroxide, in the presence of Cu(II)triflate (Cu(OTf)<sub>2</sub>) as catalyst to allow the homolytic O-O bond cleavage at room temperature.<sup>13</sup> BPO results strong enough to activate the substrate but, at the same time, mild enough to avoid the complete decomposition of TMSCHN<sub>2</sub>. To improve the performance of the copper catalyst, available, cheap and simple N,N-ligands such as 2,2'-bipyridine were tested. The best result was obtained with 2,2'-bipyridine, leading to **4a** in a good 55% yield (Table 1). This methodology could be extended to different substituted xanthenes and acridanes, as well as the less reactive sulfur-derivative thioxanthene.

**Table 1.** Scope of the reaction.<sup>[a][b]</sup>



[a] Conditions: **1** (0.2 mmol), TMSCHN<sub>2</sub> (0.48 mmol), (PhCO<sub>2</sub>)<sub>2</sub> (0.24 mmol), Cu(OTf)<sub>2</sub> (10 mol%), and bpy (30 mol%) in MeCN (2.0 mL) at r.t. for 18 h under argon atmosphere. [b] Yields are of isolated products. [c] Reaction in the presence of KF (1.1 equiv.).

Xanthenes provided dibenzoxepines in moderate to good yields (40-55%), whereas aryl and alkyl N-substituted acridanes led to dibenzazepines in typically higher yields (58-75%).<sup>14</sup> Interestingly, the N-Boc protected acridane also participated in this reaction, providing with a benzazepine with an easily removable protecting group (**4f**, 41%). Both electron-withdrawing and -donating substituents at the aromatic rings in acridanes were well tolerated, providing **4** in good yields. Conversely, a substitution in the C9 position was not tolerated, leading to no reaction (e.g. **4m** was not observed). An interesting point is the potential competitive elimination between the TMS group and a proton for the final formation of the double bond, which would lead to a mixture of two benzazepines. Accordingly, in some cases the use of 1.1 equivalents of KF provided higher yields on the desired product **4**. The presence of KF might then help in the removal of the TMS, especially for substrates where the elimination of the TMS group is slow. It is important to mention that a critical issue in this transformation is the presence of water. Even traces in the catalyst, wet reagents and/or solvent can hinder the reaction, leading almost exclusively to 9-oxo-compounds in significant amounts. Based on all the experimental observations, a reaction mechanism was postulated (Scheme 4). The exact role of the metal catalyst is still not fully understood, however we have excluded a carbene intermediate since similar results were obtained with different transition metals.<sup>1</sup> Consequently, a first copper(I)-catalyzed reductive homolytic cleavage of the O-O bond of the benzoyl peroxide, giving benzoyl radical and copper(II) benzoate was prepared. Then, benzoyl radical abstracts a hydrogen from the C9 position of **1**, forming the radical intermediate **A**. The copper(II) species will then oxidize the intermediate **A** to generate the carbocation **B** and regenerate the copper(I) catalyst. Besides this copper reduction step, it cannot be excluded that the excess of TMSCHN<sub>2</sub> operates as the main reducing agent, helping the metal species to return to the catalytic active oxidation state.



**Scheme 4.** The proposed mechanism.

Thus, an alternative mechanism may be involved in the formation of the carbocation **C**. This carbocation can also be formed by the reaction between the benzoyl radical and **A**. Then, an unstable covalent intermediate **B** will be formed, which is in equilibrium with the reactive ionic form **C**. Next, the TMSCHN<sub>2</sub> react as a nucleophile with the carbocationic intermediate. After the addition, the reaction evolves to a three-member ring system **E** promoted by the elimination of nitrogen. Ring expansion and restore of the aromaticity leads to the carbocationic species **F**, which provided the final product by subsequent elimination of the silyl group upon assistance of the phenyl benzoate. This was supported by the formation of trimethylsilyl benzoate, which presence was confirmed by NMR analysis.

### 3.1.2 Conclusions and Outlooks

In this chapter I wanted to show the unexpressed potentiality of TMSCHN<sub>2</sub> as expansion ring reagent combined with oxidative C-H functionalization. This unexplored approach is far to be exhausted, and the investigation of other substrates that might undergo in similar expansion process is a demanding challenge we want to continue to face off. In this regard, the main issue relies in the choice of the appropriate oxidant, which should be capable of a selective activation on the desire target, preventing over-oxidations or undesired reactions of the diazo reagent. In addition, considering that seven members heterocycles are important biological scaffolds, general and easy approaches that not involve several steps and harsh conditions are still missing. In conclusion, in the next sections, our last results on the development of new diazocompound-based Csp<sup>3</sup>-H functionalization/expansion ring methodologies are presented.

### 3.1.3 References

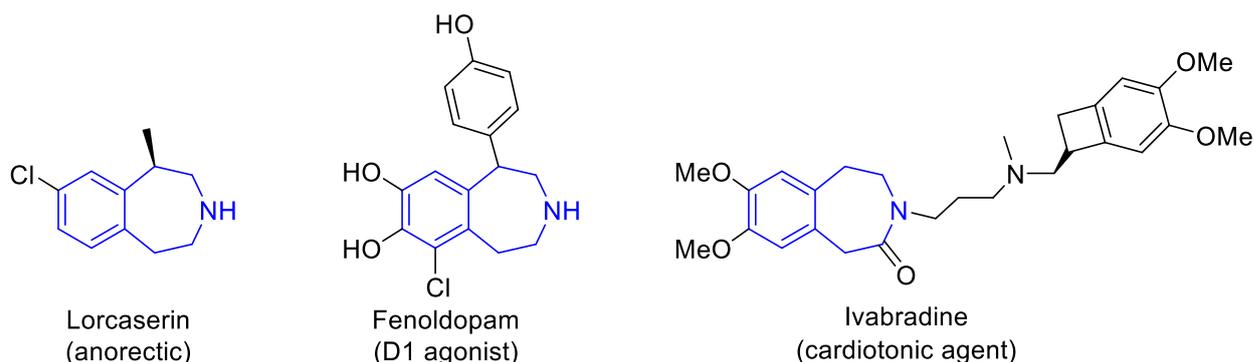
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- 14 With non-symmetrical xanthenes and acridanes a competitive addition takes place, leading to a mixture of products where the C-atom of the nucleophile TMSCHN<sub>2</sub> ends either in position C9 or C10 in favor of the attack of the more electron-rich phenyl ring. This was recognized by the reaction with bis-deuterated C9-2D **4b**, providing a 1.8:1 mixture of C9-D and C10-D **4b**.

## 3.2 C-Based expansion ring of THIQs

### 3.2.1 Introduction

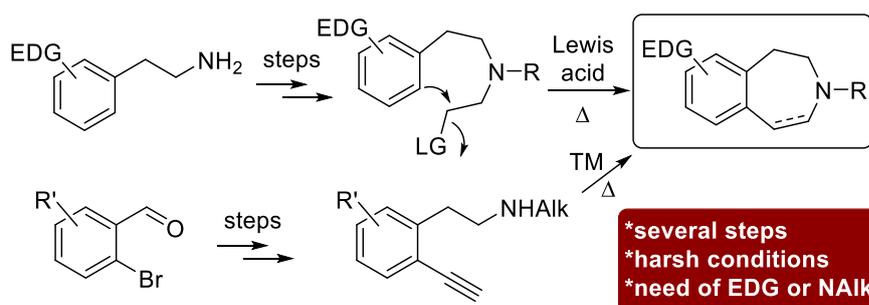
3-Benzazepines are a unique class of compounds important in drug discovery. In particular, the tetrahydro-3-benzazepine is a common skeleton in a number of natural and pharmaceutical products.<sup>1</sup> In the last half century, these compounds have been explored as a potent dopaminergic and antidopaminergic agents.<sup>2</sup> They also present other pharmacological activities such as analgesic, antihypertensive or anticancer properties.<sup>3</sup> Thus, e.g. (Figure 1) Lorcaserin has serotonergic properties and acts as an anorectic compound, which is currently used as a weight-loss drug.<sup>4</sup> Furthermore, Fenoldopam is employed as antihypertensive agent,<sup>5</sup> whereas Ivabradine is a cardiotoxic agent used for the symptomatic management of angina pectoris by inhibition of the funny channel.<sup>6</sup>



**Figure 1.** Selected examples of biologically active 3-benzazepines.

The main strategy to synthesize the 3-benzazepine core is based on a Lewis-acid mediated Friedel-Crafts-type cyclization approach (Scheme 1, top).<sup>7,8</sup> In all these cases, the 2-arylethyl amines are used as starting materials, which must be derived to an acyclic key intermediate for the final cyclization through several synthetic steps. Recently, *N*-alkyl 3-benzazepines have been afforded by an osmium-catalyzed hydroamination reaction.<sup>9</sup> This methodology also requires a multi-step synthesis of the substrates and is limited to *N*-alkyl derivatives. Besides these principal approaches, other synthetic routes include Pummerer cyclizations, electrophilic aromatic substitutions or the condensation of ketoacids with amines, among few others.<sup>8</sup> However, most of these methods required: i) several steps, ii) harsh conditions, iii) prolonged reaction times and iv) do not tolerate a broad substitution pattern on the nitrogen atom and the aromatic ring (e.g. need of electron-rich groups). These issues limit the preparation of diverse substituted 3-benzazepines. Therefore, there is still a need of simple, mild and direct synthetic methods for their synthesis.

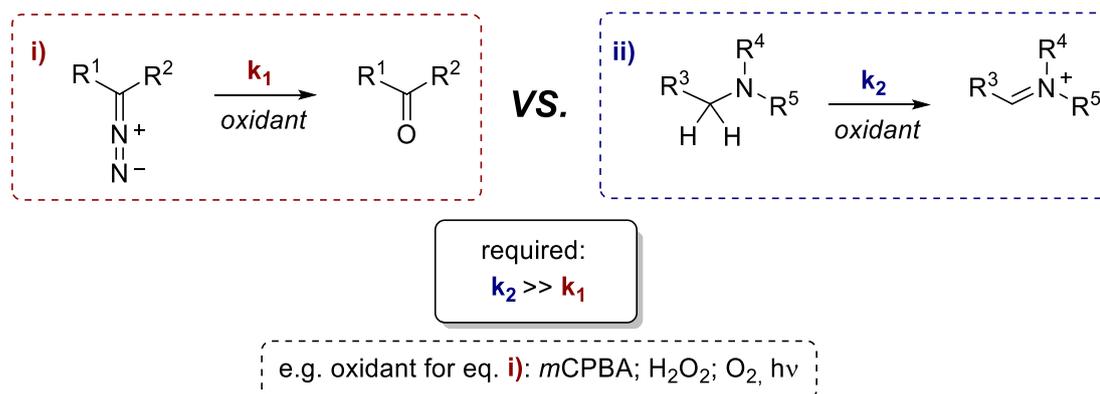
#### Classical approaches:



**Scheme 1.** Classical synthetic approach to 3-benzazepines.

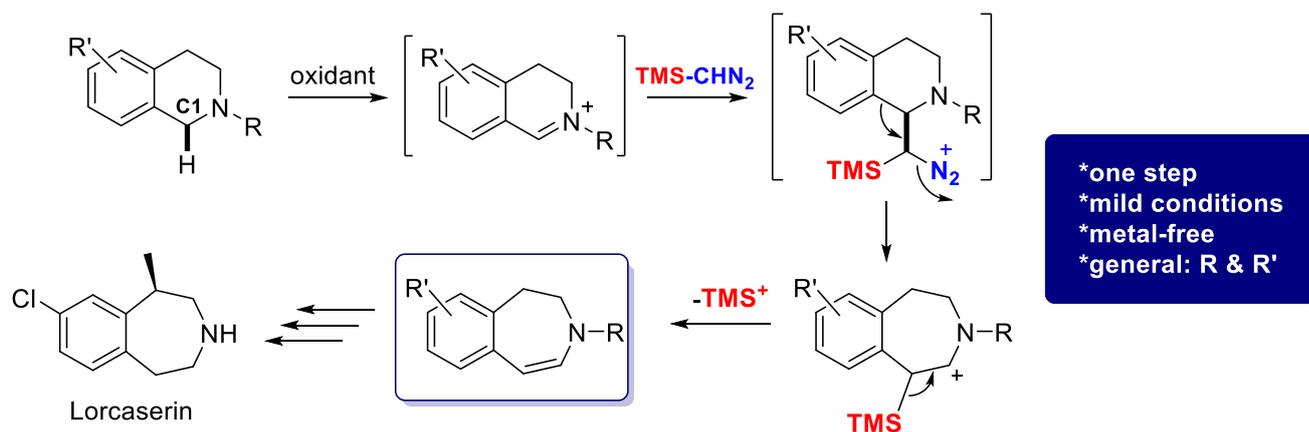
### 3.2.2 Objectives

Based on the previously discussed TMSCHN<sub>2</sub>-based direct C-H functionalization/expansion ring process for the synthesis of dibenz[b,f]oxepines/azepines (Chapter 3.1), the extension to THIQ substrates was aimed. In this regard, THIQs are ready available and easy to handle substrates, and the intrinsic properties of their C1-H bond open the way for several valid options for the selective oxidative activation. Indeed, the main challenge consisted again in the choice of the right oxidant, considering the natural reaction of diazomethanes into carbonyls under oxidative conditions (Scheme 2). Thus, the employed oxidant should activate the target in a selective manner, meanwhile interacting with the sensitive diazocompound slowly and weakly.



**Scheme 2.** Diazo compound decomposition *vs.* Target activation

More in detail, our main goal is the development of a novel one-pot oxidative Csp<sup>3</sup>-H bond functionalization/expansion ring tandem reaction applied to THIQS, for the formation of valuable benzoazepine scaffolds (Scheme 3).<sup>10,11</sup> In addition, we will also value the potential of the methodology in a synthetic application of demanding drugs, such as the anorectic medicine Lorcaserin.



**Scheme 3.** Our direct Csp<sup>3</sup>-H functionalization/expansion ring tandem reaction proposal.

### 3.2.3 Results and Discussion

We started our screening with N-phenyl-THIQ **1a** as model substrate and TMSCHN<sub>2</sub> as nucleophile for the optimization study of the reaction conditions (Table 1). A variety of standard oxidants in C-H functionalization were tested in dichloromethane at room temperature (Table 1, entries 1-8). DDQ (**I**) and *t*BuOOH (**II**) led to a complex mixture or no conversion, respectively. To our delight, the use of 1.2 equivalents of the TEMPO oxoammonium salt **III** (T<sup>+</sup>BF<sub>4</sub><sup>-</sup>)<sup>12</sup> provided for the first time the desired benzazepine **3a** (Table 1, entry 3). The initial low conversion of 43% was enhanced to 88% by employing 1.5 equivalents of the oxidant (Table 1, entry 4). Other TEMPO salts (**IV-VI**) with different counter-anions and substitution in the backbone also promoted this reaction (Table 1, entries 5-7). With the best oxoammonium salt **III**, the temperature was increased to 60 and 80 °C, finding full conversion and good isolated yields (77-78%) in both cases after 4 and 1 hours, respectively (entries 8 and 9). However, when the amount of **2a** was decreased to 1.5 equivalents, lower conversions were found at both temperatures (Table 1, entries 10 and 11). An important thing to mention is that the oxidative system (Cu(OTf)<sub>2</sub>, bipyridyne, BPO) previously employed in our lab for the expansion ring of xanthene and acridane moieties (Chapter 3.2) lead to a complex mixture of methylation and esterification THIQ side-products (Table 1, entry 12).

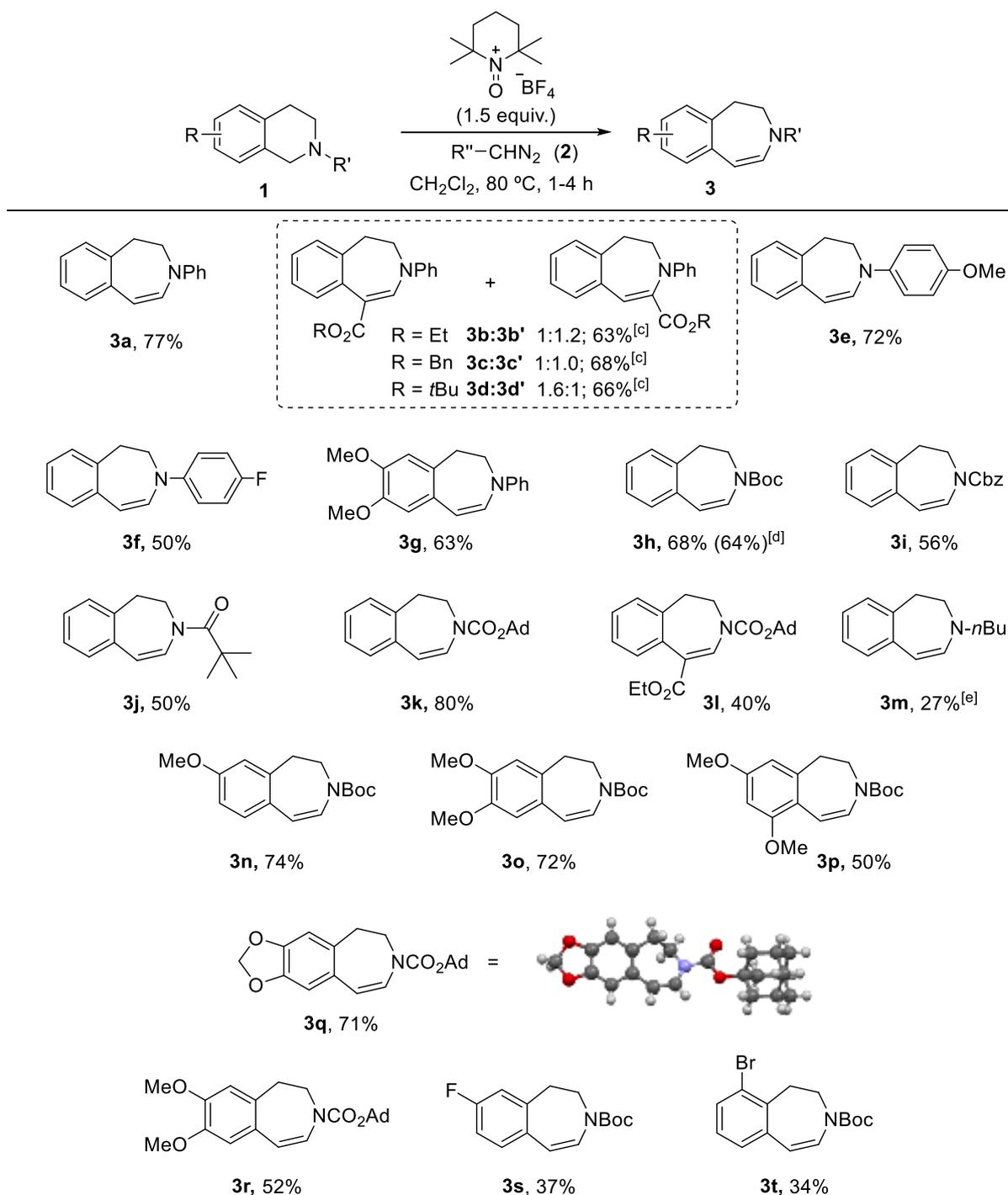
**Table 1.** Optimization of the reaction conditions.<sup>[a]</sup>

c1ccc2c(c1)CN(C2)c3ccccc3 **1a**
 $\xrightarrow[\text{CH}_2\text{Cl}_2, \text{ temp.}]{\text{oxidant (x equiv.)}, \text{TMS-CHN}_2 \text{ (2a) (x equiv.)}}$ 
c1ccc2c(c1)CN(C2)c3ccccc3 **3a**

Entry	Oxidant (x equiv.)	<b>2a</b> (equiv.)	T [°C]	t [h]	Conversion (yield) <sup>[b]</sup> [%]
1	DDQ ( <b>I</b> ) (1.2)	2.4	r.t.	18	-- <sup>[c]</sup>
2	<i>t</i> -BuOOH ( <b>II</b> ) (1.2)	2.4	r.t.	18	-- <sup>[d], [e]</sup>
3	T <sup>+</sup> BF <sub>4</sub> <sup>-</sup> ( <b>III</b> ) (1.2)	2.4	r.t.	18	43(26)
4	T <sup>+</sup> BF <sub>4</sub> <sup>-</sup> ( <b>III</b> ) (1.5)	2.4	r.t.	18	88
5	T <sup>+</sup> ClO <sub>4</sub> <sup>-</sup> ( <b>IV</b> ) (1.5)	2.4	r.t.	18	45
6	T <sup>+</sup> OTf <sup>-</sup> ( <b>V</b> ) (1.5)	2.4	r.t.	18	88
7	AcNH-T <sup>+</sup> BF <sub>4</sub> <sup>-</sup> ( <b>VI</b> ) (1.5)	2.4	r.t.	18	8
8	T <sup>+</sup> BF <sub>4</sub> <sup>-</sup> ( <b>III</b> ) (1.5)	2.4	60	4	>99(78)
9	T <sup>+</sup> BF <sub>4</sub> <sup>-</sup> ( <b>III</b> ) (1.5)	2.4	80	1	>99(77)
10	T <sup>+</sup> BF <sub>4</sub> <sup>-</sup> ( <b>III</b> ) (1.5)	1.5	60	4	75
11	T <sup>+</sup> BF <sub>4</sub> <sup>-</sup> ( <b>III</b> ) (1.5)	1.5	80	1	88
12 <sup>[f]</sup>	BPO ( <b>VII</b> ) (1.2)	2.4	r.t.	18	-- <sup>[c]</sup>

[a] **1a** (0.2 mmol), oxidant and TMSCHN<sub>2</sub> (**2a**) in DCM (0.1 M) at the desired temperature in a sealed tube. [b] Conversion of **1a** determined by <sup>1</sup>H-NMR. Isolated yield in brackets. [c] Complex mixture. [d] No reaction observed. [e] Reaction in MeCN. (TEMPO =2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl). [f] Cu(OTf)<sub>2</sub> (10 mol%) and bipyridyl (30 mol%) were enrolled in the reaction.

Under the optimized conditions (Table 1, entry 9), the scope of the reaction was investigated (Table 2). Although we focussed on the synthesis of highly versatile 1,2-unsubstituted unsaturated 3-benzazepines, which allows a rich variety of further functionalization of the double bond, other commercially available diazomethanes were also tested to show the generality of the method. Thus, the reaction of **1a** with less nucleophilic diazoacetates such as ethyl (**2b**), benzyl (**2c**) and *tert*-butyl (**2d**) led to a mixture of the corresponding isomeric C1- and C2-substituted 3-benzazepines **3/3'** in good yields (**3b/3b'** 1:1.2, 63%; **3c/3c'** 1:1, 68%; **3d/3d'** 1.6:1, 66%). **Table 2.** Substrate scope.<sup>[a],[b]</sup>

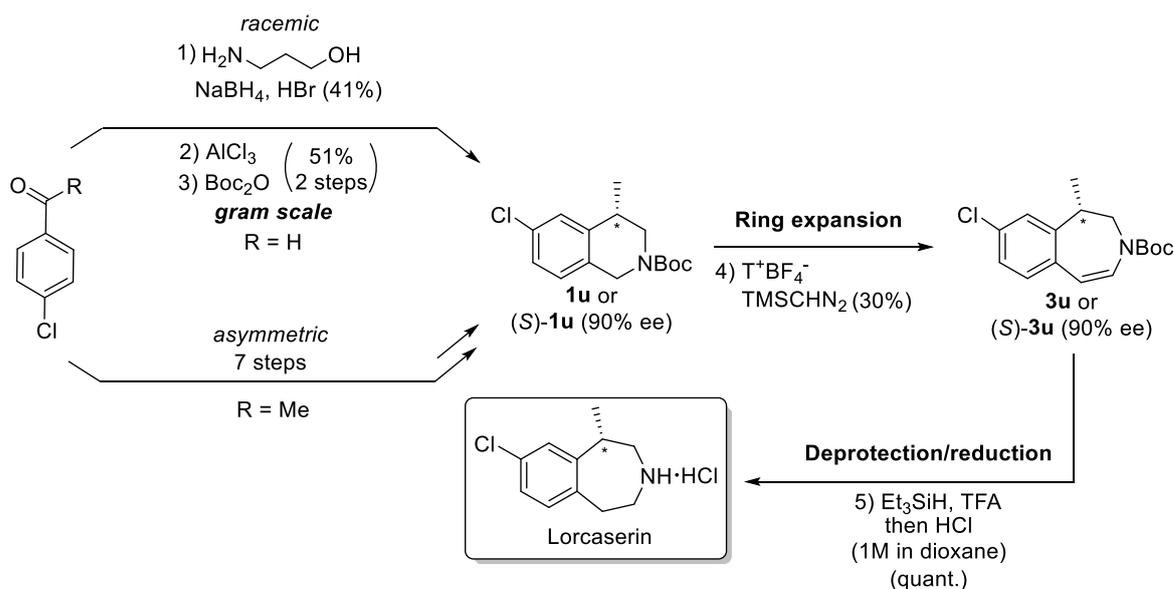


[a] **1** (0.2 mmol),  $\text{T}^+\text{BF}_4^-$  (1.5 equiv.) and  $\text{RCHN}_2$  (1.5-2.4 equiv.) in DCM (0.1 M) at  $80^\circ\text{C}$  for 1-4 h. [b] Isolated yield. [c] Isomeric ratio determined by  $^1\text{H-NMR}$ . [d] 1.0 mmol scale. [e] Concomitant formation of the corresponding *N*-methylated salts.

Next, different substituted THIQ derivatives **1** were explored. The reaction with *N*-aryl THIQs bearing both electron donating and withdrawing groups proceeded efficiently, providing the 3-benzazepines **3e-g** in 50-72% yield. Furthermore, the reaction tolerated different common *N*-protecting groups like Boc or Cbz (**3h** and **3i**) or acyl groups like pivaloyl (**3j**), and it could be scaled-up to 1.0 mmol with no significant detriment in the final yield (64 *vs.* 69%, **3h**). Further derivatives bearing bulky carbamates like adamantyl derivatives **3k-l** were obtained in moderate to good yields, whereas the alkylic substituted amine **3m** was formed in a lower 27% yield. We next explored the substitution at the aromatic unit of the THIQ. Because many 3-benzazepines contains methoxy or oxygenated groups (see e.g. Fenoldopam or Ivabradine, Figure 1), different oxygenated derivatives (**1n-1r**) were next studied. The reaction with the 6-methoxy substituted THIQ (**3n**, 74%), as well as with 6,8-dimethoxy (**3p**, 50%) and two methoxy groups at the 6 and 7 positions with both a *N*-Boc (**3o**, 72%) and a *N*-adamantyl carbamate (**3r**, 52%) as protecting groups proceeded smoothly. The methylene bridge compound **1q** was also supported without observing partial demethylenation under the oxidative reaction conditions and the structure of **3q** was confirmed by X-ray analysis.<sup>13</sup> Substrates with deactivating electron withdrawing groups such as fluoro or bromo also provided 3-benzazepines **3s-t**.

### 3.2.4 A new proposal for the synthesis of Lorcaserin

The synthetic applicability of the developed methodology was demonstrated by the synthesis of the drug Lorcaserin (Scheme 4). Initially, the synthesis the racemic drug was carried out. Therefore, the corresponding THIQ **1u** was prepared in gram scale in three steps from cheap *p*-chlorobenzaldehyde following a literature procedure.<sup>14</sup> The enantioenriched version was also accomplished in a longer sequence to achieve (*S*)-**1u** in 90% ee.<sup>17</sup> The reaction of **1u** under the developed ring expansion methodology led to the 3-benzazepine **3u** or (*S*)-**3u** in a moderate 30% yield. A further one-pot enamine reduction and *N*-Boc deprotection of **3u** with Et<sub>3</sub>SiH in trifluoroacetic acid/dichloromethane, followed by treatment with HCl (1M in dioxane), provided the targeted derivative Lorcaserin hydrochloride salt in a quantitative yield.

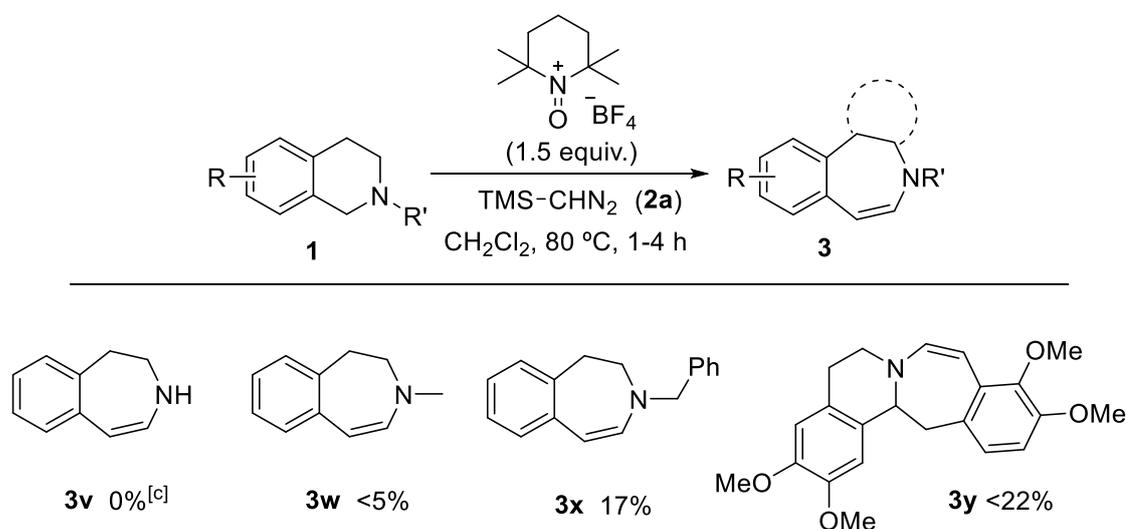


**Scheme 4.** Synthetic application: Synthesis of the drug Lorcaserin.

### 3.2.5 Unsuccessful applications on special substrates

In this section, some of the most interesting unsuccessful attempts to extend the application of the developed strategy are listed (Table 3). In first instance, the reaction with unprotected THIQ (**1v**) gave a complex mixture of oxidation side-products together with N-methylated THIQ salts (Table 3). A similar behavior was observed with N-alk THIQs, such as **1w** and **1x**, where a difficult to separate mixture of starting material and products, both N-methylated or not, was obtained. Thus, only in the case of N-benzyl THIQ **1x** it was possible to collect the pure product **3x** in low 17% of yield. Next, the strategy was applied to a highly demanding and complex substrate such as tetrahydropalmatine **1y**. Although the oxidation was successful and a small amount of the corresponding methylated salt was observed, a competitive oxidation for the formation of palmatine salt was recognize as main product and the desired 7-member ring product **3y** could be isolated in <22% yield. In addition, **3y** was found as a not air stable molecule.

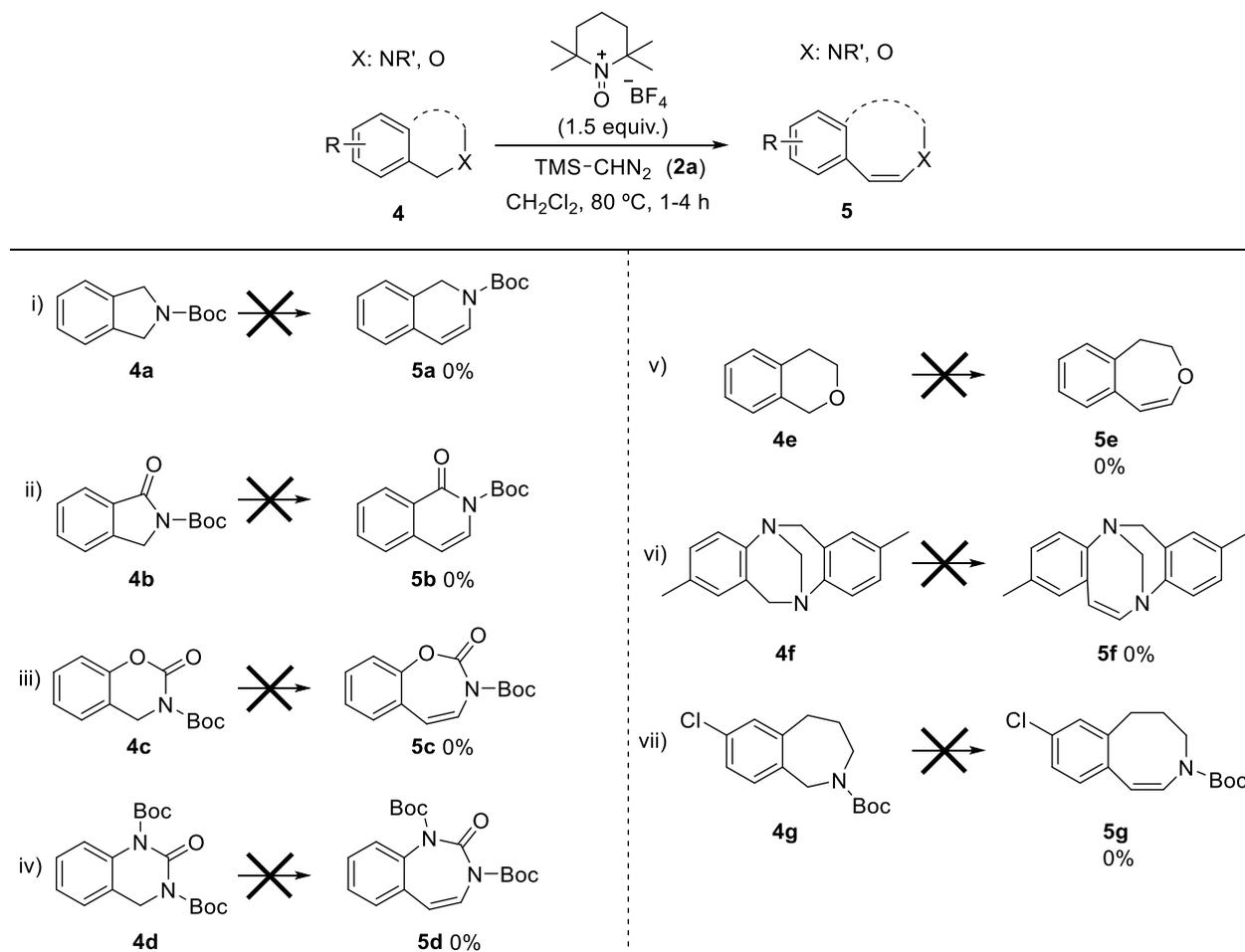
**Table 3.** Attempts for the application on N-Free and N-Alk THIQ



[a] **1** (0.2 mmol), T<sup>+</sup>BF<sub>4</sub><sup>-</sup> (1.5 equiv.) and TMSCHN<sub>2</sub> (2.4 equiv.) in DCM (0.1 M) at 80 °C for 1-4 h. [b] Isolated yield. [c] 4.8 equiv. of TMSCHN<sub>2</sub> was used.

Besides THIQ, many different structures bearing a  $\alpha$ -Csp<sup>3</sup>-H bond to nitrogen or oxygen were enrolled in the developed methodology (Table 4). In several cases, the oxidative system was not capable to activate the desire target (Table 4, eq. i, ii, v, vi and vii) and the starting material was almost completely recovered. Instead, TEMPO+BF<sub>4</sub> turned out to be a potent oxidant with **4c** and **4d**, but TMSCHN<sub>2</sub> resulted an inefficient reagent, most probably for its low nucleophilic proprieties. Indeed, although the starting material was half consumed, no traces of the desire product were observed (entry Table 4, entries iii and iv).

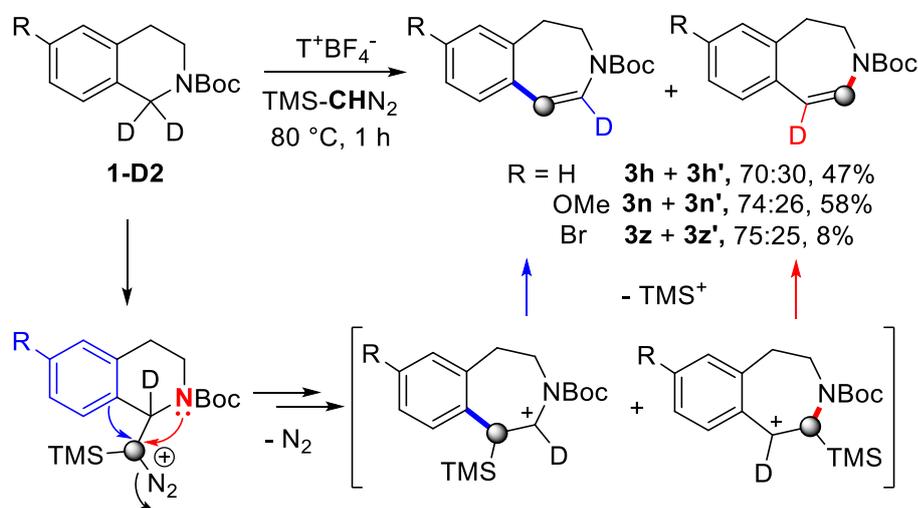
**Table 4.** Unreactive THIQ-like tested species.



[a] **1** (0.2 mmol), T<sup>+</sup>BF<sub>4</sub><sup>-</sup> (1.5 equiv.) and TMSCHN<sub>2</sub> (2.4 equiv.) in DCM (0.1 M) at 80 °C for 1-4 h. [b] Isolated yield.

### 3.2.6 Reactivity and Mechanistic Studies

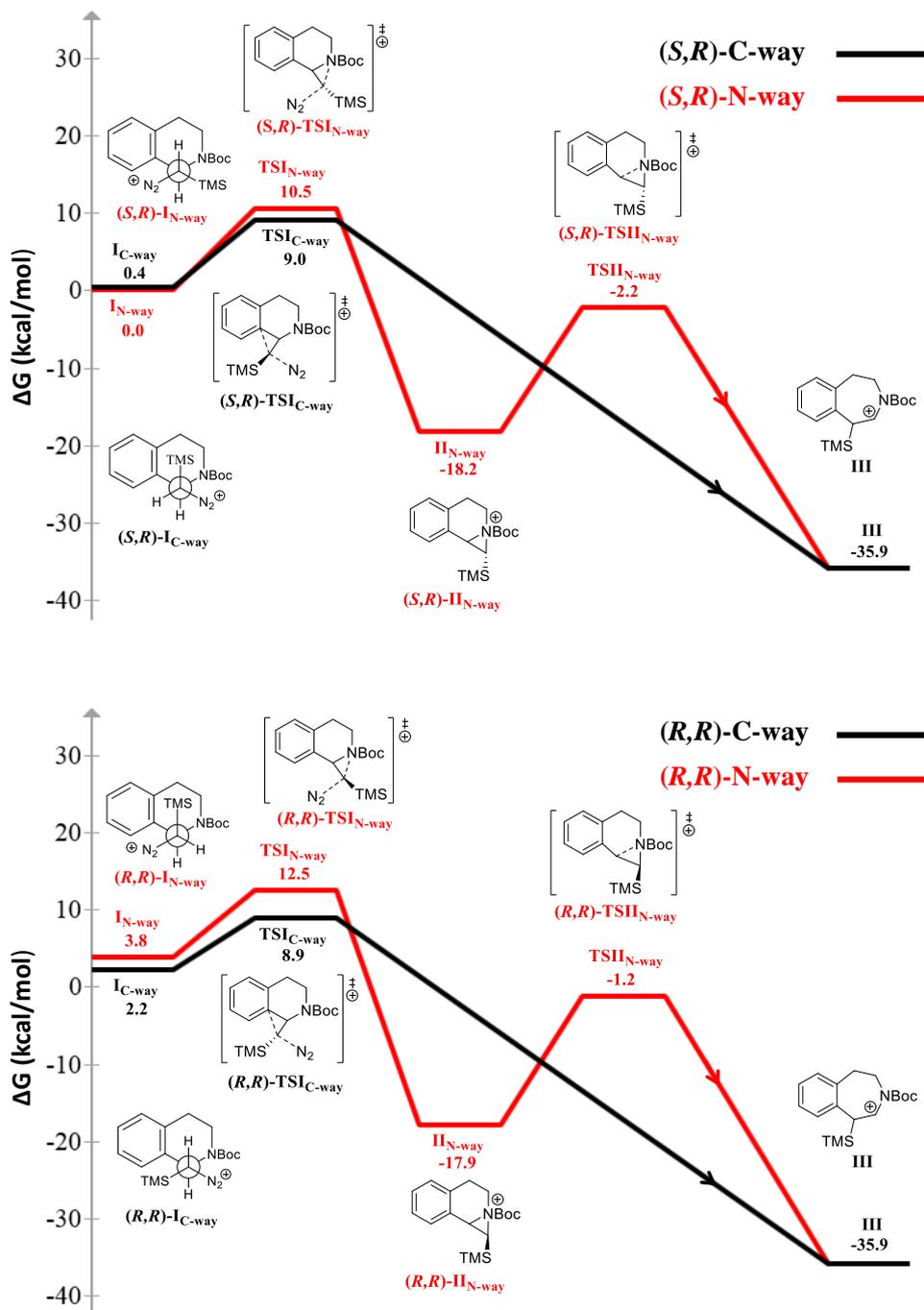
Aiming at bringing some light into the mechanism of the reaction, several experiments were carried out. Considering the observed substrate-dependent **3:3'** selectivity with substituted diazomethanes (Table 2, e.g. **3b:3b'** vs. **3l** as single isomer), further experiments with representative deuterium containing N-Boc precursors were carried out. This study indicates two possible competitive parallel mechanisms for the second step with TMSCHN<sub>2</sub>. In particular, the reactivity of labelled **1h**, **1n** and **1z** with dissimilar substituents at *para* position to the reactive centre were investigated (Scheme 5). Differences on the performances were found, showing a higher reactivity for the more electron rich derivative **1n-D2** bearing the *p*-MeO substituent (58% yield), whereas the *p*-Br substituted THIQ **1z-D2** was the last reactive (8% yield). However, only slightly changes in the final isomeric ratio of the two possible labelled deuterated compounds were found. Thus, in all cases a mixture nearly to 70:30 of the regioisomers, presenting the deuterium atom in the proximal (3) and distal (3') position respect to the nitrogen moiety, was obtained.



**Scheme 5.** Mechanistic studies with D-labeled THIQs **1**.

To get a deeper understanding of such pathways, DFT calculations using the M06 functional and 6-31G(d,p) basis set were performed by J. Luis-Barrera and Ruben Mas-Ballasté at UAM. In particular, the reactions of **1h**, **1n** and **1z** with TMSCHN<sub>2</sub> were studied. For each substrate, we considered the (*R,R*) and (*S,R*) diastereoisomers, which have been specifically oriented to allow the aromatic C-atom or the N-atom to act as the nucleophilic centre, respectively (Figure 2). For simplicity, the scenario found for the starting material **1h** is primarily presented. First, the (*S,R*) diastereoisomer is significantly more stable (~2 kcal/mol) than the (*R,R*). It is also observed that the activation energies of the nucleophilic attack are just slightly lower for the initial C-C bond formation (from the most stable (*S,R*) isomer,  $E_a = 6.8$  kcal/mol for C-C pathway and 8.6 kcal/mol for C-N pathway, see Figure 2). Interestingly, while the N-attack results on the formation of an aziridine intermediate, the cyclopropane analogue (C-attack) has not been found as a minimum in the potential energy surface. An exhaustive exploration of the reaction coordinates indicated that, although a saddle region corresponding to geometries close to the cyclopropane putative intermediate is found, an energy minimum cannot be located with such structure. Therefore, when the initial step consists in the formation of the C-C bond, the system evolves barrier-less towards the benzazepine product. In contrast, when the initial step consists in the C-N bond formation, an aziridine intermediate is produced, which further evolves through a ring

expansion process to generate the final benzazepine product. Such process from the aziridine intermediate has a significant activation energy of 16-17 kcal/mol. The high thermodynamic stability of the aziridine **II** intermediate (18 kcal/mol more stable than **I**), makes very improbable the backward reaction to **I**, which should overpass the activation energy of ~27 kcal/mol. Thus, regardless of the pathway followed, once the first transition state is overpassed, the reaction proceeds irreversibly towards the benzazepine product. Therefore, the formation of aziridine intermediate does not affect the overall tendency of the system to evolve through one or another pathway.



**Figure 2.** DFT-calculated reaction pathways for THIQ **1h**.

In fact, the comparable values for the initial activation energies suggest that both pathways are plausible and that the disappearance of the substrate **1h** through one or another pathway should follow similar kinetics. Interestingly, while the consumption of **1h** by means of the C-C pathway proceeds to the direct formation of the product, in the case of the C-N pathway the accumulation of the aziridine intermediate could result in a slower rate for the benzazepine production.<sup>15</sup> One of the most surprising results of the mechanistic investigations shown above is the fact that the occurrence of one or another pathway is independent on the presence of the electronic nature of the phenyl ring. A priori, if the reaction pathways were triggered by the initial nucleophilic attack of either the aromatic carbon or the nitrogen center, the substitution on the aromatic ring should direct the reactivity towards one or another mechanism. In particular, electron-donating groups should enhance the C-C pathway and electron-withdrawing groups should tip the scales towards the C-N mechanism. However, such tendency was not observed experimentally. Regarding the analysis of the values of natural charges and the geometries in relevant atoms present in reagents and transition states,<sup>16</sup> we found that the extrusion of the nitrogen molecule is the driven force for the formation of the species **III** from the intermediate **I**. Once the N<sub>2</sub> fragment is taking place, the formation of the carbocation and the C- or N-driven nucleophilic attack takes place in a barrier-less concerted asynchronous process. In consequence, the modulation of the nucleophilicity of the aromatic carbon has a minor effect on the reaction pathway that results in the formation of the 3-benzazepine structures.

### 3.2.7 Conclusions and Outlooks

In conclusion, we achieved the oxidative Csp<sup>3</sup>-H functionalization/ring expansion tandem reaction on THIQs. However, some significant modifications regarding the oxidative system were required. Indeed, the oxidant resulted again a main feature in the strategy planning. Thus, mild TEMPO<sup>+</sup>BF<sub>4</sub> revealed itself the best oxidant, whereas the previous developed Cu(I)/BPO system for xanthene and acridane was inefficient for mediate the reaction with THIQs. Beside its poor nucleophilicity, TMSCHN<sub>2</sub> emerged again as privileged agent. In addition, several examples involving other diazocompounds were reported, and the challenging regioselectivity issue was explored. We have shown two concurrent possible operative mechanistic pathways based on experimental proofs and DFT calculations. Finally, the synthetic utility of this methodology was proven by the preparation of the 3-benzazepine drug Lorcaserin.

### 3.2.7 References

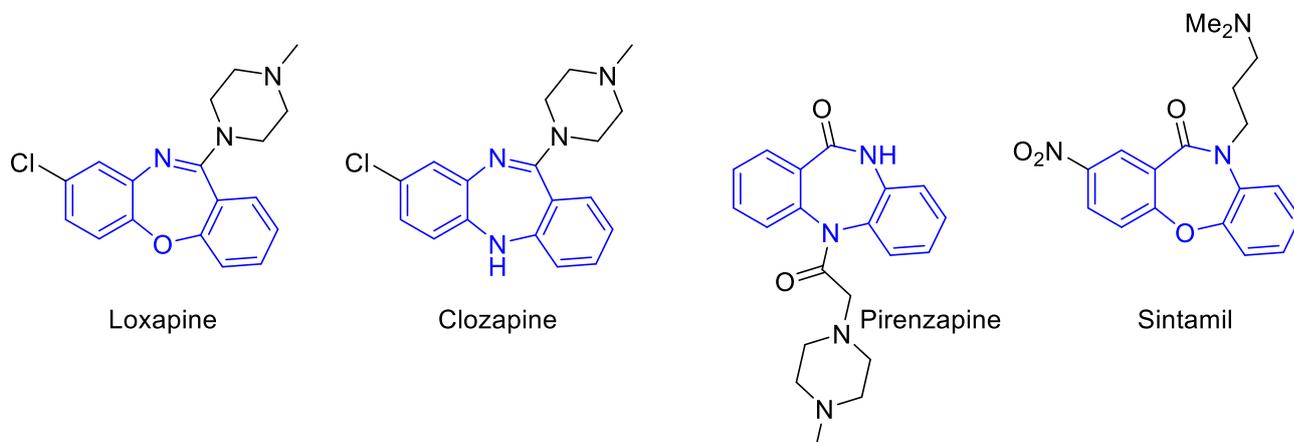
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- 15 A minimum in the potential surface for the 7-ring **IIIN**-pathway could not be found. The optimization evolved unavoidably to the **IIIC**-pathway suggesting that, after the N-attack, a migration of the TMS-group to the benzylic carbon takes place. Thus, both pathways end with the same energy
- 16 The values of natural charges in relevant atoms in both the reagents and the TS were evaluated. The C or the N atoms involved in the nucleophilic attack did not present significant differences, whereas the C-N<sub>2</sub><sup>+</sup> fragment showed the main electronic rearrangement. Furthermore, an increase on the electron density of atoms in the diazo group and a decrease of the adjacent C-atom was observed.
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### 3.3 N-Based expansion ring reaction

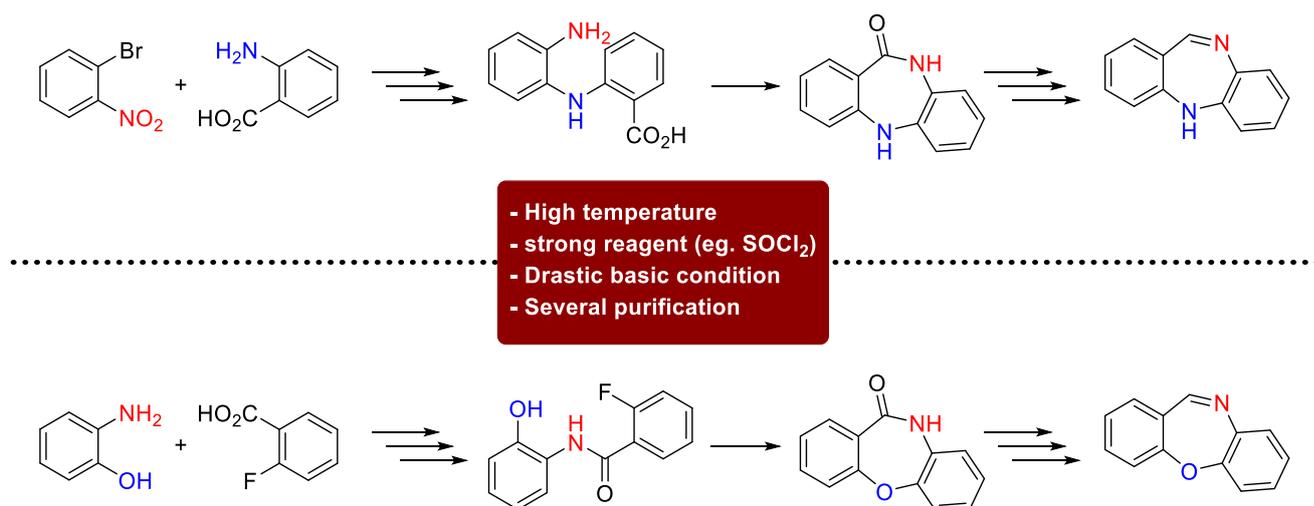
#### 3.3.1 Introduction

Dibenzodiazepines and dibenzooxazepines and their structural analogues have been revealed themselves as common cores in many potent drugs with a broad variety of bioactivities (Figure 1).<sup>1</sup>



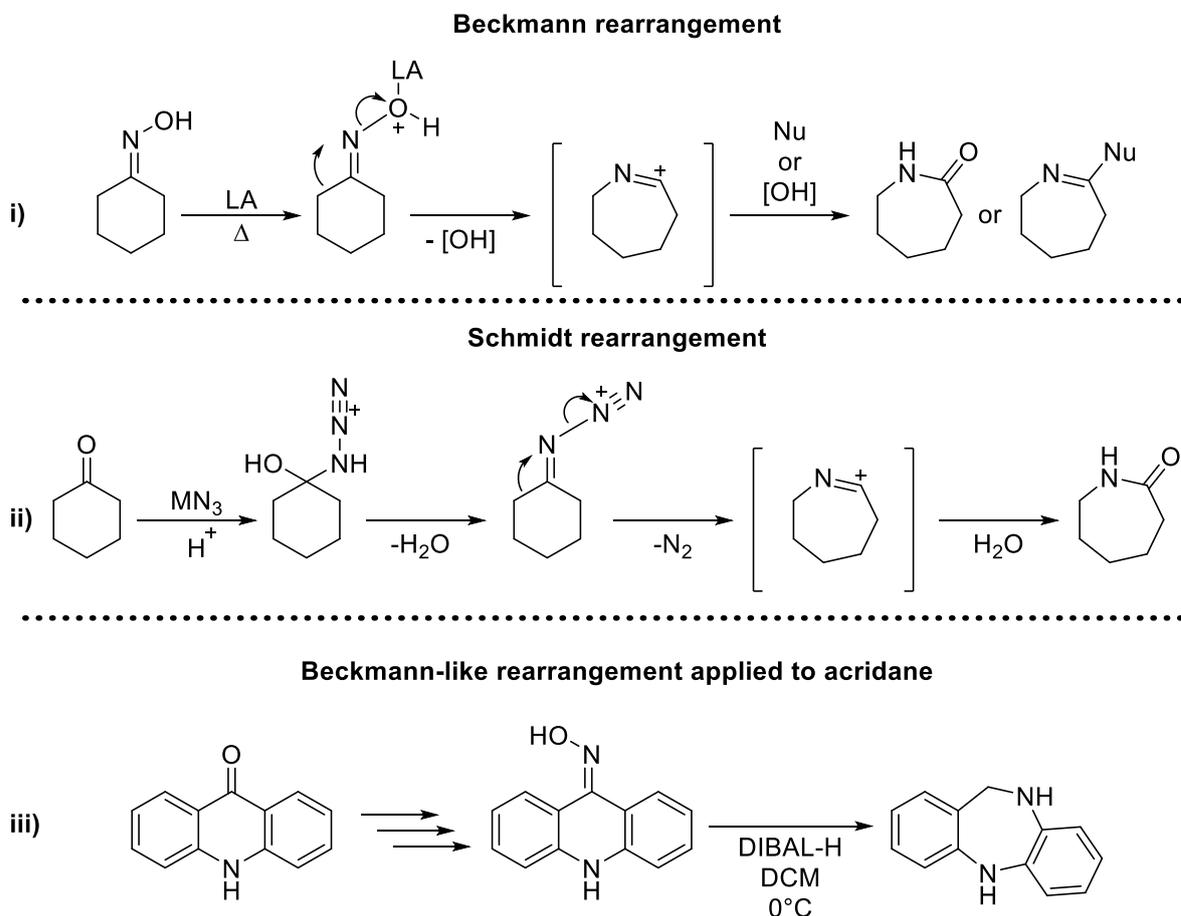
**Figure 1.** Selected examples of biologically active dibenzodiazepine and dibenzooxazepines.

Unfortunately, the complex multistep procedures commonly needed for the synthesis of these heterocycles limits the access to a broad number of structurally derivatives. Generally, the existing synthetic strategies rely on hetero cross-coupling reactions and a next imine or amide formation reaction, which usually involve both harsh conditions and the application of protecting groups (Scheme 1).<sup>2</sup> For example, in most reported pathways the intermediate has to carry a NO<sub>2</sub> group as a protected amine. Therefore, a consecutive reduction is required, limiting the compatibility with other functional groups (Scheme 1, above). Thus, it is evident the drawback of enrolling such a complex strategy, which make practically impossible its application to a late stage functionalization.



**Scheme 1.** Typical route for the synthesis of dibenzo(oxo/di)azepine and analogues.

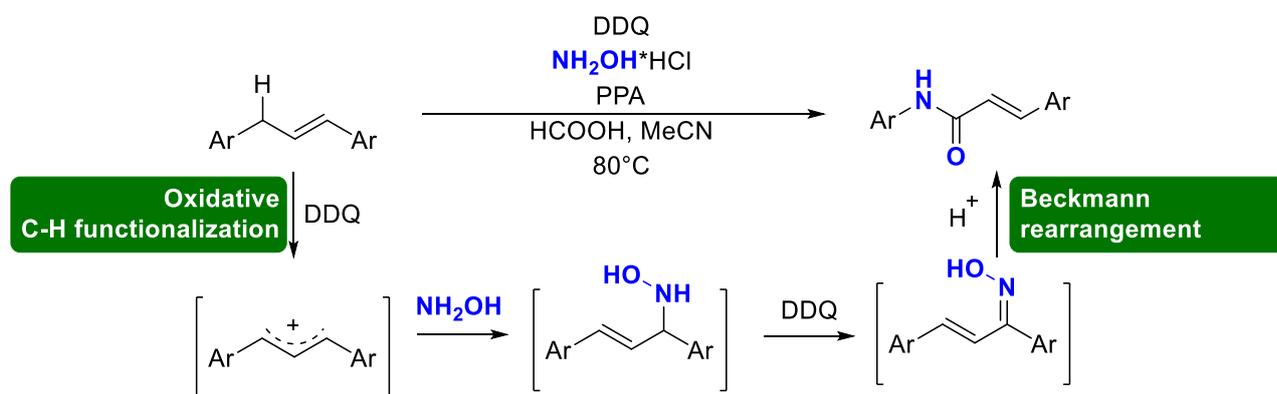
Another possible approach for the synthesis of such substrates is the N-based expansion ring of xanthenes or acridanes, employing a Beckmann-like or Schmidt-like rearrangement (Scheme 2, eq. i and ii).<sup>3,4</sup> In this context, not many methods are reported. The most relevant example involved a Beckmann-like rearrangement of 9-acridine-oxime with diisobutylaluminium hydride (DIBAL-H) (Scheme 2, eq. iii).<sup>5</sup> Despite the potential of the application, the multi-step approach required for obtaining the oxime intermediate and the strong involved reactants limit extraordinarily the strategy.



**Scheme 2.** Beckmann and Schmidt rearrangement.

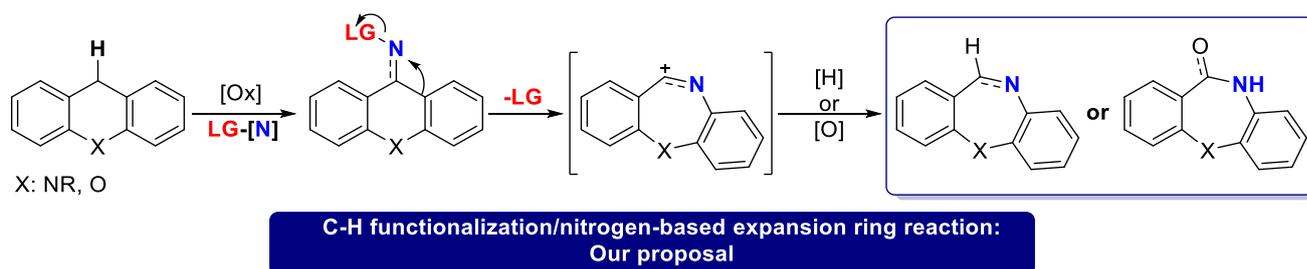
### 3.3.2 Objectives

The demand of new strategies for the synthesis of dibenzodiazepines or dibenzoxazepines and analogues is still high, especially taking in consideration that there are not available reactions for the N-based expansion ring applicable in late stage functionalization. To tackle this challenge, a similar procedure to what we developed for the C-based expansion ring reaction was envisioned as a reasonable option. Thus, we aimed at starting from a nitrogen-based nucleophile, which contains a good leaving group that could promote the rearrangement. In this context, to the best of our knowledge, only one similar approach based on the C-H functionalization/Beckmann rearrangement was developed by J. Qiu and R. Zhang in recent years. The procedure involved a DDQ mediated Csp<sup>3</sup>-H bond functionalization of allyl/propargyl-benzyl or dibenzyl moiety, which undergoes an oxime formation followed in the acid catalysed Beckmann rearrangement (Scheme 3).<sup>6</sup>



**Scheme 3.** Example of Csp<sup>3</sup>-H functionalization/Beckmann rearrangement reported by J. Qiu and R. Zhang.

Following this perspective, it is evident that the application of a nitrogen-based expansion ring rearrangement in a Csp<sup>3</sup>-H bond functionalization contest is still an unexplored field, even with standard targets employed in the C-H bond activation. Thus, inspired by well-known process, such as Beckmann or Schmidt rearrangements, we envisioned several reagents and oxidative systems for achieving the expansion ring reaction on the xanthenone and acridane core (Scheme 4).

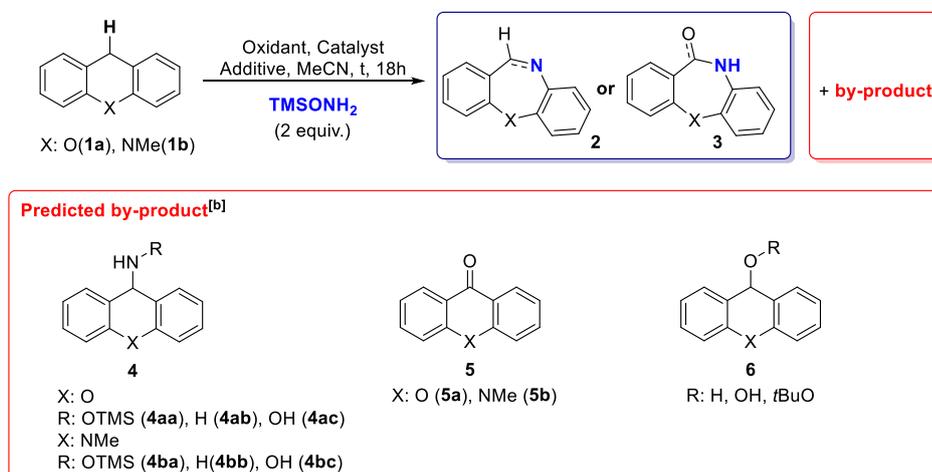


**Scheme 4.** Our proposed strategy.

### 3.3.3 Results and discussion

In first instance, we tested *o*-trimethylsilyl hydroxylamine as reagent for the N-based expansion ring (Table 1). Following our experience, a benzoylperoxide/copper(II) triflate system was initially enrolled in the activation of xanthene (**1a**). However, no desire product was detected. Only a small amount of possible N-addition products **4** were observed (Table 1, entry 1).

**Table 1.** Reaction screening involving TMSONH<sub>2</sub>.<sup>[a]</sup>



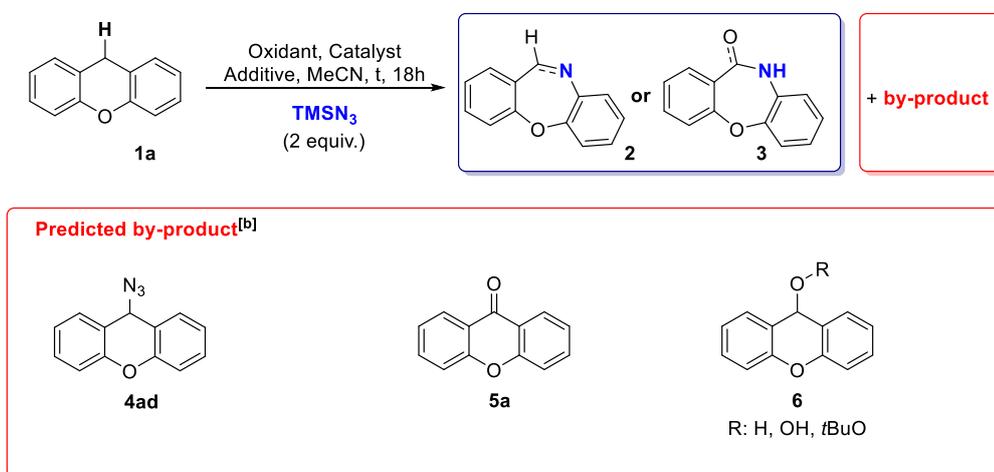
Entry	X	Oxidant (x equiv.)	Cat. (x mol%)	T [°C]	Additive (x equiv.)	Conversion [%] <sup>[c]</sup>
						<b>2/3/4/5/6</b>
1 <sup>[d]</sup>	O	BPO (1.2)	Cu(OTf) <sub>2</sub> (10%)	r.t.	-	-/-/16/9/-
2	O	BPO (2)	-	110	-	-/-/-/- <sup>[e]</sup>
3	O	PIDA (1.2)	-	r.t.	-	-/-/70/30/-
4	O	<i>t</i> BuOOH <sup>[g]</sup> (2)	CuBr (10%)	50	-	-/-/48(28)/27/7 <sup>[f]</sup>
5	O	<i>t</i> BuOOH <sup>[h]</sup> (2)	CuBr (10%)	50	LiOH (2)	-/-/17/17/-
6 <sup>[i][j]</sup>	O	TEMPO (2)	-	r.t.	-	-/-/5/-/-
7 <sup>[k]</sup>	O	DDQ (2)	-	80	-	-/-/62/-
8 <sup>[d]</sup>	NMe	BPO (1.2)	Cu(OTf) <sub>2</sub> (10%)	r.t.	-	-/-/99/-
9 <sup>[i]</sup>	NMe	T <sup>+</sup> BF <sub>4</sub> <sup>-</sup>	FeCl <sub>3</sub> (20%)	r.t.	-	-/-/-/-
10	NMe	<i>t</i> BuOOH <sup>[h]</sup> (2)	CuBr (10%)	50	-	-/-/99/-

[a] **1** (0.4 mmol), oxidant, additive, catalyst and TMSONH<sub>2</sub> (2 equiv.) in MeCN (0.1 M) at the desired temperature in a sealed tube. [b] Our hypothesis of possible by-products formed among the desire product. [c] Conversion of **1** determined by <sup>1</sup>H-NMR respect to the products observed. [d] Bipyridyl (30 mol%) was enrolled in the reaction. [e] Full conversion in opening ring product. [f] Conversion of **4aa** reported in brackets. [f] Cu(OTf)<sub>2</sub> (10 mol%) and bipyridyl (30 mol%) were enrolled in the reaction. [g] *t*BuOOH 70% in water was used as oxidant. [h] *t*BuOOH 3M in iso-octane was used as oxidant. [i] The reaction was performed in DCM (0.1 M). [j] The reaction was performed under O<sub>2</sub> atmosphere (1 atm). [k] The reaction was performed in HCOOH/MeCN 1:1 (0.1 M).

Instead, the use of PIDA as oxidant lead to full conversion, giving a mixture of addition products **4** and xanthone **5a** (Table 1, entry 3). When, *t*BuOOH and CuBr were enrolled in the reaction, several side products were observed (Table 1, entry 4). In this case, we could clearly identify for the first time one of the addition products by NMR analysis. Thus, we decide to repeat the reaction adding LiOH, which should have a double role as Lewis acid for mediating the rearrangement and as a base for enhance the nucleophilicity of TMSONH<sub>2</sub>. Unfortunately, a lower reactivity was detected (Table 1, entry 5). DDQ and a TEMPO/O<sub>2</sub> systems didn't allowed the addition of TMSONH<sub>2</sub> on the target (Table 1, entries 6-7). Finally, acridane **1b** gave no interesting result, leading exclusively the oxidized by-product acridone **5** (Table 1, entries 8-10).

Next, trimethylsilyl azide was enrolled for the N-based expansion ring reaction mediated by peroxides (Table 2).

**Table 2.** Attempts involving TMSN<sub>3</sub>.<sup>[a]</sup>



Entry	X	Oxidant (x equiv.)	Cat. (x mol%)	T [°C]	Additive (x equiv.)	Conversion [%] <sup>[c]</sup>
						<b>2/3/4/5/6</b>
1	O	<i>t</i> BuOOH <sup>[d]</sup> (1.2)	CuBr (10%)	50	-	-/-/99/-/-
2	O	<i>t</i> BuOOH <sup>[e]</sup> (1.2)	FeCl <sub>3</sub> (20%)	50	-	-/-/-/31/-
3	O	<i>t</i> BuOOH <sup>[e]</sup> (1.2)	FeCl <sub>3</sub> (100%)	50	-	-/-/-/24/-
4	O	<i>t</i> BuOOH <sup>[e]</sup> (1.2)	-	50	AlCl <sub>3</sub> (1)	-/-/-/-/-
5	O	<i>t</i> BuOOH <sup>[e]</sup> (1.2)	-	50	BF <sub>3</sub> *OEt <sub>2</sub> (1)	-/-/-/-/-
6	O	<i>t</i> BuOO <i>t</i> Bu (1.2)	FeCl <sub>3</sub> (20%)	50	-	-/-/-/-/-
7	O	<i>t</i> BuOO <i>t</i> Bu (1.2)	FeCl <sub>3</sub> (20%)	80	-	-/-/-/-/-
8	O	<i>t</i> BuOOH <sup>[e]</sup> (1.2)	ZnClO <sub>4</sub> (10%)	50	-	-/-/-/-/-
9	O	<i>t</i> BuOOH <sup>[e]</sup> (1.2)	CuBr (10%)	50	FeCl <sub>3</sub> (20%)	-/-/50/-/-

[a] **1** (0.4 mmol), oxidant, additive, catalyst and TMSN<sub>3</sub> (2 equiv.) in MeCN (0.1 M) at the desired temperature in a sealed tube. [b] Our hypothesis of possible by-product formed among the desire product. [c] Conversion of **1** determined by <sup>1</sup>H-NMR respect to the products observed. [d] *t*BuOOH 70% in water was used as oxidant. [e] *t*BuOOH 3M in isot-octane was used as oxidant.

In this case, to achieve both the functionalization and the rearrangement process, several lewis acids capable of the activation of both the oxidant and the azide intermediate were tested. Although we observed full conversion into **4ad** when the reaction was mediated by copper(I)bromide (Table 2, entry 1, see also chapter 2.2), the enrolling of other lewis acids did not allowed even the formation of the azide intermediate **4ad**. Finally, a loss of conversion of **4ad** was observed when both copper(I)bromide and iron(III)chloride were involved (Table 2, entry 9).

### 3.3.4 Conclusion and Outlook.

Herein several preliminary results on the Csp<sup>3</sup>-H functionalization/N-based expansion ring reaction were showed. Even though we could not observe any of the desire products, some interesting addition by-products were detected. Those, especially when TMSNH<sub>2</sub> was employed, could potentially be enrolled in a subsequent rearrangement reaction. Thus, it is evident that, in order to mediate the achievement and the activation of the addition intermediate **4**, other lewis acids have to be tested in the reaction.

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### 3.4 Experimental part

#### 3.4.1 C-Based expansion ring of THIQs

##### *General Information and Materials:*

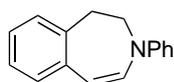
$^1\text{H}$ ,  $^{13}\text{C}$  and  $^{19}\text{F}$  NMR spectra were recorded in  $\text{CDCl}_3$  and  $\text{DMSO-D}_6$  (reference signals:  $^1\text{H} = 7.26$  ppm,  $^{13}\text{C} = 77.16$  ppm,  $\text{CDCl}_3$ ) on a Bruker ARX-300 and a Varian AV-300, 400 or 600 MHz. Chemical shifts ( $\delta$ ) are given in ppm and spin-spin coupling constants ( $J$ ) are given in Hz. Analytical thin layer chromatography was performed using silica gel 60 F<sub>254</sub> and a solution of  $\text{KMnO}_4$  or phosphomolybdic acid served as staining agent. Column chromatography was performed on silica gel 60 (0.040-0.063 mm). Exact masses (HRMS) were recorded on an Agilent Q-TOF 6540 UHD spectrometer (samples in  $\text{CH}_3\text{OH}$  as solvent) using electrospray (ES) or chemical (CI) ionization techniques. Chiral High Pressure Liquid Chromatography (HPLC) analyses were performed on an Agilent 1200 series instrument.

$\text{CH}_2\text{Cl}_2$  and  $\text{Et}_3\text{N}$  were distilled over  $\text{CaH}_2$ . THF and  $\text{Et}_2\text{O}$  were distilled and dried over Na. The starting materials and the oxoammonium salts such as  $\text{T}^+\text{BF}_4^-$  were prepared following known literature procedures.<sup>1,2,3,4</sup> Other solvents and commercially available reagents were used without further purification.

##### *General Procedure:*

In a flame-dried pressure schlenk tube, the TEMPO oxoammonium salt  $\text{T}^+\text{BF}_4^-$  (72.9 mg, 0.30 mmol, 1.5 equiv.) and the corresponding tetrahydroisoquinoline **1** (0.20 mmol, 1.0 equiv.) were suspended in dry DCM (0.1 M) under argon atmosphere. Afterwards the nucleophile TMS- $\text{CHN}_2$  (**2**) or  $\text{EtO}_2\text{C-CHN}_2$  (0.48 mmol, 2.4 equiv.) was added dropwise (exothermic reaction, fumes!). Depending on the substrate, the reaction mixture was stirred at 80 °C for 1 h, 4 h or overnight. After evaporating the solvent, the crude product was purified by flash column chromatography.

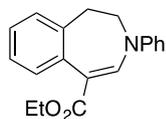
#### 3-Phenyl-2,3-dihydro-1H-benzo[d]azepine (**3a**)



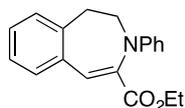
According to the general procedure, using  $\text{T}^+\text{BF}_4^-$  (72.9 mg, 0.3 mmol, 1.5 equiv.), THIQ **1a** (41.8 mg, 0.20 mmol, 1.0 equiv.) and  $\text{TMSCHN}_2$  (2 M in hexane, 240  $\mu\text{L}$ , 0.48 mmol, 2.4 equiv.), the title compound was obtained after 1 h by flash column chromatography (cyclohexane/ $\text{EtOAc}$ , 50:1) as a slightly brown solid (34.1 mg, 0.15 mmol, 77%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 7.32$  (t,  $J = 7.9$  Hz, 2H), 7.21-7.13 (m, 2H), 7.10-7.00 (m, 4H), 6.53 (d,  $J = 10.0$  Hz, 1H), 5.47 (d,  $J = 10.0$  Hz, 1H), 3.99-3.88 (m, 2H), 3.13-3.02 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 147.9, 138.5, 136.7, 132.3, 129.3, 128.9, 127.3, 126.3, 125.6, 124.0, 122.1, 119.6, 103.7, 50.8, 38.1$ . HRMS (ESI-MS): Mass calc. for  $\text{C}_{17}\text{H}_{23}\text{NO}_4$  [ $\text{M}^+$ ] $^+$ :  $m/z = 221.1199$ , found:  $m/z = 211.1195$ .

**Ethyl 3-phenyl-2,3-dihydro-1H-benzo[d]azepine-5-carboxylate (3b) and ethyl 3-phenyl-2,3-dihydro-1H-benzo[d]azepine-4-carboxylate (3b')**

According to the general procedure, using  $T^+BF_4^-$  (72.9 mg, 0.3 mmol, 1.5 equiv.), THIQ **1a** (41.8 mg, 0.20 mmol, 1.0 equiv.) and  $EtO_2C-CHN_2$  (51  $\mu$ L, 0.48 mmol, 2.4 equiv.), a 1:1.2 mixture of the title compounds **3b:3b'** was obtained as after 1 h by flash column chromatography (cyclohexane/EtOAc, 50:1).



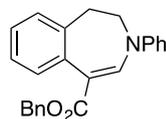
**3b:** Colorless oil (12.5 mg, 0.056 mmol, 28%).  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 8.10 (s, 1H), 7.63 (dd,  $J$  = 7.9, 1.0 Hz, 1H), 7.37 (dd,  $J$  = 8.6, 7.4 Hz, 2H), 7.24 (dt,  $J$  = 8.0, 2.0 Hz, 1H), 7.19 – 7.05 (m, 5H), 4.28 (q,  $J$  = 7.1 Hz, 2H), 4.06 – 3.99 (m, 2H), 3.20 – 3.11 (m, 2H), 1.33 (t,  $J$  = 7.1 Hz, 3H);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 169.5, 148.1, 143.3, 140.1, 134.4, 130.5, 129.8, 129.4, 128.0, 126.0, 125.7, 124.4, 120.8, 103.7, 60.2, 55.7, 35.7, 14.6; **HRMS (EI):** Mass calc. for  $C_{19}H_{19}NO_2$  [ $M^+$ ]:  $m/z$  = 293.1410, found:  $m/z$  = 293.1409.



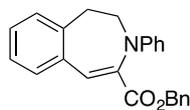
**3b':** Yellow oil (15.3 mg, 0.069 mmol, 35%).  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 7.43 (d,  $J$  = 7.5 Hz, 1H), 7.32 – 7.21 (m, 3H), 7.19 – 7.15 (m, 2H), 7.06 – 6.94 (m, 4H), 4.06 (q,  $J$  = 7.1 Hz, 2H), 3.84 – 3.75 (m, 2H), 3.00 – 2.89 (m, 2H), 0.97 (t,  $J$  = 7.1 Hz, 3H);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 167.2, 148.5, 140.8, 135.5, 133.5, 133.2, 129.9, 129.3, 126.8, 126.3, 123.0, 122.6, 121.7, 61.3, 51.8, 36.6, 13.9; **HRMS (EI):** Mass calc. for  $C_{19}H_{19}NO_2$  [ $M^+$ ]:  $m/z$  = 293.1410, found:  $m/z$  = 293.1413.

**Benzyl 3-phenyl-2,3-dihydro-1H-benzo[d]azepine-5-carboxylate (3c) and benzyl 3-phenyl-2,3-dihydro-1H-benzo[d]azepine-4-carboxylate (3c')**

According to the general procedure, using  $T^+BF_4^-$  (72.9 mg, 0.3 mmol, 1.5 equiv.), THIQ **1a** (41.8 mg, 0.20 mmol, 1.0 equiv.) and  $BnO_2C-CHN_2$  (72  $\mu$ L, 0.48 mmol, 2.4 equiv.), a 1:1 mixture of the title compounds **3c:3c'** was obtained as after 1 h by flash column chromatography (PE  $\rightarrow$  PE/EtOAc 9:1).



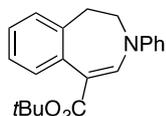
**3c:** Yellow oil (24.8 mg, 0.070 mmol, 35%).  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 8.14 (s, 1H), 7.63 (d,  $J$  = 7.8 Hz, 1H), 7.42 – 7.37 (m, 2H), 7.37 – 7.31 (m, 5H), 7.31 – 7.27 (m, 1H), 7.23 – 7.18 (m, 1H), 7.16 – 7.10 (m, 3H), 7.10 – 7.03 (m, 1H), 5.27 (s, 2H), 4.05 – 3.95 (m, 2H), 3.19 – 3.07 (m, 2H);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 169.2, 148.2, 143.8, 140.1, 137.1, 134.4, 130.6, 129.5, 128.5, 128.1, 128.0, 127.9, 126.0, 125.8, 124.6, 121.0, 103.3, 66.0, 55.9, 35.8; **HRMS (EI):** Mass calc. for  $C_{24}H_{21}NO_2$  [ $M^+$ ]:  $m/z$  = 355.1572, found:  $m/z$  = 355.1575.



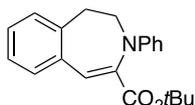
**3c':** Yellow oil (23.6 mg, 0.066 mmol, 33%).  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 7.41 (d,  $J$  = 7.5 Hz, 1H), 7.37 – 7.34 (m, 2H), 7.33 (s, 1H), 7.24 – 7.19 (m, 4H), 7.15 (d,  $J$  = 4.0 Hz, 2H), 7.05 (s, 1H), 7.03 – 6.98 (m, 1H), 6.95 – 6.91 (m, 3H), 5.02 (s, 2H), 3.80 – 3.75 (m, 2H), 2.95 – 2.90 (m, 2H);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 167.1, 148.3, 140.8, 135.6, 135.0, 133.3, 129.9, 129.4, 128.8, 128.6, 128.4, 128.14, 128.0, 126.9, 126.3, 122.9, 122.4, 67.2, 51.6, 36.5; **HRMS (EI):** Mass calc. for  $C_{24}H_{21}NO_2$  [ $M^+$ ]:  $m/z$  = 355.1572, found:  $m/z$  = 355.1577.

***tert*-Butyl 3-phenyl-2,3-dihydro-1*H*-benzo[*d*]azepine-5-carboxylate (3d) and *tert*-butyl 3-phenyl-2,3-dihydro-1*H*-benzo[*d*]azepine-4-carboxylate (3d')**

According to the general procedure, using T<sup>+</sup>BF<sub>4</sub><sup>-</sup> (72.9 mg, 0.3 mmol, 1.5 equiv.), THIQ **1a** (41.8 mg, 0.20 mmol, 1.0 equiv.) and *t*BuO<sub>2</sub>C-CHN<sub>2</sub> (67 μL, 0.48 mmol, 2.4 equiv.), a 1.6:1 mixture of the title compounds **3d:3d'** was obtained as after 1 h by flash column chromatography (PE → PE/EtOAc 9:1).

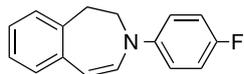


**3d:** Yellow oil (26.9 mg, 0.084 mmol, 41%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ/ppm = 8.04 (s, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.41 – 7.30 (m, 2H), 7.24 – 7.18 (m, 1H), 7.16 – 7.01 (m, 5H), 4.03 – 3.96 (m, 2H), 3.19 – 3.10 (m, 2H), 1.53 (s, 9H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ/ppm = 168.8, 148.2, 142.7, 140.1, 134.8, 130.7, 129.4, 127.9, 125.8, 125.6, 124.1, 120.4, 105.6, 79.9, 55.7, 35.7, 28.5; **HRMS (EI):** Mass calc. for C<sub>21</sub>H<sub>23</sub>NO<sub>4</sub> [M<sup>+</sup>]: *m/z* = 321.1729, found: *m/z* = 321.1727.



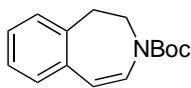
**3d':** Yellow oil (16.7 mg, 0.052 mmol, 25%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ/ppm = 8.04 (s, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.41 – 7.30 (m, 2H), 7.24 – 7.18 (m, 1H), 7.16 – 7.01 (m, 5H), 4.03 – 3.96 (m, 2H), 3.19 – 3.10 (m, 2H), 1.53 (s, 9H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ/ppm = 166.1, 148.9, 140.6, 136.8, 133.8, 132.9, 129.8, 129.2, 126.4, 126.2, 123.2, 123.0, 120.3, 81.2, 52.0, 36.6, 27.6; **HRMS (EI):** Mass calc. for C<sub>21</sub>H<sub>23</sub>NO<sub>4</sub> [M<sup>+</sup>]: *m/z* = 321.1729, found: *m/z* = 321.1733.

**3-(4-Fluorophenyl)-2,3-dihydro-1*H*-benzo[*d*]azepine (3f)**



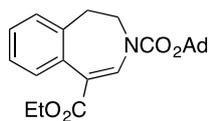
According to the general procedure, using T<sup>+</sup>BF<sub>4</sub><sup>-</sup> (72.9 mg, 0.3 mmol, 1.5 equiv.), THIQ **1c** (45.5 mg, 0.20 mmol, 1.0 equiv.) and TMSCHN<sub>2</sub> (2 M in hexane, 240 μL, 0.48 mmol, 2.4 equiv.), the title compound was obtained after 1 h by flash column chromatography (cyclohexane/EtOAc, 40:1 → 20:1) as yellow solid (24.2 mg, 0.10 mmol, 50%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ/ppm = 7.18 – 7.11 (m, 2H), 7.07 – 7.02 (m, 1H), 7.02 – 6.97 (m, 5H), 6.47 – 6.34 (m, 1H), 5.49 – 5.39 (m, 1H), 3.92 – 3.81 (m, 2H), 3.09 – 2.97 (m, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ/ppm = 158.5 (d, *J* = 243.5 Hz), 144.6, 138.5, 132.5, 129.0, 128.7, 126.6, 126.4, 124.0, 121.5 (d, *J* = 6.1 Hz), 115.9 (d, *J* = 21.0 Hz), 103.6, 51.6, 38.0; <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>): δ/ppm = -121.4; **HRMS (EI):** Mass calc. for C<sub>16</sub>H<sub>14</sub>NF [M<sup>+</sup>]: *m/z* = 239.1105, found: *m/z* = 239.1108.

***tert*-Butyl 1,2-dihydro-3*H*-benzo[*d*]azepine-3-carboxylate (3h)**



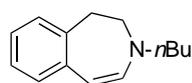
According to the general procedure, using T<sup>+</sup>BF<sub>4</sub><sup>-</sup> (72.9 mg, 0.30 mmol, 1.5 equiv.), THIQ **1d** (46.60 mg, 0.20 mmol, 1.0 equiv.) and TMSCHN<sub>2</sub> (2 M in Et<sub>2</sub>O, 240 μL, 0.48 mmol, 2.4 equiv.), the title compound was obtained after 1 h by flash column chromatography (PE → PE/EtOAc, 20:1) as a slightly yellow solid (33.2 mg, 0.14 mmol, 68%). *Note:* The reaction was also carried out in a 1.0 mmol scale with a reaction time of 2 h and a reproducible result is reported (66 %). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.20-7.15 (m, 2H), 7.10-7.05 (m, 2H), 6.93 (bs, 1H), 5.56 (bs, 1H), 3.95-3.90 (m, 2H), 3.06-3.00 (m, 2H), 1.53 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ/ppm = 152.2, 139.2, 135.1, 130.2, 128.9, 126.6, 126.4, 125.8, 108.3, 81.7, 39.5, 37.2, 28.3; **HRMS (ESI):** Mass calc. for C<sub>15</sub>H<sub>19</sub>NO<sub>2</sub>-Na [M+Na]<sup>+</sup>: *m/z* = 268.1308 found: *m/z* = 268.1310.

### 3-(Adamantan-1-yl) 1-ethyl 4,5-dihydro-3*H*-benzo[*d*]azepine-1,3-dicarboxylate (3l)



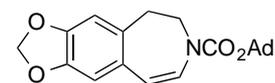
According to the general procedure, using  $T^+BF_4^-$  (72.9 mg, 0.30 mmol, 1.5 equiv.), THIQ **1g** (62.3 mg, 0.20 mmol, 1.0 equiv.) and  $EtO_2C-CHN_2$  (51  $\mu$ L, 0.48 mmol, 2.4 equiv.), the title compound was obtained after 1 h by flash column chromatography (PE  $\rightarrow$  PE/EtOAc, 20:1) as a white solid (30.5 mg, 0.079 mmol, 40%).  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 8.42 (s, 1H), 7.49 (dd,  $J$  = 7.7, 1.2 Hz, 1H), 7.22 (td,  $J$  = 7.7, 1.5 Hz, 1H), 7.17 (td,  $J$  = 7.3, 1.5 Hz, 1H), 7.08 (dd,  $J$  = 7.4, 1.3 Hz, 1H), 4.28 (q,  $J$  = 7.1 Hz, 2H), 3.98 – 3.87 (m, 2H), 3.06 – 2.77 (m, 2H), 2.20 (bs, 3H), 2.16 (bs, 6H), 1.67 (bs, 6H), 1.34 (t,  $J$  = 7.1 Hz, 3H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 168.6, 151.9, 140.4, 137.0, 132.8, 130.5, 129.8, 127.9, 127.1, 126.1, 82.9, 60.8, 51.3, 41.3, 36.1, 34.0, 30.9, 14.4; HRMS (ESI): Mass calc. for  $C_{24}H_{29}NO_4H$   $[M+H]^+$ :  $m/z$  = 396.2169, found:  $m/z$  = 396.2173.

### 3-Butyl-2,3-dihydro-1*H*-benzo[*d*]azepine (3m)



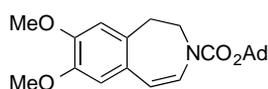
According to the general procedure using  $T^+BF_4^-$  (72.9 mg, 0.30 mmol, 1.5 equiv.), THIQ **1h** (39  $\mu$ L, 37.9 mg, 0.200 mmol, 1.0 equiv.) and  $TMSCHN_2$  (2 M in  $Et_2O$ , 150  $\mu$ L, 0.30 mmol, 1.5 equiv.), the title compound was obtained after 4 h by flash column chromatography (petroleum ether  $\rightarrow$  petroleum ether: ethyl acetate 30:1) as a brown oil (11.3 mg, 0.06 mmol, 28%).  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 7.10-7.00 (m, 2H), 6.95-6.90 (m, 1H), 6.90-6.84 (m, 1H), 6.04 (d,  $J$  = 9.8 Hz, 1H), 4.99 (d,  $J$  = 9.8 Hz, 1H), 3.45-3.30 (m, 2H), 3.07 (t,  $J$  = 7.1 Hz, 2H), 3.00-2.90 (m, 2H), 1.51 (m, 4H), 1.31 (m, 3H), 0.91 (t,  $J$  = 7.3 Hz, 3H);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 138.5, 137.8, 137.5, 128.8, 127.8, 126.2, 122.7, 96.4, 57.8, 51.3, 38.2, 31.3, 20.1, 13.9; HRMS (ESI-MS): Mass calc. for  $C_{14}H_{19}N$   $[M]^+$ :  $m/z$  = 201.1512, found:  $m/z$  = 201.1515.

### (3*r*)-Adamantan-1-yl 5,6-dihydro-7*H*-[1,3]dioxolo[4',5':4,5]benzo[1,2-*d*]azepine-7-carboxylate (3q)



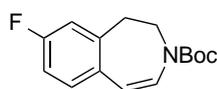
According to the general procedure using  $T^+BF_4^-$  (72.9 mg, 0.30 mmol, 1.5 equiv.), THIQ **1n** (70.9 mg, 0.200 mmol, 1.0 equiv.) and  $TMSCHN_2$  (2 M in  $Et_2O$ , 240  $\mu$ L, 0.480 mmol, 2.4 equiv.), the title compound was obtained after 4 h by flash column chromatography (petroleum ether  $\rightarrow$  petroleum ether: ethyl acetate 4:1) as a white solid (52.0 mg, 0.142 mmol, 71%).  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 6.86 (bs, 1H), 6.63 (s, 1H), 6.57 (s, 1H), 5.91 (s, 2H), 5.34 (bs, 1H), 3.90-3.85 (m, 2H), 2.95-2.90 (m, 2H), 2.25-2.15 (m, 9H), 1.68 (bs, 6H);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 151.7, 146.2, 145.8, 133.5, 128.9, 125.3, 109.9, 109.4, 107.8, 101.0, 81.6, 46.6, 44.9, 41.6, 36.9, 36.2, 31.0, 29.8; HRMS (ESI-MS): Mass calc. for  $C_{22}H_{25}NO_4$   $[M]^+$ :  $m/z$  = 368.1784, found:  $m/z$  = 368.1782.

**(3r)-Adamantan-1-yl 7,8-dimethoxy-1,2-dihydro-3H-benzo[d]azepine-3-carboxylate (3r)**



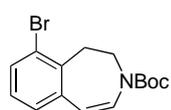
According to the general procedure using  $T^+BF_4^-$  (72.9 mg, 0.30 mmol, 1.5 equiv.), THIQ **1o** (74.3 mg, 0.200 mmol, 1.0 equiv.) and  $TMSCHN_2$  (2 M in  $Et_2O$ , 240  $\mu L$ , 0.480 mmol, 2.4 equiv.), the title compound was obtained after 4 h by flash column chromatography (petroleum ether  $\rightarrow$  petroleum ether: ethyl acetate 4:1) as a white solid (39.8 mg, 0.104 mmol, 52 %).  $^1H$  NRM (300 MHz,  $CDCl_3$ ):  $\delta/ppm = 6.85$  (bs, 1H), 6.70-6.55 (m, 2H), 5.43 (bs, 1H), 3.90-3.80 (m, 2H), 3.86 (s, 6H), 2.97 (s, 2H), 2.25-2.10 (m, 9H), 1.70-60 (m, 6H);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta/ppm$  (presence of rotamers) = 154.7, 151.8 and 151.0 (rotamers), 147.2 and 147.1 (rotamers), 132.2, 127.6, 125.5, 113.5, 112.6, 108.6 and 108.1 (rotamers), 81.5 and 81.5 (rotamers), 68.3, 56.0, 45.4, 41.6, 36.3, 36.2, 31.0, 30.8, 29.8, 29.1, 22.7; HRMS (ESI-MS): Mass calc. for  $C_{23}H_{29}NO_4Na$   $[M+Na]^+$ :  $m/z = 406.1987$ , found:  $m/z = 406.1989$ .

**tert-Butyl 6-fluoro-1,2-dihydro-3H-benzo[d]azepine-3-carboxylate (3s)**



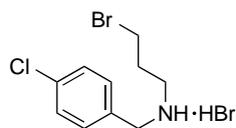
According to the general procedure using  $T^+BF_4^-$  (72.9 mg, 0.30 mmol, 1.5 equiv.), THIQ **1p** (50.3 mg, 0.200 mmol, 1.0 equiv.) and  $TMSCHN_2$  (2 M in  $Et_2O$ , 240  $\mu L$ , 0.480 mmol, 2.4 equiv.), the title compound was obtained after 1 h by flash column chromatography (petroleum ether  $\rightarrow$  petroleum ether: ethyl acetate 20:1) as a yellow solid (20.7 mg, 0.074 mmol, 37%).  $^1H$  NRM (300 MHz,  $CDCl_3$ ):  $\delta/ppm = 7.10$  (dd,  $J = 8.5, 5.8$  Hz, 1H), 6.88 (bs, 1H), 6.84 (td,  $J = 8.4, 2.7$  Hz, 1H), 6.80-6.75 (m, 1H), 5.50 (bs, 1H), 3.92-3.85 (m, 2H), 3.02-2.95 (m, 2H), 1.51 (s, 9H);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta/ppm = 160.98$  (d,  $J = 245.6$  Hz), 152.18, 131.7 (d,  $J = 4.7$  Hz), 131.6 (d,  $J = 6.4$  Hz), 131.3, 126.0 (d,  $J = 4.4$  Hz), 115.7 (d,  $J = 20.2$  Hz), 113.2 (d,  $J = 21.2$  Hz), 107.2, 81.8, 37.1, 31.7, 28.3;  $^{19}F$  NMR (282 MHz,  $CDCl_3$ ):  $\delta/ppm = -117.3$  HRMS (ESI-MS): Mass calc. for  $C_{15}H_{18}FNO_2Na$   $[M+Na]^+$ :  $m/z = 286.1214$ , found:  $m/z = 286.1218$ .

**tert-Butyl 5-bromo-1,2-dihydro-3H-benzo[d]azepine-3-carboxylate (3t)**



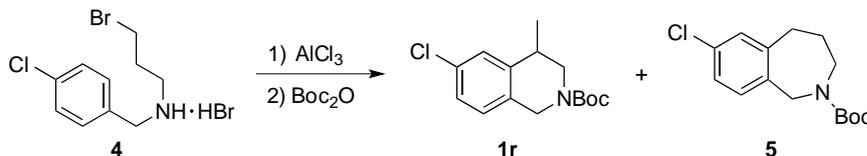
According to the general procedure using  $T^+BF_4^-$  (58.6 mg, 0.24 mmol, 1.5 equiv.), THIQ **1q** (50.0 mg, 0.16 mmol, 1.0 equiv.) and  $TMSCHN_2$  (2 M in  $Et_2O$ , 190  $\mu L$ , 0.380 mmol, 2.4 equiv.), the title compound was obtained after 1 h by flash column chromatography (petroleum ether  $\rightarrow$  petroleum ether: ethyl acetate 20:1) as a yellow oil (17.6 mg, 0.054 mmol, 34 %).  $^1H$  NRM (300 MHz,  $CDCl_3$ ):  $\delta/ppm = 7.35$  (d,  $J = 7.8$  Hz, 1H), 7.08 (d,  $J = 7.5$  Hz, 1H), 7.03 (bs, 1H), 6.97 (t,  $J = 7.7$  Hz, 1H), 5.49 (s, 1H), 3.88 (s, 2H), 3.26 (s, 2H), 1.51 (s, 9H);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta/ppm = 151.9, 137.5, 129.9, 129.7, 129.1, 127.7, 127.5, 124.7, 107.5, 82.0, 53.5, 35.7, 28.3$ ; HRMS (ESI-MS): Mass calc. for  $C_{15}H_{19}BrNO_2Na$   $[M+H]^+$ :  $m/z = 326.0575$ , found:  $m/z = 326.0575$ .

### 3-[(4-Chlorobenzyl)amino]-1-bromopropane hydrobromide<sup>4</sup>

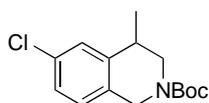


In a flame-dried round bottom schlenk, a solution of 4-chloro benzaldehyde (7.00 g, 50.0 mmol, 1.00 equiv.), 3-amino-1-propanol (3.80 g, 3.80 mL, 50.0 mmol, 1.00 equiv.) and EtOH (125 mL) was stirred under nitrogen at room temperature for 19 h. Solid NaBH<sub>4</sub> (2.50 g, 65.0 mmol, 1.30 equiv.) was portion wise added over 1 h (foam formation!), and the obtained mixture was stirred for another 4 h. A 1 M HCl water solution was added, and after neutralization the product was extracted with EtOAc. The collected organic fractions were dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure to afford the crude 1-(4-chloro-benzylamino)propyl alcohol, which was cooled in ice and dissolved in 48% HBr water solution (50 mL). The reaction mixture was concentrated (approx. 30 mL of solvent was distilled off) and the residue was cooled to 0 °C in an ice-bath. The resulting formed solid was filtered and recrystallized from MeOH-Et<sub>2</sub>O, affording the hydrobromide salt **4** as a white solid (7.01 g, 20.5 mmol, 41%). <sup>1</sup>H NMR (300 MHz, H<sub>2</sub>O): δ/ppm = 7.42-7.36 (m, 2H), 7.35-7.30 (m, 2H), 4.13 (s, 2H), 3.40 (t, *J* = 6.1 Hz, 2H), 3.12 (t, *J* = 6.2 Hz, 2H), 2.20-2.10 (m, 2H); <sup>13</sup>C NMR (75 MHz, H<sub>2</sub>O): δ/ppm = 148.3, 135.2, 131.4, 129.3, 50.4, 45.7, 29.5, 28.3; HRMS (ESI): Mass calc. for C<sub>10</sub>H<sub>14</sub>NCIBr·H [M+H]<sup>+</sup>: *m/z* = 263.9970, found: *m/z* = 263.9974.

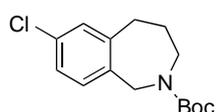
### *tert*-Butyl 6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (**1r**) and *tert*-butyl 7-chloro-1,2,4,5-tetrahydro-3H-benzo[d]azepine-3-carboxylate (**4g**)<sup>5</sup>



The salt **4** (3.00 g, 8.70 mmol, 1 equiv.) and NH<sub>4</sub>Cl (0.48 g, 9.00 mmol, 1.05 equiv.) were added under nitrogen in a flame-dried pressure schlenk pre-heated at 160 °C. AlCl<sub>3</sub> (5.80 g, 43.5 mmol, 5.00 equiv.) was then added over 5-10 min, causing the mixture to liquefy with the evolution of gas. After 15 min, the mixture was dissolved in 50 mL of ice-cooled 3 N HCl and basified with 40% NaOH. The product was extracted with EtOAc, the extract was washed with brine, dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure to afford the desired 6-membered ring cyclization product, along with the corresponding 7-membered ring product. Without further purification, the crude mixture was dissolved in DCM (50 mL) and di-*tert*-butyl dicarbonate (1.90 g, 0.87 mmol, 1.00 equiv.) was added. The result solution was stirred for 16 h at room temperature. The crude reaction mixture was washed with water and brine, dried over MgSO<sub>4</sub> and the solvent removed under reduced pressure. After flash chromatography (petroleum ether → petroleum ether: ethyl acetate 4:1), **1r** (1.25 g, 4.44 mmol, 51%) was obtained as yellow oil, along with **4g** (434.1 mg, 1.54 mmol, 18%).

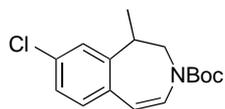


**1r**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ/ppm = 7.20-7.10 (m, 2H), 7.01 (bd, *J* = 7.0 Hz, 1H), 4.80-4.50 (m, 1H), 4.39 (bs, 1H), 3.50 (bs, 2H), 2.90 (bs, 1H), 1.48 (s, 8H), 1.25 (d, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ/ppm = 155.1, 141.8, 132.2, 131.6, 127.7, 127.53, 126.4, 80.0, 47.6, 45.0, 33.2, 28.5, 19.4; HRMS (CI-MS): Mass calc. for C<sub>15</sub>H<sub>20</sub>ClNO<sub>2</sub>·H [M+H]<sup>+</sup>: *m/z* = 282.1261, found: *m/z* = 282.1256.



**5:**  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.25-7.20 (m, 1H), 7.15-7.05 (m, 2H), 4.40-4.30 (m, 2H), 3.68-3.64 (m, 2H), 2.90-2.85 (m, 2H), 1.80-1.70 (m, 2H), 1.37 (s, 9H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 154.8, 144.0 and 143.5 (rotamers), 137.5 and 137.2 (rotamers), 132.8, 131.0 and 130.39 (rotamers), 129.6 and 129.4 (rotamers), 126.1 and 125.7 (rotamers), 79.8, 51.7 and 51.4 (rotamers), 50.7 and 50.3 (rotamers), 31.7, 28.5 and 27.9 (rotamers), 22.7.

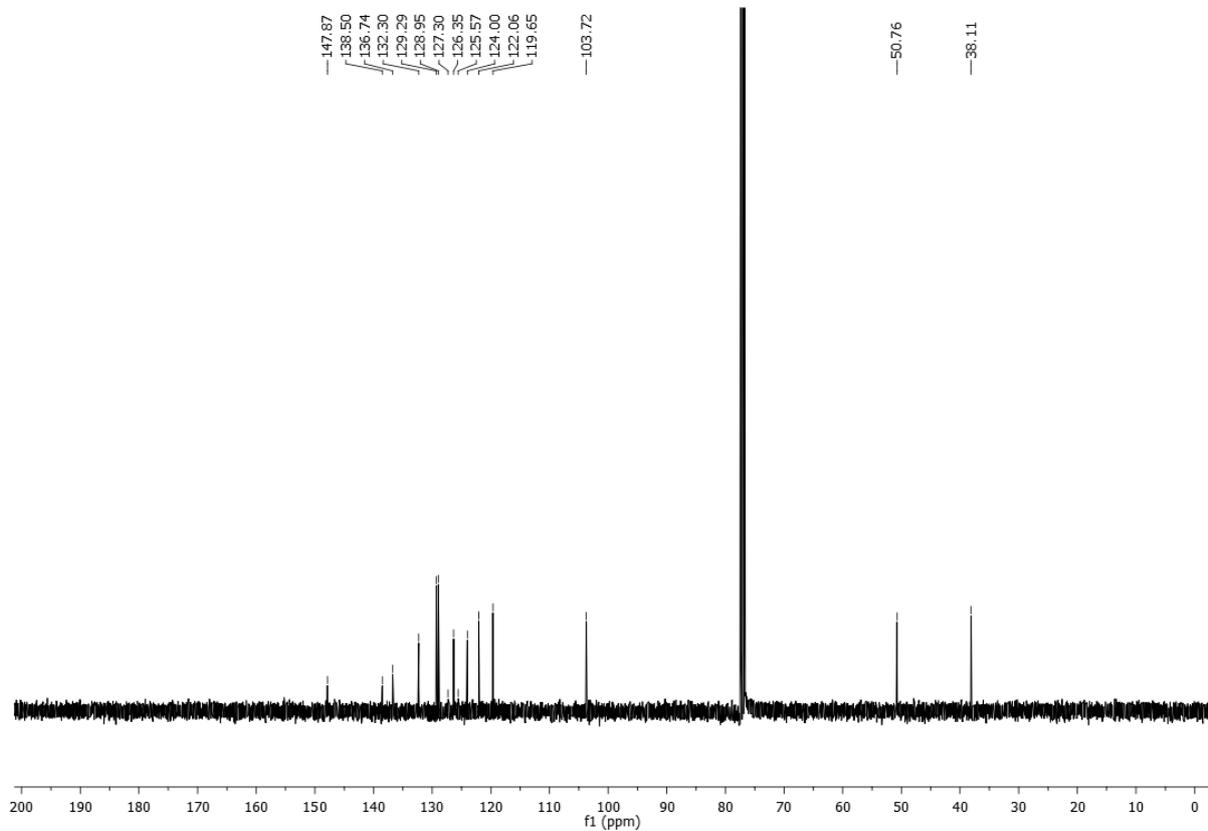
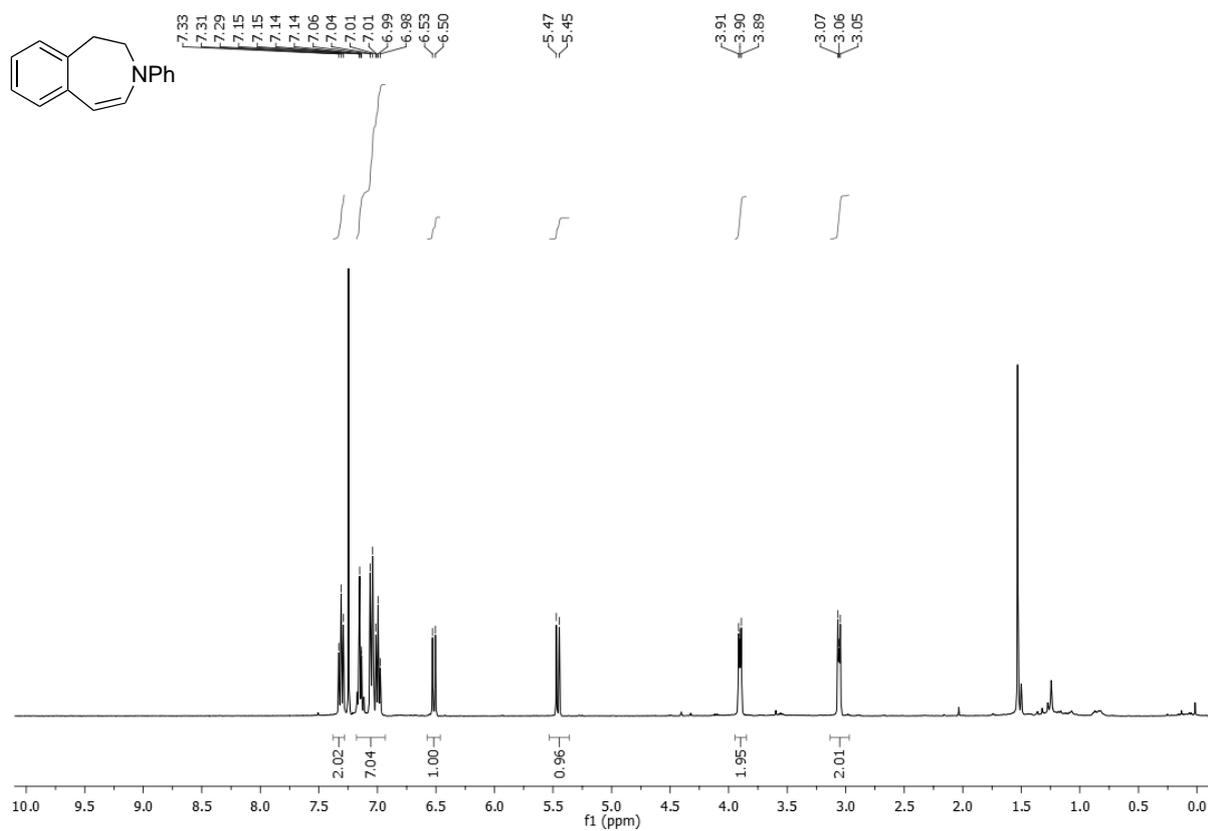
***tert*-Butyl 8-chloro-1-methyl-1,2-dihydro-3*H*-benzo[*d*]azepine-3-carboxylate (3u)**



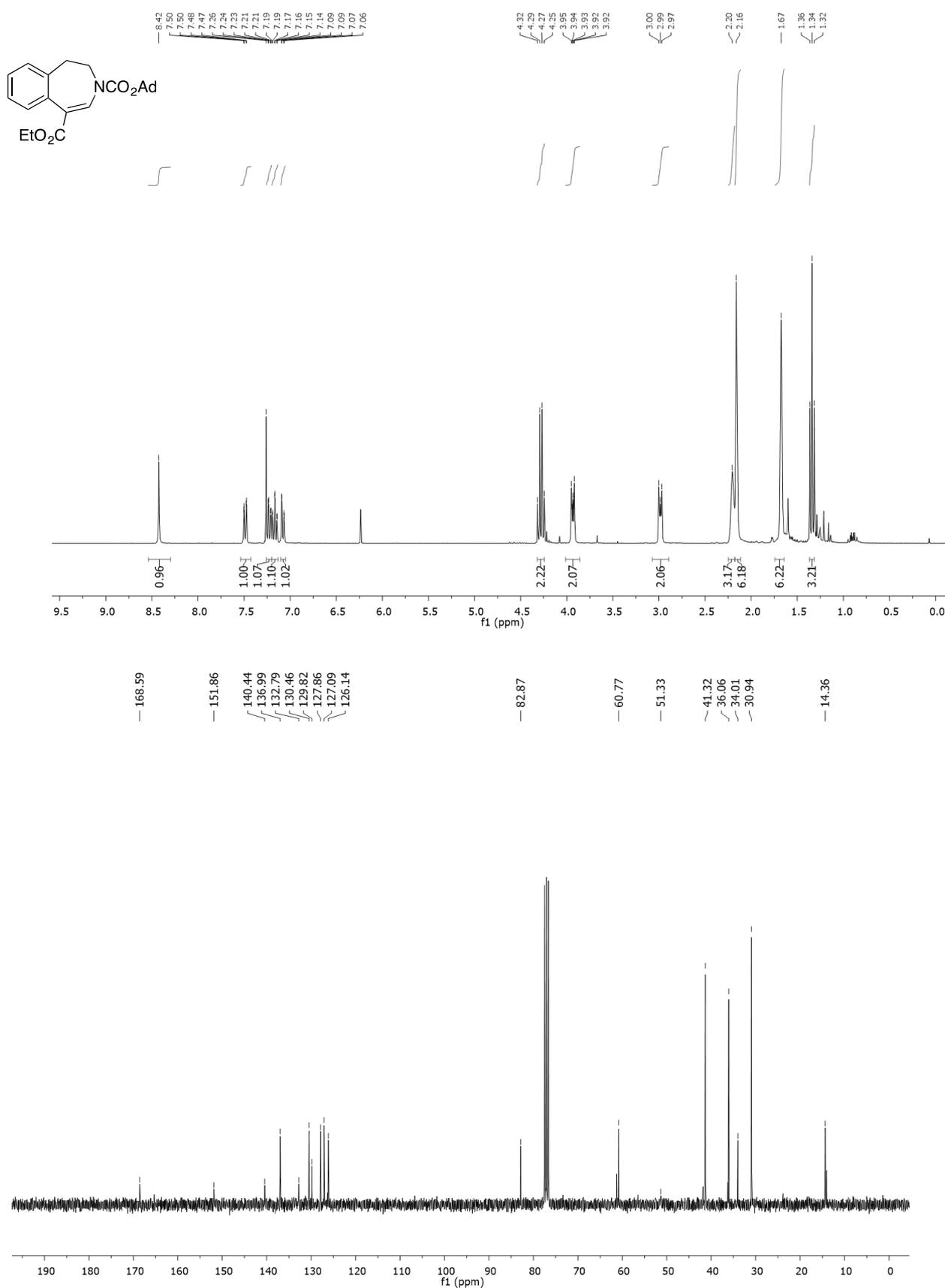
According to the general procedure for the expansion ring reaction, using  $\text{T}^+\text{BF}_4^-$  (732.2 mg, 3.00 mmol, 1.5 equiv.), **THIQ 1u** (563.5 mg, 2.00 mmol, 1.0 equiv.) and  $\text{TMSCHN}_2$  (2 M in  $\text{Et}_2\text{O}$ , 2.40 mL, 4.80 mmol, 2.4 equiv.), dichloromethane (20 mL), the title compound was obtained after 1 h by flash column chromatography (petroleum ether  $\rightarrow$  petroleum ether: ethyl acetate 19:1) as a yellow oil (159.0 mg, 0.54 mmol, 27%).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.15-7.05 (m, 3H), 6.91 (bs, 1H), 5.52 (bs, 1H), 4.52 (bs, 1H), 3.32-3.20 (m, 1H), 3.09 (d,  $J$  = 12.7 Hz, 1H), 1.52 (s, 9H), 1.08 (d,  $J$  = 7.2 Hz, 3H);  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 152.9, 145.8, 132.4, 132.3, 131.2, 128.4, 127.5, 126.4, 107.2, 81.8, 47.3, 40.8, 28.3, 16.6; **HRMS** (ESI-MS): Mass calc. for  $\text{C}_{17}\text{H}_{23}\text{NO}_4\text{Na}$   $[\text{M}+\text{Na}]^+$ :  $m/z$  = 316.1075, found:  $m/z$  = 316.1079

Selected NMR spectra

3-Phenyl-2,3-dihydro-1H-benzo[d]azepine (3a)



**3-(Adamantan-1-yl) 1-ethyl 4,5-dihydro-3H-benzo[d]azepine-1,3-dicarboxylate (3I)**



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- 4 C. D. Perchonok and J. A. Finkelstein, *J. Org. Chem.*, 1980, **45**, 2000.
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### 3.4.2 N-Based expansion ring reactions

#### *General Information and Materials:*

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded in  $\text{CDCl}_3$ , (reference signal:  $^1\text{H} = 7.26$  ppm,  $^{13}\text{C} = 77.16$  ppm,  $\text{CDCl}_3$ ) on a Bruker ARX-300 and a Varian AV-300, 400 or 600 MHz. Chemical shifts ( $\delta$ ) are given in ppm and spin-spin coupling constants (J) are given in Hz. Analytical thin layer chromatography was performed using silica gel 60 F254 and a solution of  $\text{KMnO}_4$  or a Iodine camera served as staining agent. Column chromatography was performed on silica gel 60 (0.040-0.063 mm). GM-MS (EI) analysis were performed with Shimadzu GC-MS QP 2010. MeCN was distilled over  $\text{CaH}_2$ . Other solvents and commercially available reagents were used without further purification.

#### *General procedure involving $\text{TMSONH}_2$ :*

In a screw-cap schlenk tube, the corresponding target 1 (0.4 mmol, 1.00 equiv.), catalyst (10-20 mol%) and additive were dissolved in distilled MeCN (1.00 mL).  $\text{TMSONH}_2$  (1.2 equiv.) and oxidant (1.2-2 equiv.) were added and the reaction mixture was stirred at the corresponding temperature for 18 h. The solvent was removed under reduced pressure to give the corresponding crude product.

#### *General procedure involving $\text{TMSN}_3$ :*

In a screw-cap schlenk tube, xanthene 1a (0.4 mmol, 1.00 equiv.), catalyst (10-20 mol%) and additive were dissolved in distilled MeCN (1.00 mL).  $\text{TMSN}_3$  (1.2 equiv.) and tert-butyl peroxide or di-tert-butyl peroxide (1.2 equiv.) were added and the reaction mixture was stirred at the corresponding temperature for 18 h. The solvent was removed under reduced pressure to give the corresponding crude product.

# 4

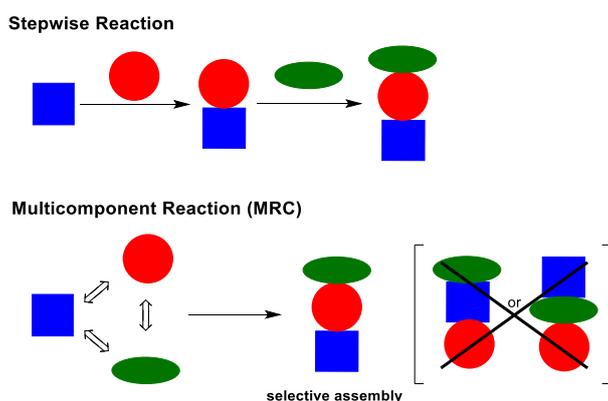
## Oxidative C-H functionalization/Ugi-type tandem reaction

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[1] Contents of table 6 entries **3qa**, **3qf**, **3ra** and **3rf** were performed by T. Brandhofer and S. Stockerl

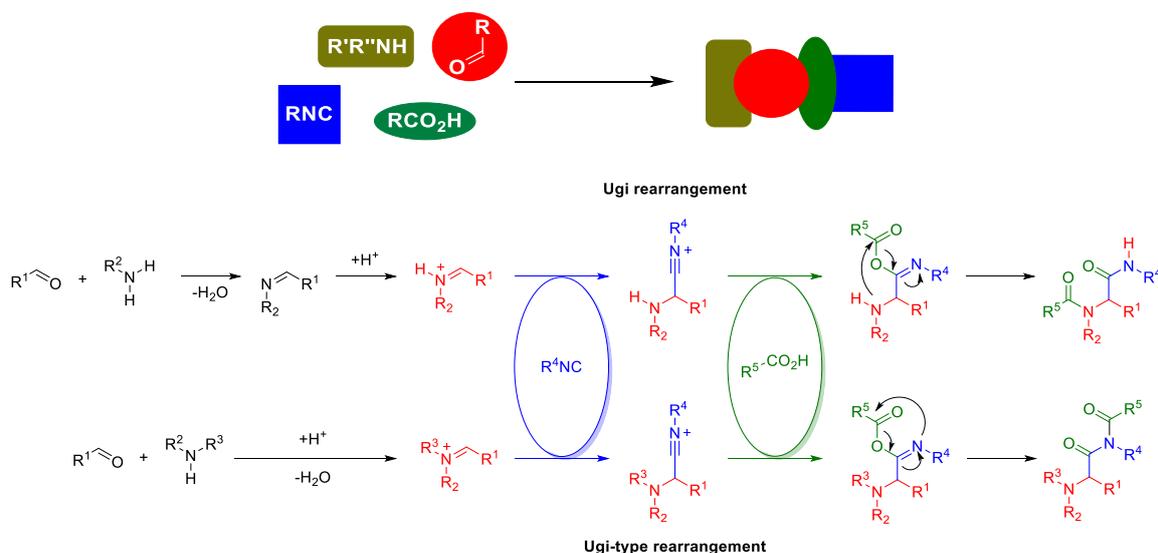
## 4.1 Introduction

Multicomponent Reactions (MCRs) – sometimes referred to as a "Multi-component Assembly Process" – imply the reaction of three or more reactants placed together in a single reaction vessel. The mechanism of such transformations involves linear and parallel sequences or a cascade of elementary chemical reactions to assemble a single product that contain essentially all or most of the atoms of the reactants in its final structure.<sup>1h,1i</sup> The main challenge in the design and discovery of new MCRs rely on the generated network of multiple pre-equilibrated reactions between the different reactants. Therefore, it is crucial to carefully tune the reaction conditions (catalyst, temperature, solvent, nature of starting materials, etc), in order to drive the reaction into a main product, avoiding the formation of undesired side-products (Figure 1).<sup>1d</sup>



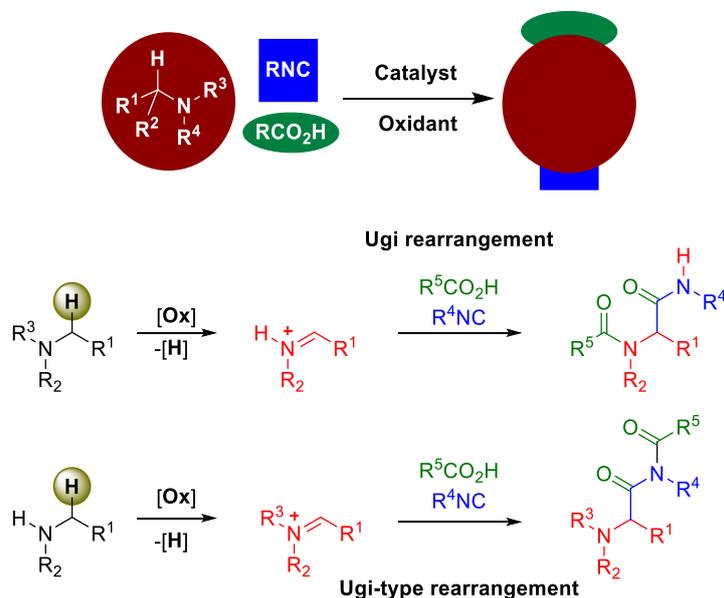
**Figure 1.** Concept of Multicomponent Reaction (MRC)

Among the MCRs, the Ugi-type reaction, discovered in 1959 by I. Ugi,<sup>1a</sup> is a potent and convenient methodology for the ready accessible synthesis of a large variety of bisamides (Scheme 1, top) and imides (Scheme 1, bottom).<sup>1</sup> With this approach, in which amines, aldehydes (or ketones), isocyanides and carboxylic acids are combined, a wide range of natural products and bioactive compounds,<sup>2</sup> as well as intermediates for the synthesis of different heterocycles,<sup>3</sup> are easily available.



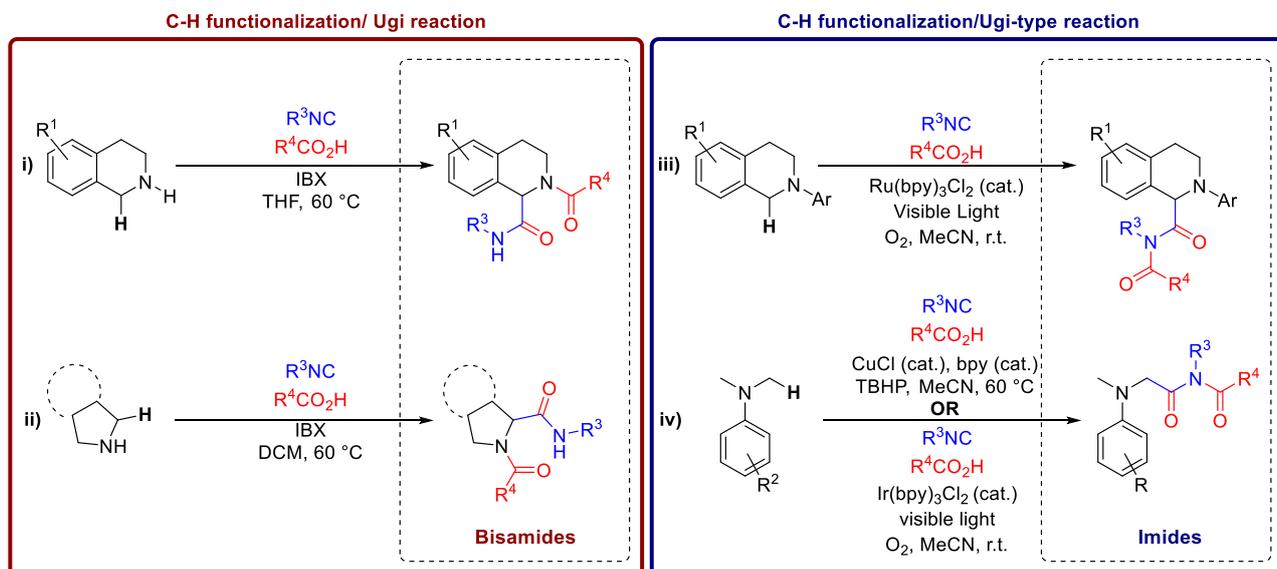
**Scheme 1.** Ugi and Ugi-type multicomponent reactions.

From the atom- and step-economy perspective of such transformation, the development of new processes based on the Ugi-type reaction is highly attractive. Especially interesting is the formation of the key imine or iminium salt intermediate by a direct C-H bond activation of a simple substrate or a more complex envisioned target (Scheme 2).



**Scheme 2.** Oxidative Ugi-type reaction approach.

Despite the multitude of diverse and outstanding applications developed in the past decades, examples of Ugi-type reactions, in which the imines or the iminium salts are formed in an oxidative manner, have only been reported in the last few years (Scheme 3). In this context, even though the potential of such promising strategies, there are still some important limitations. As far as we know, the reported applications are limited to common substrates, such as tetrahydroisoquinolines (THIQs)<sup>4</sup> (Scheme 3, i and iii) and *N,N*-dialkyl substituted anilines<sup>5</sup> (Scheme 3, iv). In addition to those known targets in oxidative C-H functionalization, R. V. A Orru and co-workers recently reported a similar approach on bi/tri-cyclic *NH*-pyrrolidines towards the corresponding bisamides (Scheme 3, ii).<sup>6</sup>



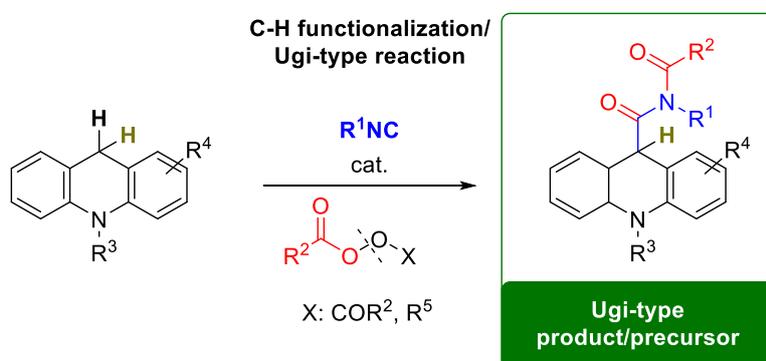
**Scheme 3.** Previously reported C-H functionalization/Ugi-type reaction in alpha to amines.

More in detail, the two reported procedures concerning the functionalization of THIQs resulted very attractive, especially regarding the achieved yields and functional group tolerance (Scheme 2, eq. i and iii). Instead, N,N-dimethyl anilines resulted a less performing substrate class under the reported conditions, leading to moderate average yields on the Ugi-products. Furthermore, in the case of the procedure developed by T. Xie and co-workers using Cu-catalysis and TBHP as oxidant (Scheme 3, eq. iv-top conditions),<sup>5a</sup> the method was also limited to electron-neutral and electron-poor anilines. However, in all the reported substrates the functionalization takes place on the Csp<sup>3</sup>-H bond next to a nitrogen atom, leading to an iminium salt or an imine active intermediate. By this means, all the potentiality of the oxidative C-H bond functionalization to activate unusual substrate for Ugi-type reactions resulted unexpressed. In addition, difficult applications in many synthetic strategies towards highly valuable molecules might be achieved by fully exploiting the direct C-H bond functionalization technology. Following this perspective, it is evident the demand of new methodologies that can increase the number of accessible targets by a Csp<sup>3</sup>-H bond activation/Ugi-type approach. Moreover, it would provide new possibilities to employ this strategy in the ready-to-shape synthesis of products with relevant proprieties.

## 4.2 Objectives

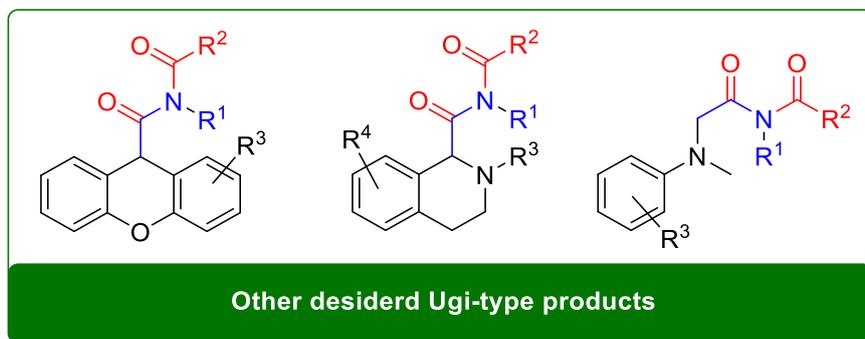
Following our experience in the oxidative functionalization of dibenzyl Csp<sup>3</sup>-H bonds, we envisioned the suitability of the Ugi-type rearrangement on carbocation intermediates like the involved during the activation of acridane and xanthene derivatives previously described in section 3.1. To the best of our knowledge, the class of compounds that will be obtained in this way was not reported to date.

Following this perspective, the main goal of this project was the development of a versatile methodology for the first oxidative benzylic C-H bond functionalization/Ugi-type reaction. In addition, we aimed at performing the reaction in an easy and green way, by employing diacylperoxide or acylalkylperoxide reagents as both the oxidant and the required source of carboxylic acid for this multicomponent transformation (Scheme 4).



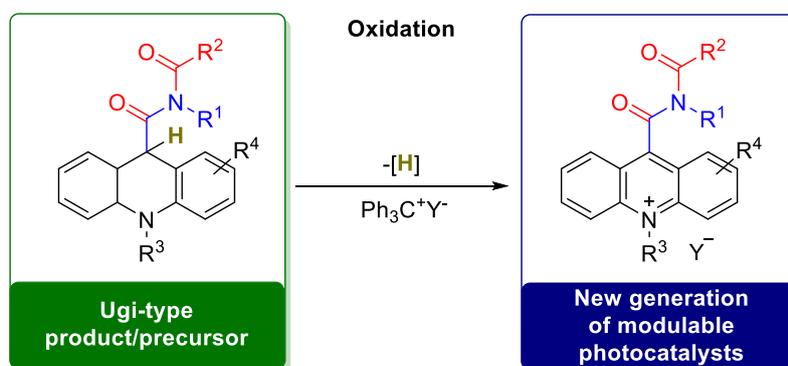
**Scheme 4.** Our direct Csp<sup>3</sup>-H functionalization/Ugi-type reaction proposal.

To proof the potentiality of this approach, the method will be extended to several diverse targets. Thus, further dibenzylic substrates such as xanthenes will be studied, as well as tetrahydroisoquinolines and N,N-dimethyl anilines to be able to compare the new developed method with the already reported systems (Scheme 5).



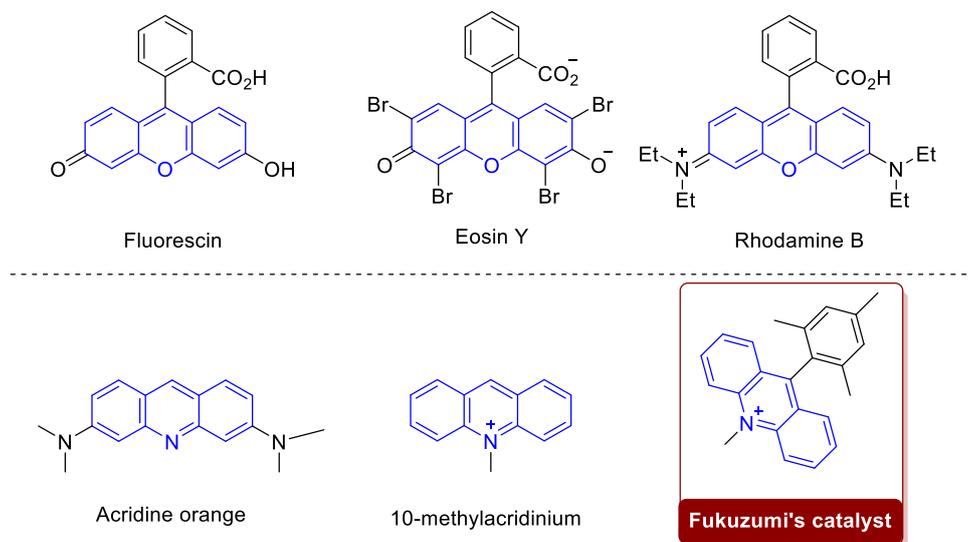
**Scheme 5.** Extension to other target classes.

Finally, we envisioned that the imide-acridine products of the Ugi-type reaction will be highly interesting for the synthesis of novel “ready-to-shape” class of photocatalyst based on the acridane scaffold (Scheme 6).



**Scheme 6.** Application of the Ugi-products for a novel photocatalyst-design.

We figured out this possibility starting from the several well established photocatalysts containing xanthene or acridane scaffolds as main core (Figure 2).<sup>7,8</sup>



**Figure 2.** Example of acridinium- and xanthene-based dyes.

In this context, one of the most recent developed and potent oxidant organo-photocatalyst is the 9-mesityl acridinium salt,<sup>8</sup> also called Fukuzumi's catalyst. This catalyst was designed by S. Fukuzumi in 2004 to solve the susceptibility of acridinium salts to the nucleophilic and radical addition, by the introduction of a mesityl group in 9-position.<sup>8a</sup> However, although this protection highly stabilizes the catalyst, its remarkable electrochemical performances are still lower than the corresponding 10-methyl-acridinium salt.<sup>7e</sup> Thus, the development of novel class of 9-substituted acridinium derivatives is strongly demanding, both to preserve the stability of such potent class of photocatalysts and to enhance the electrochemical proprieties.

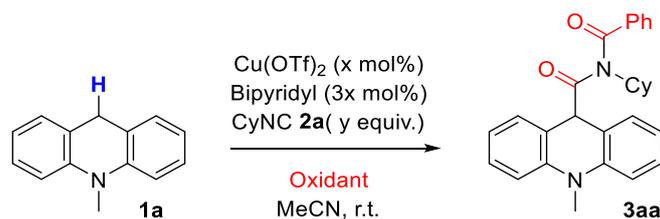
## 4.3 Result and discussion

### 4.3.1 Acridanes as target substrates

Based on our previous work on acridane and xanthene C-H functionalization, we started our screening on the C-H oxidation/Ugi-type reaction of 10-methyl acridane (**1a**) (Table 1). Accordingly, our developed Cu(OTf)<sub>2</sub>/bipyridyl/benzoyl peroxide (BPO) oxidative system was employed with 1.2 equivalents cyclohexyl isocyanide (**2a**) as nucleophilic reactant (entry 1). In this case, the reagent BPO has a double role as both the oxidant and the carboxylic acid or carboxylate source. Therefore, the addition of external carboxylic acids was not required to obtain the desired imide Ugi-products. The initial obtained result was very promising, leading to **3aa** in 29% yield, but further improvements were needed. In order to optimise the reaction, several peroxide systems were then tested (Table 1, entries 2-3). Unexpectedly, when we used hydroperoxides such as *t*BuOOH (TBHP) in the presence of benzoic acid as additive, which was already described in oxidative Ugi reactions with other type of targets, the formation of the desire product was not observed by <sup>1</sup>H-NMR or GC-MS (Table 1, entry 2). Two of the main issues of this reaction are the low stability of the products **3** under oxidative conditions, as well as the competition between the desired Ugi-type reaction and the formation of oxidised side-products

such as 10-methylacridone. Thus, to avoid the formation of undesired by-products, a shorter reaction time and a higher amount of isocyanide were analysed.

**Table 1.** Optimization of the reaction conditions.<sup>[a]</sup>



Entry	Cu(OTf) <sub>2</sub> (mol%) <sup>[b]</sup>	Oxidant (equiv.)	CyNC (equiv.)	Time (h)	Yield (%) <sup>[c]</sup>
1	10%	(PhCO <sub>2</sub> ) <sub>2</sub> (1.2)	1.2	18	29
2	10%	<i>t</i> BuOOH (1.2) /PhCO <sub>2</sub> H	1.2	18	--
3	10%	<i>t</i> BuO- <i>Ot</i> Bu (1.2) /PhCO <sub>2</sub> H	1.2	18	--
4	10%	(PhCO <sub>2</sub> ) <sub>2</sub> (1.2)	2.4	18	36
5	10%	(PhCO <sub>2</sub> ) <sub>2</sub> (1.2)	2.4	4	49
6	10%	(PhCO <sub>2</sub> ) <sub>2</sub> (1.2)	2	4	61
7 <sup>[d]</sup>	10%	(PhCO <sub>2</sub> ) <sub>2</sub> (1.2)	2	4	66
8 <sup>[e]</sup>	10%	(PhCO <sub>2</sub> ) <sub>2</sub> (1.2)	2	4	35
9	15%	(PhCO <sub>2</sub> ) <sub>2</sub> (1.2)	2	4	42
10	5%	(PhCO <sub>2</sub> ) <sub>2</sub> (1.2)	2	4	53
11	10%	(PhCO <sub>2</sub> ) <sub>2</sub> (1.5)	2	4	22

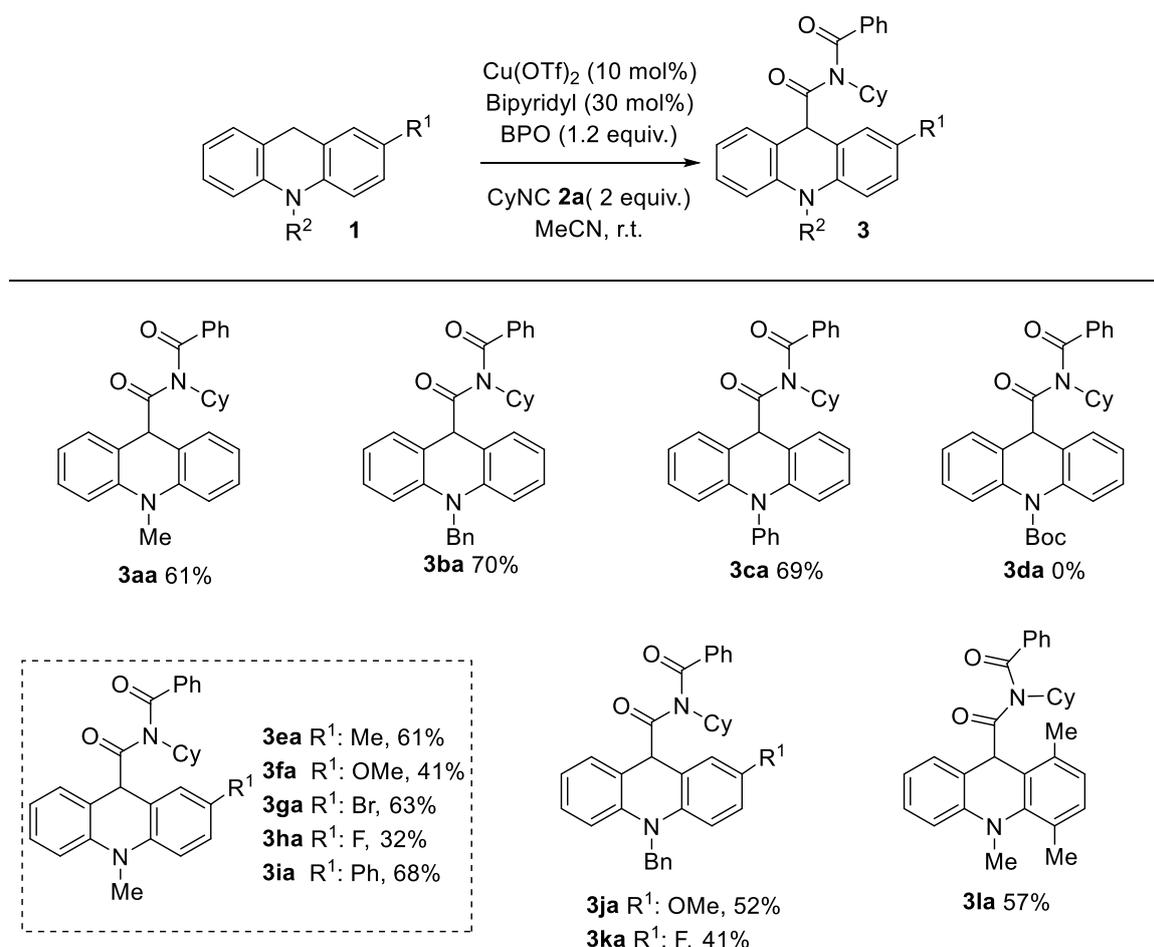
[a] **1a** (0.1-0.4 mmol), peroxide, Cu(OTf)<sub>2</sub>, bipyridyl, and CyNC in MeCN (0.1 M) at the room temperature in a sealed tube. [b] Cu(OTf)<sub>2</sub> was pre-dried under vacuum at 60°C. [c] Isolated yields. [d] 2 mmol scale reaction. [e] Cu(OTf)<sub>2</sub> was not pre-dried.

We found that the use of 2 equivalents of **2a** and 4 hours reaction time led to the best results, providing the desired product **3aa** in a synthetically useful 61% yield (Table 1, entry 6). Noteworthy, under the same conditions, a larger scale reaction (2.0 vs. 0.1 mmol) gave a slightly better result (66% yield, Table 1, entry 7). However, during the development of the strategy we encountered some important issues regarding the reproducibility of the methodology. For example, traces of moisture brought to a not efficient reactivity of the oxidative system, especially concerning the catalyst. The Cu(OTf)<sub>2</sub> needed to be pre-dried for several hours at 50/60 °C under vacuum to achieve an adequate and reproducible reactivity. In this context, under the best condition but involving wet or no properly dry catalysts, we observed various inconsistent performances with yields up to 35% were observed (Table 1). However, the use of a dried catalyst stored in the glove box did not improve the yield. It is interesting to note that the

reaction is also sensitive to the addition order of the reagents. To avoid undesired side-reaction of acridane, the oxidant must be the last component added, and it is recommended to mix the  $\text{Cu}(\text{OTf})_2$  and the bpy before adding the other reagent to form a more active pre-catalyst. Finally, the increase of the amount of the isocyanide (2.4 equiv., entry 5), the catalyst (15 vs. 10 mol%, entry 9) or the oxidant (1.5 vs. 1.2 equiv., entry 11) led in all cases to a lower performance.

Next, with the best conditions in our hand, several different substituted acridanes were enrolled in the process (Table 2). Methyl, benzyl and phenyl N-protecting groups were well tolerated, giving the desired products in good yields (61-70%). Instead, N-carbamoyl acridanes, such as N-Boc protected derivative **1d**, were not participating in the reaction, leading mainly to over-oxidised and decomposition products. In one hand, the performances with acridanes containing weak electron donating (**1e** and **1i**,  $\text{R}^1 = \text{Me}$  and  $\text{Ph}$ ) or weak electron withdrawing substituents (**1g**,  $\text{R}^1 = \text{Br}$ ) were comparable with the unsubstituted pattern substrate **1a**. In other hand, strong electron donating (**1f**,  $\text{R}^1 = \text{OMe}$ ) or strong electron withdrawing groups (**1h**,  $\text{R}^1 = \text{F}$ ) lead to lower yields (32-41% yields). It is noteworthy to point out that the N-benzyl acridanes showed a superior reactivity than the N-methyl derivatives, giving better results even in the more demanding cases (**3ja** 52% vs. **3fa** 41% and **3ka** 41% vs. **3ha** 32%). It is also interesting to note that the steric hindered substrate **1l** (1,4-dimethyl substituted) was also well tolerated, leading to **3la** in a good 57% yield.

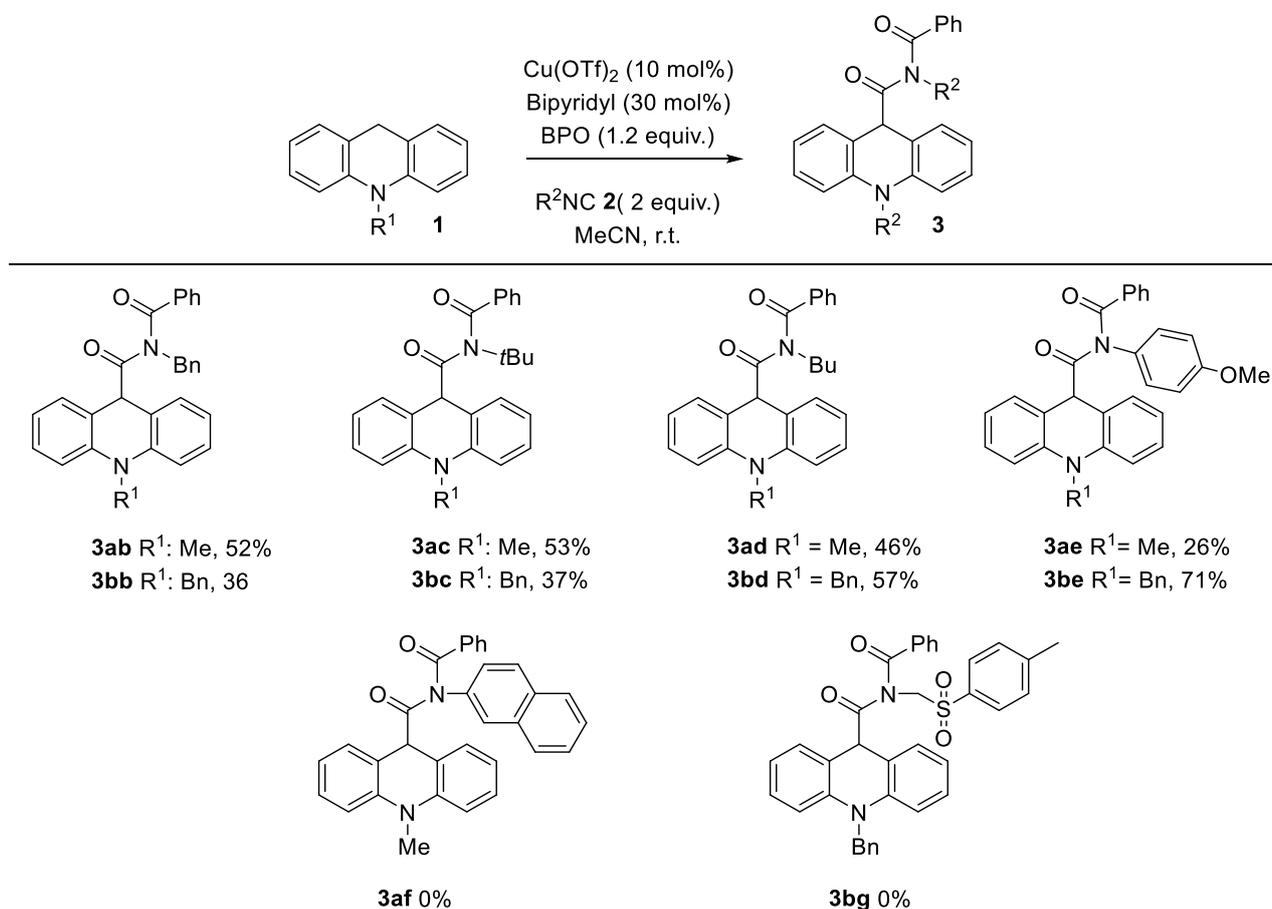
**Table 2.** Scope: Screening of different acridanes. [a][b]



[a] **1** (0.1-0.4 mmol), BPO (1.2 equiv.), pre-dried  $\text{Cu}(\text{OTf})_2$  (10 mol%), bipyridyl (30 mol%) and CyNC (2 equiv.) in MeCN (0.1 M) at the room temperature in a sealed tube. [b] Isolated yields.

We tested various isocyanides with both N-methyl (**1a**) and N-benzyl (**1b**) acridanes as targets for the C-H functionalization/Ugi-type reaction (Table 3). In this case, the steric hindrance showed an important role in the trend of the reaction. Indeed, when large isocyanide, such as naphthyl isocyanides (**2f**) or 1-((isocyanomethyl)sulfonyl)-4-methylbenzene (**2g**) were involved in the process, the product was observed in traces among several decomposition side-products. Furthermore, the steric hindrance influenced the performances of benzyl isocyanide (**2b**) and *tert*-butyl isocyanide (**2c**) when involved in the reaction. As consequence, comparing N-methyl acridane (**1a**) and N-benzyl acridane (**1b**), a significant lower yield was observed with **1b** due to the bigger protecting group (**3ab** 52% *vs.* **3bb** 36%, **3ac** 53% *vs.* **3bc** 37%). Instead, the less steric hindered *n*-butyl isocyanide (**2d**) and *para*-methoxy phenyl isocyanide (**2e**) gave better results with N-benzyl acridane **1b**, following the same trend that we observed with the cyclohexyl isocyanide.

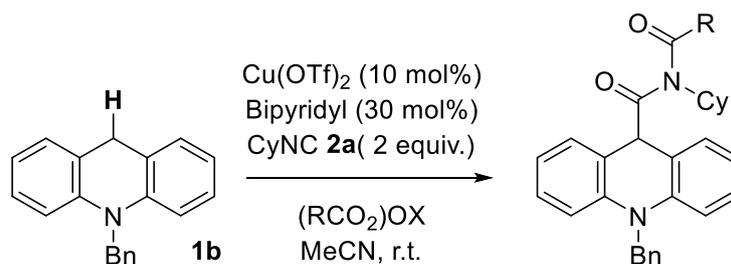
**Table 3.** Scope: Screening of different isocyanides. <sup>[a][b]</sup>



[a] **1** (0.1-0.4 mmol), BPO (1.2 equiv.), pre-dried Cu(OTf)<sub>2</sub> (10 mol%), bipyridyl (30 mol%) and CyNC (2 equiv.) in MeCN (0.1 M) at the room temperature in a sealed tube. [b] Isolated yields.

Next, several acyl peroxides were tested using as target the N-benzyl acridane. First, we enrolled a dialkyl or a non-symmetric peroxide containing a benzoyl moiety, such as dilauroylperoxid and benzoyl *tert*-butyl peroxide, respectively (Table 4, entries 1 and 2). However, none of them provided the Ugi product. Instead, the bis(2,4-dichlorobenzoyl) peroxide mediated the reaction, even though the desired product **4bb** was obtained in a low 18% yield (Table 4, entry 3). The reason of this poor reactivity could be related to the polymer in which this commercial peroxide is stabilised (50% w/w in polysiloxane), from which it cannot be easily and safely separated

**Table 4.** Scope: testing other peroxides. <sup>[a][b]</sup>

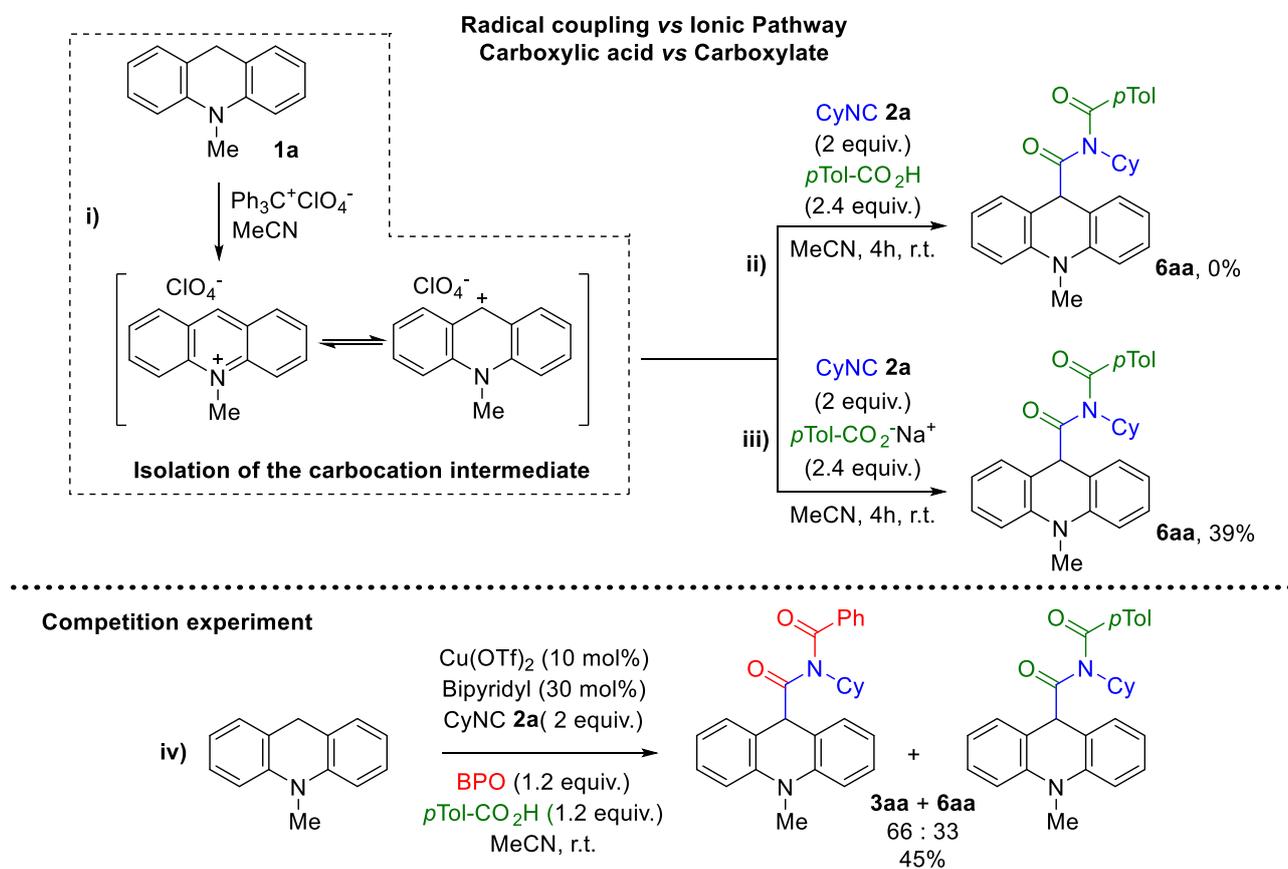


Entry	Oxidant	R	Yield (%) <sup>[b]</sup>
1	(PhCO <sub>2</sub> )- <i>Ot</i> Bu	PhCO <sub>2</sub> - ( <b>3ba</b> )	--
2	( <i>n</i> C <sub>11</sub> H <sub>23</sub> CO <sub>2</sub> ) <sub>2</sub>	<i>n</i> C <sub>11</sub> H <sub>23</sub> CO <sub>2</sub> - ( <b>4ba</b> )	--
3	[2,4-(Cl) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CO <sub>2</sub> ] <sub>2</sub> <sup>[c]</sup>	2,4-(Cl) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CO <sub>2</sub> - ( <b>5ba</b> )	18

[a] **1a** (0.15-0.2 mmol), oxidant (1.2 equiv.), pre-dried Cu(OTf)<sub>2</sub> (10 mol%), bipyridyl (30 mol%) and CyNC **2a** (2 equiv.) in MeCN (0.1 M) at the room temperature in a sealed tube. [b] Isolated yields. [c] 2,4-dichlorobenzoyl peroxide 50% w/w in polysiloxane.

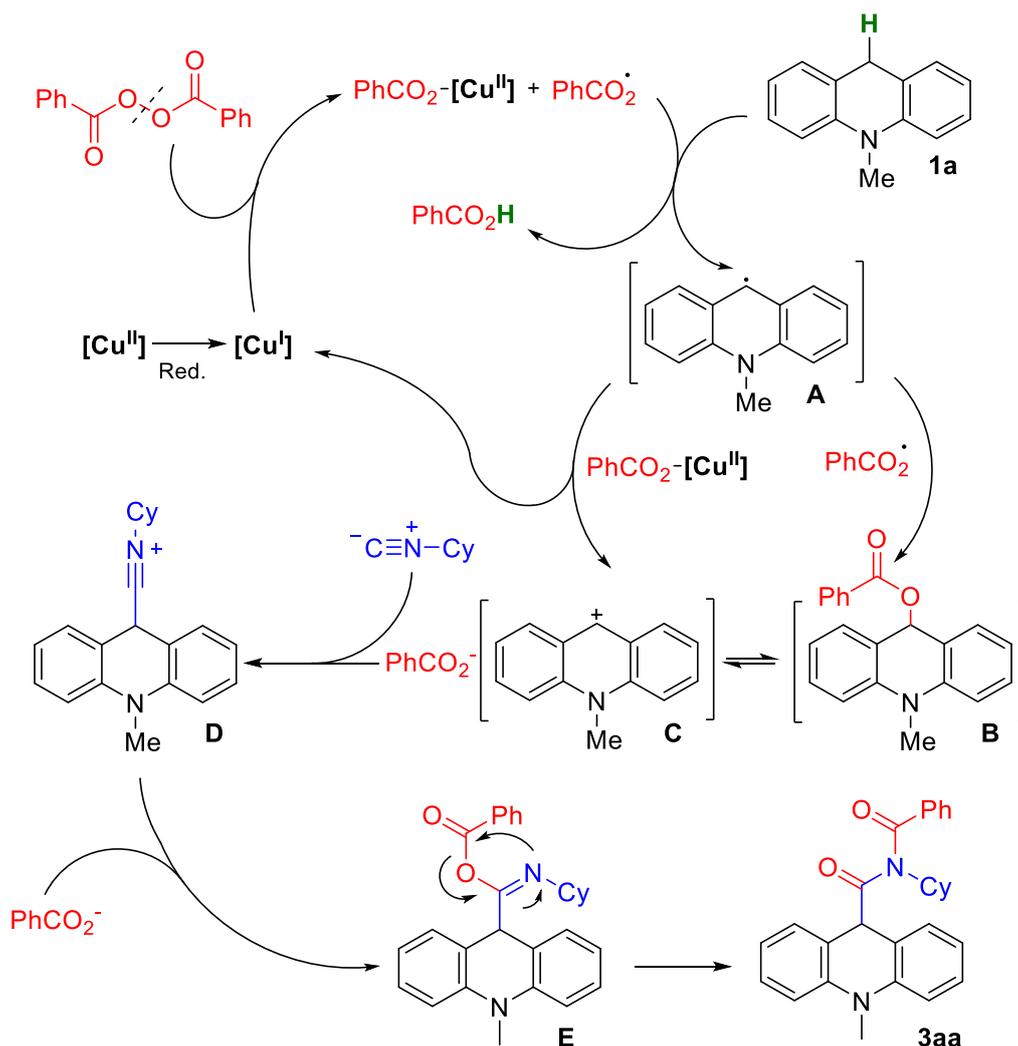
### 4.3.2 Reactivity and Mechanistic Studies

Aiming at bringing some light into the mechanism of the reaction, several experiments were carried out to understand which species were involved in the reaction (Scheme 7). In first instance, we prepared and isolated the N-methyl acridinium salt **1a'** by simple oxidation of the acridane **1a**, using the mild oxidant trityl tetrafluoroborate (Scheme 7, eq. i). Next, **1a'** was enrolled in two classical Ugi-type reactions using only cyclohexyl isocyanide (**2a**) and *p*-toluic acid or sodium *p*-toluate (Scheme 7, eq. ii and iii). Even though a carboxylic acid is commonly used as reagent in the standard procedures for the Ugi-type methodology, when *p*-toluic acid was enrolled in the reaction with **1a'**, just traces of the desire product among polymeric side-products were observed (Scheme 7, eq. ii). Instead, the reaction with the corresponding carboxylate proceed efficiently, leading the Ugi product **6aa** in 39% yield. Thus, These results strongly suggest that the acridinium salt is involved in the reaction as active acridane intermediate, and the carboxylate derived from the benzoyl peroxide resulted the real partner in our developed approach (Scheme 7, eq. iii). Next, an interesting competition experiment was performed between the *in situ* formed side product/reagent of the diacyl peroxide, such as benzoic acid and an external carboxylic acid with similar pKa, such as *p*-toluic acid (Scheme 7, eq. iv). We found both the possible Ugi-type products, **3aa** and **6aa**, in 49% yield overall, and a complete statistical ratio (**3aa** : **6aa**, 66 : 33). Indeed, the optimized conditions were involving 1.2 equivalent of benzoyl peroxide, forming at most 2.4 equivalents of a benzoic acid/benzoate mixture. Considering that 1.2 equivalents of the external carboxylic acid were added in the reaction mixture, the ratio between the two carboxylate sources (2:1) determine their contribution and observed outcome of the reaction.



**Scheme 7.** Mechanistic experiments.

Based on all the experimental observations and the experience of the García's group regarding the oxidative functionalization of acridanes (Chapter 3.1), a reaction mechanism was postulated (Scheme 8). A first copper(I)-catalysed reductive homolytic cleavage of the O-O bond of the benzoyl peroxide gave a benzoyl radical, which can abstract one hydrogen atom from the acridane substrate **1a** giving the radical intermediate **A**. Next, a second oxidation of **A**, promoted by the copper(II), formed the active carbocation intermediate **C**. Noteworthy, another possible pathway for the formation of **C** involved a radical coupling between the benzoyl radical and **A**, forming the unstable covalent intermediate **B**, which is in equilibrium with **C**. The addition of the isocyanide and the benzoate formed the intermediate **E**, which underwent rapidly in a rearrangement process to give the desire product **3aa**.

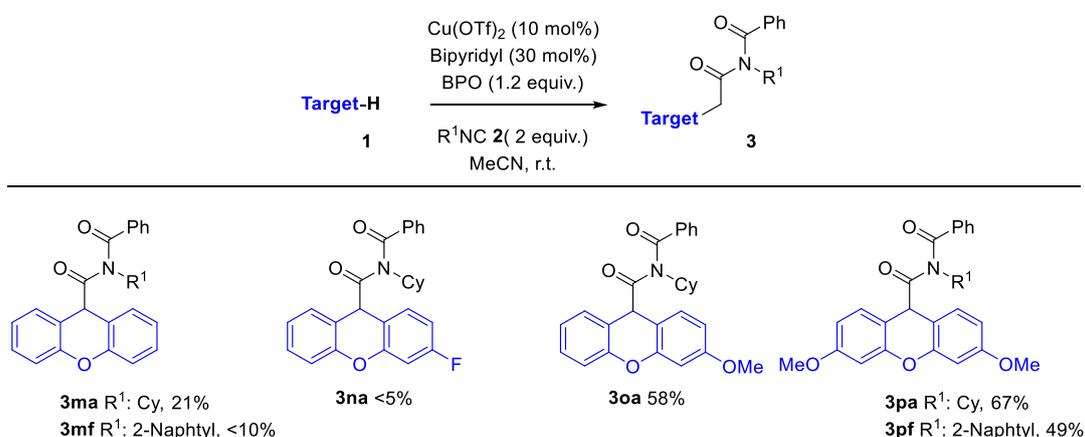


**Scheme 8.** Proposed mechanism.

### 4.3.3 Extension to other substrate classes

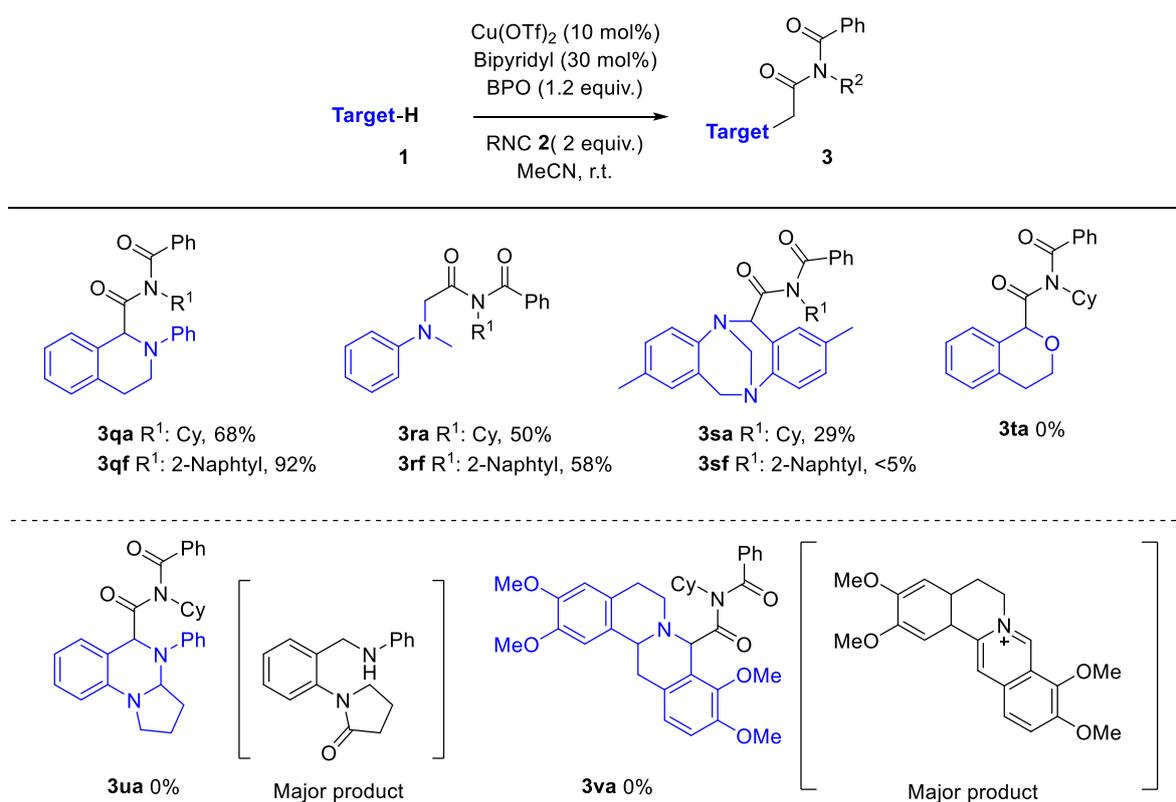
To proof the potentiality of the above-developed oxidative Ugi-type methodology, several diverse targets were next explored under the standard conditions using cyclohexyl isocyanide (**2a**) or 2-naphthyl isocyanide (**2m**) as nucleophilic reagent. These two isocyanides were selected to control the standard reactivity and the influence of the steric hindrance. In first instance, further dibenzylic substrates, such as various substituted xanthenes, were enrolled in the process (Table 5). The pattern unsubstituted xanthene (**1m**), which is less electron rich than the corresponding acridanes, could be enrolled in the reaction, providing the Ugi-products in moderate (21%, R<sup>1</sup> = Cy) and low yields (<10%, R<sup>1</sup> = 2-naphth). Similarly, electron poor xanthenes such as **1n** led to low conversions and yields. Interestingly, electron-rich xanthenes bearing methoxy groups granted good yields with **2a** (**3oa**, 58% and **3pa**, 67%). In addition, the bulky isocyanide **2f** was also suitable with electron-rich xanthenes, providing the products in an only slightly lower yield (**3pf**, 49%).

**Table 5.** Other dibenzylic substrates.<sup>[a][b]</sup>



[a] **1** (0.2 mmol), BPO (1.2 equiv.), pre-dried Cu(OTf)<sub>2</sub> (10 mol%), bipyridyl (30 mol%) and RNC (2 equiv.) in MeCN (0.1 M) at the room temperature in a sealed tube overnight. [b] Isolated yield.

Common substrates in the C-H bond functionalization/Ugi-type approach, such as THIQ (**1q**) and N,N-dimethyl aniline (**1r**) were next investigated (Table 6). Surprisingly, those targets gave better results with the bulkier isocyanide **2m** in comparison with **2a**, leading to almost a quantitative yield in the case of the THIQs (**3qf**, 92%) and a good yield for the N,N-dimethyl aniline (**3rf**, 58%). The steric issue revealed itself as prominent on dibenzylic xanthene and acridane-like structures. Moreover, the steric demanding target **1s**, also called the Tröger's base,<sup>9</sup> poorly reacted with **2a** (**3sa**, 29%), and only traces of the desire product were observed when bulky **2f** was enrolled in the process (**3sf**). However, when smaller substrate were employed, such as **1q** and **1r**, this effect was not observed.

**Table 6.** Other enrolled substrates with  $\alpha$ -Csp<sup>3</sup>-H bonds to a heteroatom [a][b]

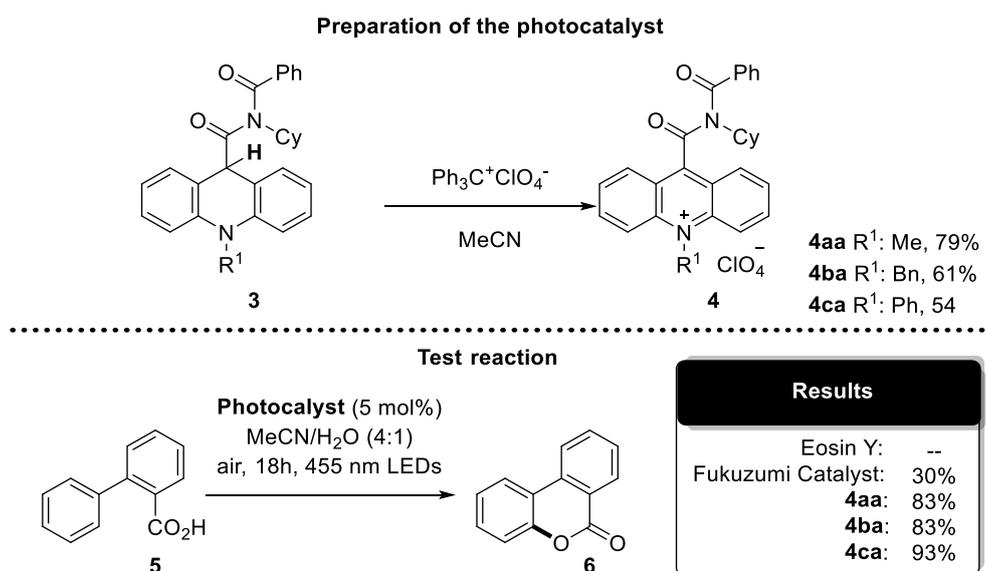
[a] **1** (0.2 mmol), BPO (1.2 equiv.), pre-dried Cu(OTf)<sub>2</sub> (10 mol%), bipyridyl (30 mol%) and RNC (2 equiv.) in MeCN (0.1 M) at the room temperature in a sealed tube. [b] Isolated yield.

It should be noticed that the employed oxidative system resulted not suitable for the activation of few other type of substrates. Thus, it was actually too weak for allowing the functionalization of isochromane. Furthermore, in the case of a more complex and highly oxidation-sensitive molecule and natural product **1u** and **1v**, respectively, our conditions resulted too strong. Consequently, we could only observe the decomposition (**3ua**) or the aromatization of the starting material (**3va**).

## 4.4 Conclusions and Outlooks

In conclusion, we introduced a new general and high modifiable strategy for the synthesis of a new class of C9-imide substituted acridanes by a novel oxidative Csp<sup>3</sup>-H bond functionalization/Ugi-type reaction. The method is very robust and applicable to a large variety of target molecules bearing different functional groups. Indeed, beside the acridane moiety, several diverse C-H functionalization/Ugi-type reactions on common and unusual targets were also achieved, leading in most cases to the desired imide-type products in good yields. Furthermore, in a green chemistry perspective, the involvement of the oxidant side-products in the Ugi-type step of the process is an outstanding innovation compared to the standard approaches in C-H bond activation/Ugi-type reaction, in which the crude product is given along with the excess of the oxidant and the unwanted oxidant by-products. This developed mild oxidative and atom-economic methodology could also be extended to xanthenes, tetrahydroisoquinolines, N,N-dimethyl anilines and further more complex substrates.

Finally, the acridinium salts **4** – derived from the acridane Ugi-type products **3** upon a selective, mild second oxidation step – showed outstanding photochemical properties, eclipsing the most common commercial available acridinium photocatalyst in a test reaction (Scheme 9).



**Scheme 9.** Preliminary results for the application in photocatalysis.

These preliminary results in the group already showed the interesting properties and reactivity of these structural unprecedented imide-acridinium-based organophotocatalysts, providing new opportunities for the future development on innovative visible light driven transformations. It is evident that this promising class of organophotocatalysts has the potential to become a new standard structure motif in photocatalysis, and their easy-to-tune synthesis provide a potent tool in order to easily adapt the catalyst's requirements for each targeted reaction. Thus, further photocatalytic tests with these derivatives, as well as computational studies in order to better understand their observed enhanced activity, are currently carrying out in collaboration with the group of Prof. Dr. J. Alemán at the Universidad Autónoma de Madrid (U.A.M.).

## 4.5 References

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## 4.5 Experimental part

### *General Information and Materials:*

$^1\text{H}$ ,  $^{13}\text{C}$  and  $^{19}\text{F}$  NMR spectra were recorded in  $\text{CDCl}_3$  and  $\text{DMSO-D}_6$  (reference signals:  $^1\text{H}$  = 7.26 ppm,  $^{13}\text{C}$  = 77.16 ppm,  $\text{CDCl}_3$ ) on a *Bruker ARX-300* and a *Varian AV-300* or 400 and *Jeol JNM-ECS* 400 MHz. Chemical shifts ( $\delta$ ) are given in ppm and spin-spin coupling constants ( $J$ ) are given in Hz. Analytical thin layer chromatography was performed using silica gel 60 F<sub>254</sub> and a solution of  $\text{KMnO}_4$  or phosphomolybdic acid served as staining agent. Column chromatography was performed on silica gel 60 (0.040-0.063 mm). Exact masses (**HRMS**) were recorded on an *Agilent Q-TOF 6540 UHD* spectrometer (samples in  $\text{CH}_3\text{OH}$  as solvent) using electrospray (ES) or chemical (CI) ionization techniques. Chiral High Pressure Liquid Chromatography (**HPLC**) analyses were performed on an Agilent 1200 series instrument.  $\text{CH}_2\text{Cl}_2$  was distilled over  $\text{CaH}_2$ . THF and  $\text{Et}_2\text{O}$  were distilled and dried over Na. The starting materials were prepared following known literature procedures.<sup>1,2</sup> Acridanes were stored at -20°C. Other solvents and commercially available reagents were used without further purification if it is not listed.

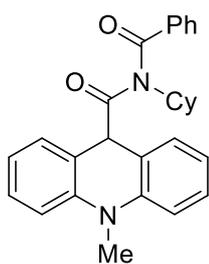
### *Preparation of the commercial reagent:*

- Copper(II) Triflate was dried under vacuum at 50 °C for 48 hours (The color change from light blue to white). The obtained dry catalyst was stored under nitrogen.
- Commercial available benzoyl peroxide contains the 30% w/w of water. In order to remove the water, the oxidant was dissolved in ethyl acetate and the obtained solution was washed 3 times with brine. The obtained organic phase was dried under  $\text{MgSO}_4$ , filtered, the solvent evaporated and the obtained white solid dried under vacuum.
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### *General Procedure:*

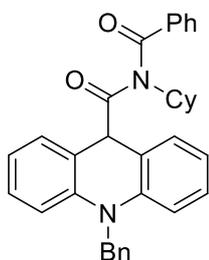
In an oven-dried screw cap schlenk dry  $\text{Cu}(\text{OTf})_2$  (10 mol %) (Copper triflate is slightly hygroscopic, weight and pour fast in the flask), 2,2'-bipyridyne (30 mol%) and target **1** (0.1-0.4 mmol, 1 equiv.) were added following this order. The solid mixture was dissolved in acetonitrile (1-4 mL), then the isocyanide **2** (2 equiv.) and peroxide (1.2 equiv.) were added following this order. The obtained mixture was stirred at room temperature for 4 h. After evaporating the solvent, the crude product was purified by flash column chromatography using hexane/ethyl acetate as eluent.

### N-Benzoyl-N-cyclohexyl-10-methyl-acridane-9-carboxamide (3aa)



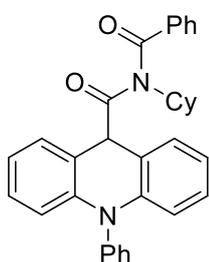
According to the general procedure, using acridane **1a** (39.0 mg, 0.2 mmol, 1 equiv.) dry  $\text{Cu}(\text{OTf})_2$  (7.2 mg, 0.02 mmol, 10 mol %), 2,2'-bipyridyne (9.4 mg, 0.06 mmol, 30 mol%), MeCN (2 mL), cyclohexyl isocyanide **2a** (49.7  $\mu\text{L}$ , 0.40 mmol, 2.0 equiv.), benzoyl peroxide (58.1 mg, 0.24 mmol, 1.2 equiv.) the title compound was obtained after 4 h by flash column chromatography (hexane/EtOAc, 9:1) as a white solid (51.8 mg, 0.122 mmol, 61%).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.77 – 7.73 (m, 2H), 7.70 – 7.64 (m, 1H), 7.59 – 7.52 (m, 2H), 7.26 – 7.20 (m, 2H), 6.96 – 6.91 (m, 2H), 6.88 – 6.83 (m, 2H), 6.76 – 6.71 (m, 2H), 4.95 (s, 1H), 4.03 (tt,  $J = 12.0, 3.5$  Hz, 1H), 3.40 (s, 3H), 1.80 – 1.67 (m, 2H), 1.65 – 1.56 (m, 2H), 1.52 – 1.42 (m, 1H), 1.32 – 1.25 (m, 2H), 1.16 – 0.96 (m, 3H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  176.8, 174.5, 142.7, 137.8, 132.9, 129.5, 129.2, 128.5, 128.4, 120.7, 120.5, 112.8, 59.4, 53.5, 33.3, 29.6, 26.3, 25.2. **HRMS** (ESI-MS): Mass calc. for  $[\text{C}_{28}\text{H}_{29}\text{N}_2\text{O}_2]^+$ :  $m/z = 425.2224$ , found:  $m/z = 425.2228$ .

### N-Benzoyl-N-cyclohexyl-10-benzyl-acridane-9-carboxamide (3ba)



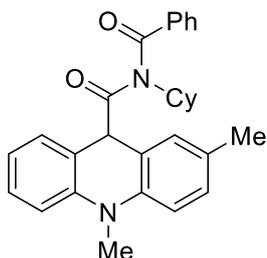
According to the general procedure, using acridane **1b** (54.3 mg, 0.2 mmol, 1.0 equiv.) dry  $\text{Cu}(\text{OTf})_2$  (7.2 mg, 0.02 mmol, 10 mol %), 2,2'-bipyridyne (9.4 mg, 0.06 mmol, 30 mol%), MeCN (2 mL), cyclohexyl isocyanide **2a** (49.7  $\mu\text{L}$ , 0.40 mmol, 2.0 equiv.), benzoyl peroxide (58.1 mg, 0.24 mmol, 1.2 equiv.) the title compound was obtained after 4 h by flash column chromatography (hexane/EtOAc, 9:1) as a white solid (70.1 mg, 0.140 mmol, 70%).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.85 – 7.75 (m, 2H), 7.75 – 7.67 (m, 1H), 7.64 – 7.55 (m, 2H), 7.33 – 7.21 (m, 3H), 7.20 – 7.15 (m, 2H), 7.14 – 7.05 (m, 2H), 6.89 – 6.82 (m, 2H), 6.79 – 6.73 (m, 4H), 5.20 (s, 2H), 5.02 (s, 1H), 4.14 – 4.02 (m, 1H), 1.82 – 1.69 (m, 2H), 1.67 – 1.60 (m, 2H), 1.56 – 1.47 (m, 1H), 1.34 – 1.26 (m, 2H), 1.17 – 0.99 (m, 3H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  176.4, 174.7, 141.6, 137.9, 137.0, 133.0, 129.5, 129.3, 128.8, 128.6, 128.5, 127.0, 126.2, 120.7, 120.3, 114.0, 59.4, 53.1, 51.0, 29.7, 26.3, 25.2. **HRMS** (ESI-MS): Mass calc. for  $[\text{C}_{34}\text{H}_{33}\text{N}_2\text{O}_2]^+$ :  $m/z = 501.2537$ , found:  $m/z = 501.2544$ .

### N-Benzoyl-N-cyclohexyl-10-phenyl-acridane-9-carboxamide (3ca)



According to the general procedure, using acridane **1c** (51.5 mg, 0.2 mmol, 1.0 equiv.) dry  $\text{Cu}(\text{OTf})_2$  (7.2 mg, 0.02 mmol, 10 mol %), 2,2'-bipyridyne (9.4 mg, 0.06 mmol, 30 mol%), MeCN (2 mL), cyclohexyl isocyanide **2a** (49.7  $\mu\text{L}$ , 0.40 mmol, 2.0 equiv.), benzoyl peroxide (58.1 mg, 0.24 mmol, 1.2 equiv.) the title compound was obtained after 4 h by flash column chromatography (hexane/EtOAc, 9:1) as slightly yellow solid (68.1 mg, 0.138 mmol, 69%).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.83 – 7.77 (m, 2H), 7.71 – 7.65 (m, 1H), 7.63 – 7.54 (m, 4H), 7.53 – 7.45 (m, 1H), 7.42 – 7.35 (m, 2H), 7.03 – 6.95 (m, 2H), 6.85 – 6.76 (m, 4H), 6.33 (d,  $J = 8.0$  Hz, 2H), 5.09 (s, 1H), 4.15 – 3.99 (m, 1H), 1.84 – 1.73 (m, 2H), 1.66 – 1.59 (m, 2H), 1.55 – 1.46 (m, 1H), 1.35 – 1.27 (m, 2H), 1.18 – 0.99 (m, 3H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  176.4, 174.8, 142.2, 140.7, 137.8, 133.0, 131.3, 130.7, 129.5, 129.2, 128.5, 128.4, 128.1, 120.6, 118.6, 114.8, 59.4, 52.7, 29.7, 26.3, 25.3. **HRMS** (ESI-MS): Mass calc. for  $[\text{C}_{33}\text{H}_{31}\text{N}_2\text{O}_2]^+$ :  $m/z = 487.2380$ , found:  $m/z = 487.23874$ .

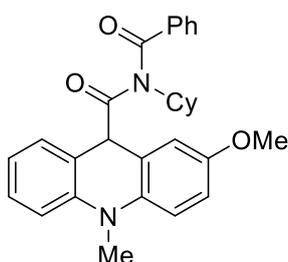
### N-Benzoyl-N-cyclohexyl-2,10-dimethyl-acridane-9-carboxamide (3da)



According to the general procedure, using acridane **1d** (41.9 mg, 0.2 mmol, 1.0 equiv.) dry Cu(OTf)<sub>2</sub> (7.2 mg, 0.02 mmol, 10 mol %), 2,2'-bipyridyne (9.4 mg, 0.06 mmol, 30 mol%), MeCN (2 mL), cyclohexyl isocyanide **2a** (49.7 μL, 0.40 mmol, 2.0 equiv.), benzoyl peroxide (58.1 mg, 0.24 mmol, 1.2 equiv.) the title compound was obtained after 4 h by flash column chromatography (hexane/EtOAc, 9:1) as white solid (53.5 mg, 0.122 mmol, 61%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 7.77 – 7.72 (m, 2H), 7.71 – 7.65 (m, 1H), 7.60 – 7.52 (m, 1H), 7.27 – 7.20 (m, 1H), 7.06 – 7.02 (m, 1H), 6.95 – 6.78

(m, 4H), 6.45 – 6.41 (m, 1H), 4.95 (s, 1H), 4.01 (tt, *J* = 12.0, 3.6 Hz, 1H), 3.39 (s, 3H), 2.21 (s, 3H), 1.90 – 1.57 (m, 4H), 1.52 – 1.43 (m, 1H), 1.39 – 1.23 (m, 3H), 1.10 – 1.00 (m, 2H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): □ 176.4, 174.6, 142.7, 140.4, 137.8, 132.8, 129.6, 129.4, 129.1, 129.0, 128.8, 128.6, 128.3, 120.6, 120.4, 120.1, 112.6, 112.5, 59.3, 53.5, 33.1, 29.9, 29.2, 26.2, 26.2, 25.1, 20.4. HRMS (ESI-MS): Mass calc. for [C<sub>29</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>Na]<sup>+</sup>: *m/z* = 461.2199, found: *m/z* = 461.2198.

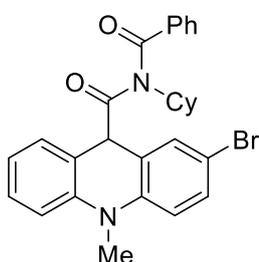
### N-Benzoyl-N-cyclohexyl-2-methoxy-10-methyl-acridane-9-carboxamide (3fa)



According to the general procedure, using acridane **1f** (45.1 mg, 0.2 mmol, 1.0 equiv.) dry Cu(OTf)<sub>2</sub> (7.2 mg, 0.02 mmol, 10 mol %), 2,2'-bipyridyne (9.4 mg, 0.06 mmol, 30 mol%), MeCN (2 mL), cyclohexyl isocyanide **2a** (49.7 μL, 0.40 mmol, 2.0 equiv.), benzoyl peroxide (58.1 mg, 0.24 mmol, 1.2 equiv.) the title compound was obtained after 4 h by flash column chromatography (hexane/EtOAc, 4:1) as white solid (37.3 mg, 0.082 mmol, 41%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 8.15 – 8.09 (m, 1H), 7.79 – 7.73 (m, 2H), 7.71 – 7.63 (m, 1H), 7.62 – 7.53 (m, 2H), 7.52 – 7.44

(m, 1H), 7.26 – 7.19 (m, 1H), 6.93 – 6.89 (m, 1H), 6.87 – 6.81 (m, 2H), 6.28 (d, *J* = 2.8 Hz, 1H), 4.94 (s, 1H), 4.03 (tt, *J* = 12.0, 3.6 Hz, 1H), 3.70 (s, 3H), 3.38 (s, 3H), 1.87 – 1.27 (m, 8H), 1.08 – 1.01 (m, 2H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 176.0, 174.6, 154.0, 142.9, 137.8, 137.0, 133.8, 133.0, 130.3, 129.5, 129.2, 128.7, 128.6, 128.5, 121.6, 120.1, 114.4, 113.7, 113.5, 112.5, 59.5, 55.8, 53.7, 33.3, 30.0, 29.2, 26.3, 26.7, 25.2. HRMS (ESI-MS): Mass calc. for [C<sub>29</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub>Na]<sup>+</sup>: *m/z* = 477.2149, found: *m/z* = 477.2152.

### N-Benzoyl-N-cyclohexyl-2-bromo-10-methyl-acridane-9-carboxamide (3ga)

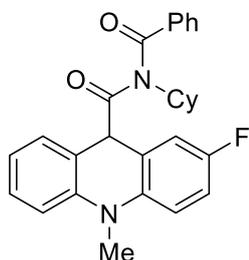


According to the general procedure, using acridane **1g** (54.6 mg, 0.2 mmol, 1.0 equiv.) dry Cu(OTf)<sub>2</sub> (7.2 mg, 0.02 mmol, 10 mol %), 2,2'-bipyridyne (9.4 mg, 0.06 mmol, 30 mol%), MeCN (2 mL), cyclohexyl isocyanide **2a** (49.7 μL, 0.40 mmol, 2.0 equiv.), benzoyl peroxide (58.1 mg, 0.24 mmol, 1.2 equiv.) the title compound was obtained after 4 h by flash column chromatography (hexane/EtOAc, 9:1) as white solid (63.7 mg, 0.126 mmol, 63%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 7.79 – 7.67 (m, 3H), 7.64 – 7.55 (m, *J* = 10.3, 4.5 Hz, 2H), 7.30 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.28 – 7.22 (m, 1H), 6.98 – 6.88 (m, *J* =

7.6, 5.6 Hz, 3H), 6.80 (d, *J* = 8.8 Hz, 1H), 6.56 (d, *J* = 2.3 Hz, 1H), 4.90 (s, 1H), 4.01 (tt, *J* = 11.9, 3.6 Hz, 1H), 3.38 (s, 3H), 1.92 – 1.77 (m, 1H), 1.72 – 1.57 (m, 4H), 1.52 – 1.36 (m, 2H), 1.15 – 1.00 (m, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 175.8, 174.6, 141.9, 141.8, 137.4, 133.2, 130.9, 129.5, 129.2, 128.7, 128.6, 122.5, 120.8, 120.3, 114.3, 112.9, 112.4, 59.4, 53.0, 33.3, 30.4, 28.8, 26.2,

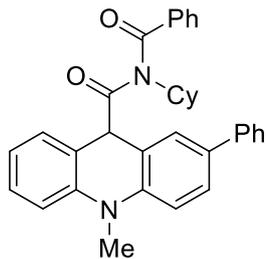
26.1, 25.1. **HRMS** (ESI-MS): Mass calc. for  $[C_{28}H_{28}BrN_2O_2]^+$ :  $m/z = 503.1329$ , found:  $m/z = 503.1309$ .

### N-Benzoyl-N-cyclohexyl-2-fluoro-10-methyl-acridane-9-carboxamide (3ha)



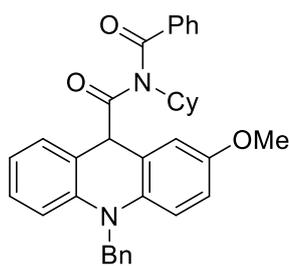
According to the general procedure, using acridane **1h** (42.6 mg, 0.2 mmol, 1.0 equiv.) dry  $Cu(OTf)_2$  (7.2 mg, 0.02 mmol, 10 mol %), 2,2'-bipyridyne (9.4 mg, 0.06 mmol, 30 mol%), MeCN (2 mL), cyclohexyl isocyanide **2a** (49.7  $\mu$ L, 0.40 mmol, 2.0 equiv.), benzoyl peroxide (58.1 mg, 0.24 mmol, 1.2 equiv.) the title compound was obtained after 4 h by flash column chromatography (hexane/EtOAc, 9:1) as white solid (28.4 mg, 0.06 mmol, 32%).  **$^1H$  NMR** (400 MHz,  $CDCl_3$ ): 7.76 – 7.71 (m, 2H), 7.71 – 7.66 (m, 1H), 7.60 – 7.54 (m, 2H), 7.23 – 7.20 (m, 1H), 6.97 – 6.82 (m, 5H), 6.35 (dd,  $J = 8.6, 2.8$  Hz, 1H), 4.92 (s, 1H), 4.01 (tt,  $J = 12.0, 3.6$  Hz, 1H), 3.40 (s, 3H), 1.87 – 1.75 (m, 1H), 1.73 – 1.64 (m, 1H), 1.56 – 1.35 (m, 4H), 1.15 – 0.93 (m, 4H).  **$^{13}C$  NMR** (100 MHz,  $CDCl_3$ ): 175.8, 174.6, 157.5 (d,  $J_{C-F} = 239.1$  Hz), 142.6, 139.4, 137.6, 133.2, 129.6, 129.2, 128.8, 128.7, 122.2 (d,  $J_{C-F} = 7.4.1$  Hz), 120.6, 120.1, 115.1 (d,  $J_{C-F} = 23.0.1$  Hz), 114.8 (d,  $J_{C-F} = 22.4$  Hz), 113.6 (d,  $J_{C-F} = 7.8$  Hz), 112.8, 59.6, 53.3, 33.6, 30.4, 29.0, 26.4.  **$^{19}F$  NMR** (376 MHz,  $CDCl_3$ ): -124.7. **HRMS** (ESI-MS): Mass calc. for  $[C_{28}H_{28}FN_2O_2]^+$ :  $m/z = 443.2129$ , found:  $m/z = 443.2136$ .

### N-Benzoyl-N-cyclohexyl-2,10-dimethyl-acridane-9-carboxamide (3ia)



According to the general procedure, using acridane **1i** (54.3 mg, 0.2 mmol, 1.0 equiv.) dry  $Cu(OTf)_2$  (7.2 mg, 0.02 mmol, 10 mol %), 2,2'-bipyridyne (9.4 mg, 0.06 mmol, 30 mol%), MeCN (2 mL), cyclohexyl isocyanide **2a** (49.7  $\mu$ L, 0.40 mmol, 2.0 equiv.), benzoyl peroxide (58.1 mg, 0.24 mmol, 1.2 equiv.) the title compound was obtained after 4 h by flash column chromatography (hexane/EtOAc, 9:1) as white solid (68.1 mg, 0.136 mmol, 68%).  **$^1H$  NMR** (300 MHz,  $CDCl_3$ ): 7.82 – 7.75 (m, 2H), 7.67 – 7.60 (m, 1H), 7.55 – 7.39 (m, 7H), 7.34 – 7.23 (m, 2H), 7.02 (d,  $J = 8.5$  Hz, 1H), 6.97 (d,  $J = 8.0$  Hz, 1H), 6.93 – 6.83 (m, 3H), 5.03 (s, 1H), 4.06 (tt,  $J = 12.0, 3.5$  Hz, 1H), 3.46 (s, 3H), 1.87 – 1.69 (m, 2H), 1.62 – 1.50 (m, 4H), 1.39 – 1.32 (m, 2H), 1.09 – 1.01 (m, 2H).  **$^{13}C$  NMR** (75 MHz,  $CDCl_3$ ):  $\square$  176.1, 174.6, 142.3, 141.9, 140.5, 137.8, 133.1, 133.0, 129.5, 129.2, 128.7, 128.6, 128.5, 127.1, 126.9, 126.6, 126.5, 120.8, 120.6, 120.5, 113.1, 112.8, 59.3, 53.5, 33.3, 29.8, 26.2, 26.2, 25.1. **HRMS** (ESI-MS): Mass calc. for  $[C_{34}H_{33}N_2O_2]^+$ :  $m/z = 501.2537$ , found:  $m/z = 501.2540$ .

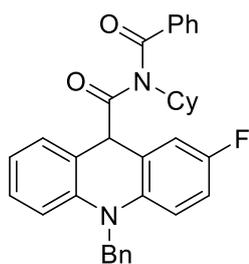
### N-Benzoyl-N-cyclohexyl-2-methoxy-10-benzyl-acridane-9-carboxamide (3ja)



According to the general procedure, using acridane **1j** (60.3 mg, 0.2 mmol, 1.0 equiv.) dry Cu(OTf)<sub>2</sub> (7.2 mg, 0.02 mmol, 10 mol %), 2,2'-bipyridyne (9.4 mg, 0.06 mmol, 30 mol%), MeCN (2 mL), cyclohexyl isocyanide **2a** (49.7 μL, 0.40 mmol, 2.0 equiv.), benzoyl peroxide (58.1 mg, 0.24 mmol, 1.2 equiv.) the title compound was obtained after 4 h by flash column chromatography (hexane/EtOAc, 4:1) as white solid (55.2 mg, 0.101 mmol, 52%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.84 – 7.79 (m, 2H), 7.72 – 7.66 (m, 1H), 7.62 – 7.57 (m, 2H), 7.32 – 7.26 (m, 2H), 7.25 – 7.21

(m, 1H), 7.18 – 7.13 (m, 2H), 7.12 – 7.04 (m, 1H), 6.86 – 6.82 (m, 2H), 6.73 – 6.69 (m, 1H), 6.69 – 6.66 (m, 2H), 6.33 – 6.26 (m, 1H), 5.16 (s, 2H), 5.01 (s, 1H), 4.07 (t, *J* = 12.0, 3.5 Hz, 1H), 3.70 (s, 3H), 1.87 – 1.60 (m, 5H), 1.54 – 1.47 (m, 1H), 1.41 – 1.33 (m, 1H), 1.18 – 0.99 (m, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): □ 176.2, 174.8, 154.1, 141.9, 137.9, 137.3, 135.9, 133.1, 129.6, 129.3, 128.9, 128.7, 128.6, 127.0, 126.3, 121.3, 120.2, 119.8, 114.9, 114.6, 113.7, 113.4, 59.4, 55.8, 53.3, 51.1, 30.2, 29.3, 26.4, 26.3, 25.3. HRMS (ESI-MS): Mass calc. for [C<sub>35</sub>H<sub>34</sub>N<sub>2</sub>O<sub>3</sub>Na]<sup>+</sup>: *m/z* = 531.2642, found: *m/z* = 531.238.

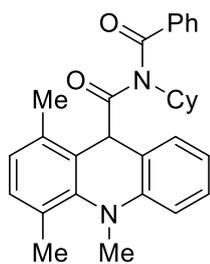
### N-Benzoyl-N-cyclohexyl-2-fluoro-10-benzyl-acridane-9-carboxamide (3ja)



According to the general procedure, using acridane **1k** (43.4 mg, 0.150 mmol, 1.0 equiv.) dry Cu(OTf)<sub>2</sub> (5.4 mg, 0.015 mmol, 10 mol %), 2,2'-bipyridyne (7.0 mg, 0.045 mmol, 30 mol%), MeCN (1.5 mL), cyclohexyl isocyanide **2a** (37.2 μL, 0.300 mmol, 2.0 equiv.), benzoyl peroxide (43.6 mg, 0.180 mmol, 1.2 equiv.) the title compound was obtained after 4 h by flash column chromatography (hexane/EtOAc, 9:1) as white solid (55.2 mg, 0.104 mmol, 52%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): (400 MHz, CDCl<sub>3</sub>): 7.83 – 7.78 (m, 2H), 7.74 – 7.68 (m, 1H), 7.62 – 7.57 (m, 2H), 7.32 – 7.26 (m, 2H), 7.24 – 7.21

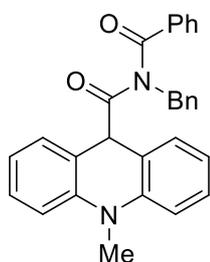
(m, 1H), 7.17 – 7.13 (m, 2H), 7.12 – 7.06 (m, 1H), 6.92 – 6.84 (m, 2H), 6.80 (dt, *J* = 8.7, 3.0 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 6.67 (dd, *J* = 9.1, 4.6 Hz, 1H), 6.36 (dd, *J* = 8.7, 2.9 Hz, 1H), 5.17 (s, 2H), 4.99 (s, 1H), 4.06 (tt, *J* = 12.0, 3.5 Hz, 1H), 1.91 – 1.78 (m, 1H), 1.74 – 1.61 (m, 2H), 1.59 – 1.47 (m, 2H), 1.44 – 1.38 (m, 1H), 1.14 – 0.98 (m, 4H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): 176.1, 174.8, 157.5 (d, *J*<sub>C-F</sub> = 239.3 Hz), 153.9, 141.6, 138.4, 137.6, 136.9, 133.4, 129.7, 129.3, 129.0, 128.8 (d, *J*<sub>C-F</sub> = 7.8 Hz), 127.2, 126.2, 121.8 (d, *J*<sub>C-F</sub> = 7.3 Hz), 120.8, 119.7, 115.0 (d, *J*<sub>C-F</sub> = 23.0 Hz), 114.9 (d, *J*<sub>C-F</sub> = 22.9 Hz), 114.0, 59.6, 52.9, 51.4, 30.4, 29.1, 26.3. <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): -124.2. HRMS (ESI-MS): Mass calc. for [C<sub>34</sub>H<sub>31</sub>FN<sub>2</sub>O<sub>2</sub>Na]<sup>+</sup>: *m/z* = 519.2442, found: *m/z* = 519.2446.

### N-Benzoyl-N-cyclohexyl-1,4,10-trimethyl-acridane-9-carboxamide (3la)



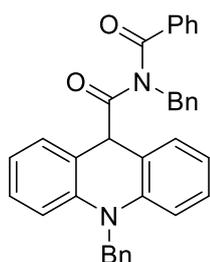
According to the general procedure, using acridane **11** (44.3 mg, 0.2 mmol, 1.0 equiv.) dry Cu(OTf)<sub>2</sub> (7.2 mg, 0.02 mmol, 10 mol %), 2,2'-bipyridyne (9.4 mg, 0.06 mmol, 30 mol%), MeCN (2 mL), cyclohexyl isocyanide **2a** (49.7 μL, 0.40 mmol, 2.0 equiv.), benzoyl peroxide (58.1 mg, 0.24 mmol, 1.2 equiv.) the title compound was obtained after 4 h by flash column chromatography (hexane/EtOAc, 9:1) as white solid (51.6 mg, 0.114 mmol, 57%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 7.64 – 7.45 (m, 5H), 7.25 – 7.19 (m, 1H), 7.13 – 7.08 (m, 1H), 7.01 – 6.95 (m, 1H), 6.83 – 6.74 (m, 2H), 6.53 – 6.47 (m, 1H), 5.35 (s, 1H), 3.83 (tt, *J* = 12.0, 3.6 Hz, 1H), 3.55 (s, 3H), 2.39 (s, 3H), 2.33 (s, 3H), 1.91 – 1.71 (m, 2H), 1.62 (s, 2H), 1.51 – 1.43 (m, 1H), 1.37 – 1.23 (m, 2H), 1.12 – 0.95 (m, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 177.0, 174.6, 147.3, 144.0, 136.9, 133.3, 132.3, 131.1, 129.1, 128.7, 128.0, 127.0, 125.8, 125.7, 124.2, 120.9, 117.3, 60.1, 49.7, 41.8, 29.9, 29.3, 26.3, 25.1, 20.7, 19.4. HRMS (ESI-MS): Mass calc. for [C<sub>29</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>Na]<sup>+</sup>: *m/z* = 461.2199, found: *m/z* = 461.2198.

### N-Benzoyl-N-benzyl-10-methyl-acridane-9-carboxamide (3ab)



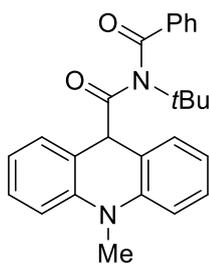
According to the general procedure, using acridane **1a** (39.0 mg, 0.2 mmol, 1.0 equiv.) dry Cu(OTf)<sub>2</sub> (7.2 mg, 0.02 mmol, 10 mol %), 2,2'-bipyridyne (9.4 mg, 0.06 mmol, 30 mol%), MeCN (2 mL), benzyl isocyanide **2b** (46.8 mg, 0.40 mmol, 2.0 equiv.), benzoyl peroxide (58.1 mg, 0.24 mmol, 1.2 equiv.) the title compound was obtained after 4 h by flash column chromatography (hexane/EtOAc, 9:1) as white solid (45.0 mg, 0.104 mmol, 52%). <sup>1</sup>H NMR ((300 MHz, CDCl<sub>3</sub>): 7.64 – 7.55 (m, 3H), 7.51 – 7.44 (m, 2H), 7.31 – 7.24 (m, 2H), 7.17 – 7.10 (m, 3H), 7.05 – 7.01 (m, 2H), 6.98 – 6.87 (m, 6H), 5.58 (s, 1H), 4.78 (s, 2H), 3.38 (s, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 175.1, 173.8, 142.6, 137.9, 134.0, 130.6, 129.5, 128.3, 128.2, 121.0, 120.4, 112.8, 60.0, 53.3, 28.8. HRMS (ESI-MS): Mass calc. for [C<sub>29</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub>Na]<sup>+</sup>: *m/z* = 433.1911, found: *m/z* = 433.1920.

### N-Benzoyl-N,10-dibenzyl-acridane-9-carboxamide (3bb)



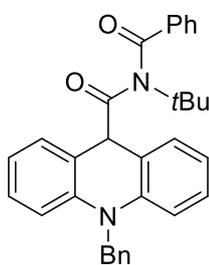
According to the general procedure, using acridane **1b** (40.7 mg, 0.15 mmol, 1.0 equiv.) dry Cu(OTf)<sub>2</sub> (5.4 mg, 0.015 mmol, 10 mol %), 2,2'-bipyridyne (7 mg, 0.045 mmol, 30 mol%), MeCN (1.5 mL), benzyl isocyanide **2b** (35.1 mg, 0.30 mmol, 2.0 equiv.), benzoyl peroxide (43.6 mg, 0.18 mmol, 1.2 equiv.) the title compound was obtained after 4 h by flash column chromatography (hexane/EtOAc, 9:1) as white solid (27.4 mg, 0.054 mmol, 36%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.63 – 7.56 (m, 3H), 7.49 – 7.44 (m, 2H), 7.30 – 7.21 (m, 3H), 7.17 – 7.08 (m, 7H), 7.04 – 7.01 (m, 2H), 6.96 – 6.92 (m, 2H), 6.89 – 6.82 (m, 2H), 6.77 – 6.73 (m, 2H), 5.64 (s, 1H), 5.14 (s, 2H), 4.82 (s, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): 176.4, 174.9, 141.9, 137.2, 136.9, 136.0, 134.5, 132.9, 129.2, 128.9, 128.6, 128.5, 127.8, 127.3, 127.0, 126.3, 120.9, 120.8, 116.3, 114.2, 51.1, 50.7, 50.4. HRMS (ESI-MS): Mass calc. for [C<sub>35</sub>H<sub>29</sub>N<sub>2</sub>O<sub>2</sub>]<sup>+</sup>: *m/z* = 509.2229, found: *m/z* = 509.2231.

### N-Benzoyl-N-*tert*-butyl-10-methyl-acridane-9-carboxamide (3ac)



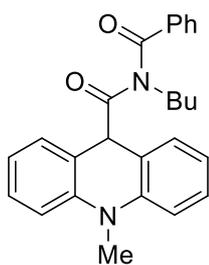
According to the general procedure, using acridane **1a** (39.0 mg, 0.2 mmol, 1.0 equiv.) dry Cu(OTf)<sub>2</sub> (7.2 mg, 0.02 mmol, 10 mol %), 2,2'-bipyridyne (9.4 mg, 0.06 mmol, 30 mol%), MeCN (2 mL), *tert*-butyl isocyanide **2c** (45.2 μL, 0.40 mmol, 2.0 equiv.), benzoyl peroxide (58.1 mg, 0.24 mmol, 1.2 equiv.) the title compound was obtained after 4 h by flash column chromatography (hexane/EtOAc, 9:1) as white solid (42.2 mg, 0.106 mmol, 53%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 8.04 – 7.98 (m, 2H), 7.76 – 7.68 (m, 1H), 7.64 – 7.53 (m, 2H), 7.25 – 7.17 (m, 2H), 6.95 – 6.88 (m, 2H), 6.87 – 6.79 (m, 2H), 6.68 – 6.60 (m, 2H), 4.63 (s, 1H), 3.39 (s, 3H), 1.37 (s, 9H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 175.1, 173.8, 142.6, 137.9, 134.0, 130.6, 129.5, 128.3, 128.2, 121.0, 120.4, 112.8, 60.0, 53.3, 28.8. HRMS (ESI-MS): Mass calc. for [C<sub>26</sub>H<sub>27</sub>N<sub>2</sub>O<sub>2</sub>]<sup>+</sup>: *m/z* = 399.2067, found: *m/z* = 399.2072.

### N-Benzoyl-N-*tert*-butyl-10-benzyl-acridane-9-carboxamide (3bc)



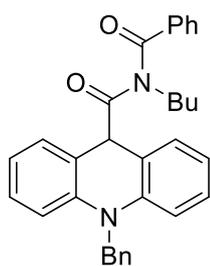
According to the general procedure, using acridane **1b** (54.3 mg, 0.2 mmol, 1.0 equiv.) dry Cu(OTf)<sub>2</sub> (7.2 mg, 0.02 mmol, 10 mol %), 2,2'-bipyridyne (9.4 mg, 0.06 mmol, 30 mol%), MeCN (2 mL), *tert*-butyl isocyanide **2c** (45.2 μL, 0.40 mmol, 2.0 equiv.), benzoyl peroxide (58.1 mg, 0.24 mmol, 1.2 equiv.) the title compound was obtained after 4 h by flash column chromatography (hexane/EtOAc, 9:1) as white solid (35.5 mg, 0.075 mmol, 37%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): □ 8.07 – 7.97 (m, 2H), 7.78 – 7.68 (m, 1H), 7.64 – 7.55 (m, 2H), 7.31 – 7.27 (m, 2H), 7.25 – 7.20 (m, 1H), 7.18 – 7.10 (m, 2H), 7.11 – 6.98 (m, 2H), 6.81 – 6.75 (m, 2H), 6.73 – 6.68 (m, 2H), 6.68 – 6.62 (m, 2H), 5.18 (s, 2H), 4.76 (s, 1H), 1.39 (s, 9H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): □ 173.9, 173.2, 141.6, 140.1, 137.2, 134.2, 130.7, 129.5, 128.8, 128.3, 128.2, 126.9, 126.2, 120.7, 120.5, 113.9, 59.9, 52.8, 51.2, 28.7. HRMS (ESI-MS): Mass calc. for [C<sub>32</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>]<sup>+</sup>: *m/z* = 475.2380, found: *m/z* = 475.2385.

### N-Benzoyl-N-butyl-10-methyl-acridane-9-carboxamide (3ad)



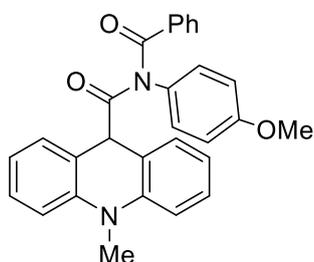
According to the general procedure, using acridane **1a** (29.3 mg, 0.15 mmol, 1.0 equiv.) dry Cu(OTf)<sub>2</sub> (5.4 mg, 0.015 mmol, 10 mol %), 2,2'-bipyridyne (7 mg, 0.045 mmol, 30 mol%), MeCN (1.5 mL), butyl isocyanide **2d** (31.4 μL, 0.30 mmol, 2.0 equiv.), benzoyl peroxide (43.6 mg, 0.18 mmol, 1.2 equiv.) the title compound was obtained after 4 h by flash column chromatography (hexane/EtOAc, 9:1) as white solid (26.3 mg, 0.066 mmol, 44%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.68 – 7.60 (m, 3H), 7.55 – 7.50 (m, 2H), 7.29 – 7.23 (m, 2H), 7.06 – 7.02 (m, 2H), 6.99 – 6.94 (m, 2H), 6.92 – 6.86 (m, 2H), 5.47 (s, 1H), 3.56 – 3.49 (m, 2H), 3.43 (s, 3H), 1.30 – 1.20 (m, 2H), 1.16 – 1.02 (m, 2H), 0.71 (t, *J* = 7.3 Hz, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): 176.4, 174.9, 142.8, 136.2, 132.7, 129.2, 128.9, 128.6, 128.4, 121.3, 120.6, 112.9, 50.9, 47.8, 33.3, 30.7, 20.1, 13.7. HRMS (ESI-MS): Mass calc. for [C<sub>26</sub>H<sub>27</sub>N<sub>2</sub>O<sub>2</sub>]<sup>+</sup>: *m/z* = 399.2067, found: *m/z* = 399.2067.

### N-Benzoyl-N-butyl-10-benzyl-acridane-9-carboxamide (3bd)



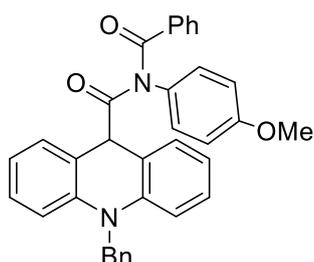
According to the general procedure, using acridane **1b** (40.7 mg, 0.15 mmol, 1.0 equiv.) dry Cu(OTf)<sub>2</sub> (5.4 mg, 0.015 mmol, 10 mol %), 2,2'-bipyridyne (7 mg, 0.045 mmol, 30 mol%), MeCN (1.5 mL), butyl isocyanide **2d** (31.4 μL, 0.30 mmol, 2.0 equiv.), benzoyl peroxide (43.6 mg, 0.18 mmol, 1.2 equiv.) the title compound was obtained after 4 h by flash column chromatography (hexane/EtOAc, 9:1) as white solid (40.7 mg, 0.085 mmol, 57%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 7.75 – 7.69 (m, 2H), 7.68 – 7.62 (m, 1H), 7.59 – 7.53 (m, 2H), 7.34 – 7.23 (m, 3H), 7.22 – 7.16 (m, 2H), 7.16 – 7.05 (m, 4H), 6.93 – 6.84 (m, 2H), 6.83 – 6.72 (m, 2H), 5.55 (s, 1H), 5.22 (s, 2H), 3.62 – 3.53 (m, 2H), 1.35 – 1.21 (m, 2H), 1.19 – 1.01 (m, 2H), 0.73 (t, *J* = 7.2 Hz, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): □ 177.0, 175.0, 142.0, 137.1, 136.2, 132.8, 129.3, 129.0, 128.9, 128.6, 127.0, 126.3, 121.0, 120.8, 114.1, 51.2, 50.4, 47.9, 30.7, 20.1, 13.7. HRMS (ESI-MS): Mass calc. for [C<sub>32</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>]<sup>+</sup>: *m/z* = 475.2380, found: *m/z* = 475.2381.

### N-Benzoyl-N-(4-methoxyphenyl)-10-methyl-acridane-9-carboxamide (3ae)



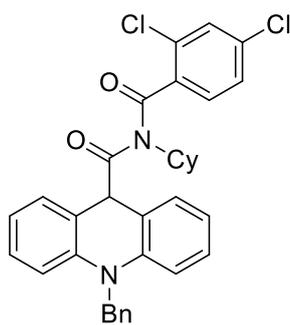
According to the general procedure, using acridane **1a** (29.3 mg, 0.15 mmol, 1.0 equiv.) dry Cu(OTf)<sub>2</sub> (5.4 mg, 0.015 mmol, 10 mol %), 2,2'-bipyridyne (7 mg, 0.045 mmol, 30 mol%), MeCN (1.5 mL), 4-methoxyphenyl isocyanide **2e** (39.0 mg, 0.30 mmol, 2.0 equiv.), benzoyl peroxide (43.6 mg, 0.18 mmol, 1.2 equiv.) the title compound was obtained after 4 h by flash column chromatography (hexane/EtOAc, 4:1) as white solid (17.5 mg, 0.039 mmol, 26%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 7.41 – 7.20 (m, 10H), 7.02 – 6.94 (m, 4H), 6.84 (s, 3H), 5.68 (s, 1H), 3.76 (s, 3H), 3.39 (s, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): □ 176.4, 173.4, 159.1, 142.8, 135.0, 132.1, 131.9, 129.6, 128.9, 128.7, 128.6, 128.3, 121.1, 120.6, 114.9, 113.0, 55.5, 50.3, 33.3. HRMS (ESI-MS): Mass calc. for [C<sub>29</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>]<sup>+</sup>: *m/z* = 449.1860, found: *m/z* = 449.1870.

### N-Benzoyl-N-(4-methoxyphenyl)-10-benzyl-acridane-9-carboxamide (3be)



According to the general procedure, using acridane **1b** (40.7 mg, 0.15 mmol, 1.0 equiv.) dry Cu(OTf)<sub>2</sub> (5.4 mg, 0.015 mmol, 10 mol %), 2,2'-bipyridyne (7 mg, 0.045 mmol, 30 mol%), MeCN (1.5 mL), 4-methoxyphenyl isocyanide **2e** (39.0 mg, 0.30 mmol, 2.0 equiv.), benzoyl peroxide (43.6 mg, 0.18 mmol, 1.2 equiv.) the title compound was obtained after 4 h by flash column chromatography (hexane/EtOAc, 4:1) as white solid (55.9 mg, 0.106 mmol, 71%). <sup>1</sup>H NMR 7.45 – 7.37 (m, 3H), 7.35 – 7.27 (m, 5H), 7.25 – 7.13 (m, 6H), 7.00 – 6.94 (m, 2H), 6.87 – 6.83 (m, 4H), 6.80 – 6.76 (m, 2H), 5.73 (s, 1H), 5.12 (s, 2H), 3.78 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): □ 177.0, 173.5, 159.2, 141.7, 137.1, 135.0, 132.1, 132.0, 129.7, 129.0, 128.9, 128.8, 128.7, 128.4, 127.0, 126.2, 120.9, 120.8, 114.9, 114.2, 55.6, 51.3, 50.0. HRMS (ESI-MS): Mass calc. for [C<sub>35</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>]<sup>+</sup>: *m/z* = 525.2173, found: *m/z* = 525.2178.

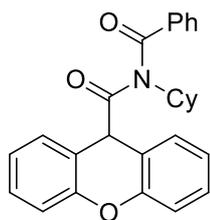
### N-Benzoyl-N-(4-methoxyphenyl)-10-benzyl-acridane-9-carboxamide (5ba)



According to the general procedure, using acridane **1b** (40.7 mg, 0.15 mmol, 1.0 equiv.) dry  $\text{Cu}(\text{OTf})_2$  (5.4 mg, 0.015 mmol, 10 mol %), 2,2'-bipyridyne (7 mg, 0.045 mmol, 30 mol%), MeCN (1.5 mL), cyclohexyl isocyanide **2a** (37.2  $\mu\text{L}$ , 0.40 mmol, 2.0 equiv.), (2,4-dichlorobenzoyl) peroxide (50% w/w in polysilyloxane, 136.8 mg, 0.18 mmol, 1.2 equiv.) the title compound was obtained after 4 h by flash column chromatography (hexane/EtOAc, 9:1) as white solid (15.4 mg, 0.027 mmol, 18%).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 7.59 (d,  $J = 2.0$  Hz, 1H), 7.37 (d,  $J = 8.2$ , 1.9 Hz, 1H), 7.33 – 7.27 (m, 3H), 7.25 – 7.17 (m, 4H), 7.16 – 7.10 (m, 2H), 7.07 – 7.00

(m, 2H), 6.94 – 6.87 (m, 2H), 6.83 – 6.76 (m, 2H), 5.46 (s, 1H), 5.21 (s, 2H), 3.69 (tt,  $J = 11.9$ , 3.5 Hz, 1H), 1.79 – 1.63 (m, 2H), 1.62 – 1.56 (m, 2H), 1.51 – 1.43 (m, 2H), 1.24 – 1.17 (m, 1H), 0.97 – 0.77 (m, 3H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ): 177.5, 169.9, 141.7, 137.4, 136.9, 135.4, 135.3, 132.8, 130.8, 129.8, 129.0, 128.9, 128.8, 127.9, 127.1, 126.3, 120.9, 120.1, 114.1, 60.2, 53.3, 51.09, 29.7, 26.3, 25.1. **HRMS** (ESI-MS): Mass calc. for  $[\text{C}_{34}\text{H}_{31}\text{Cl}_2\text{N}_2\text{O}_2]^+$ :  $m/z = 569.1763$ , found:  $m/z = 569.1705$ .

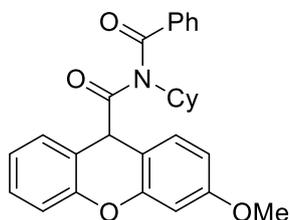
### N-Benzoyl-N-cyclohexyl-xanthene-9-carboxamide (3ma)



According to the general procedure, using xanthene **1m** (36.4 mg, 0.2 mmol, 1 equiv.) dry  $\text{Cu}(\text{OTf})_2$  (7.2 mg, 0.02 mmol, 10 mol %), 2,2'-bipyridyne (9.4 mg, 0.06 mmol, 30 mol%), MeCN (2 mL), cyclohexyl isocyanide **2a** (49.7  $\mu\text{L}$ , 0.40 mmol, 2.0 equiv.), benzoyl peroxide (58.1 mg, 0.24 mmol, 1.2 equiv.) the title compound was obtained after 18 h by flash column chromatography (hexane/EtOAc, 9:1) as a white solid (17.3 mg, 0.042 mmol, 21%).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 7.85 – 7.81 (m, 2H), 7.72 – 7.65 (m, 1H), 7.61 – 7.54 (m, 2H), 7.27

– 7.22 (m, 2H), 7.14 – 7.11 (m, 2H), 7.04 – 6.98 (m, 2H), 6.95 – 6.91 (m, 2H), 4.98 (s, 1H), 4.05 (tt,  $J = 12.0$ , 3.6 Hz, 1H), 1.86 – 1.71 (m, 3H), 1.66 – 1.59 (m, 2H), 1.45 – 1.37 (m, 2H), 1.13 – 0.96 (m, 3H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ): 178.9, 175.2, 152.2, 133.5, 129.5, 129.4, 129.1, 128.4, 123.2, 119.6, 117.2, 116.7, 59.7, 49.0, 29.8, 26.2, 25.1. **HRMS** (ESI-MS): Mass calc. for  $[\text{C}_{27}\text{H}_{26}\text{NO}_3]^+$ :  $m/z = 412.1907$ , found:  $m/z = 412.1912$ .

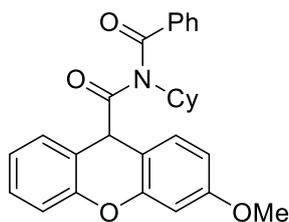
### N-Benzoyl-N-cyclohexyl-3-methoxy-xanthene-9-carboxamide (3ma)



According to the general procedure, using xanthene **1m** (42.5 mg, 0.2 mmol, 1 equiv.) dry  $\text{Cu}(\text{OTf})_2$  (7.2 mg, 0.02 mmol, 10 mol %), 2,2'-bipyridyne (9.4 mg, 0.06 mmol, 30 mol%), MeCN (2 mL), cyclohexyl isocyanide **2a** (49.7  $\mu\text{L}$ , 0.40 mmol, 2.0 equiv.), benzoyl peroxide (58.1 mg, 0.24 mmol, 1.2 equiv.) the title compound was obtained after 18 h by flash column chromatography (hexane/EtOAc, 9:1) as a white solid (47.9 mg, 0.116 mmol, 58%).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 7.87 – 7.81 (m, 2H),

7.73 – 7.66 (m, 1H), 7.62 – 7.55 (m, 2H), 7.28 – 7.22 (m, 1H), 7.14 – 7.10 (m, 1H), 7.03 – 6.98 (m, 1H), 6.95 – 6.91 (m, 1H), 6.84 (d,  $J = 8.6$  Hz, 1H), 6.68 (d,  $J = 2.5$  Hz, 1H), 6.60 (dd,  $J = 8.5$ , 2.6 Hz, 1H), 4.92 (s, 1H), 4.12 – 4.02 (m, 1H), 3.80 (s, 3H), 1.88 – 1.74 (m, 2H), 1.70 – 1.61 (m, 2H), 1.54 – 1.41 (m, 3H), 1.18 – 0.99 (m, 3H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ): 176.3, 175.2, 160.3, 153.1, 152.1, 137.2, 133.5, 129.5, 129.4, 129.0, 128.9, 128.4, 123.2, 119.8, 119.7, 117.1, 111.7, 111.6, 110.2, 102.0, 59.6, 55.5, 48.4, 29.8, 29.8, 26.2, 25.2.

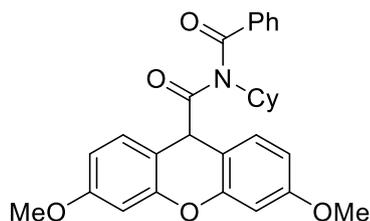
### N-Benzoyl-N-cyclohexyl-3-methoxy-xanthene-9-carboxamide (3oa)



According to the general procedure, using xanthene **1o** (42.5 mg, 0.2 mmol, 1 equiv., partially deuterated in 9-position circa 50%) dry  $\text{Cu}(\text{OTf})_2$  (7.2 mg, 0.02 mmol, 10 mol %), 2,2'-bipyridyne (9.4 mg, 0.06 mmol, 30 mol%), MeCN (2 mL), cyclohexyl isocyanide **2a** (49.7  $\mu\text{L}$ , 0.40 mmol, 2.0 equiv.), benzoyl peroxide (58.1 mg, 0.24 mmol, 1.2 equiv.) the title compound was obtained after 18 h by flash column chromatography (hexane/EtOAc, 9:1) as a white solid (47.9 mg, 0.116 mmol, 58%).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ): 7.87 – 7.81 (m, 2H), 7.73 – 7.66 (m, 1H), 7.62 – 7.55 (m, 2H), 7.28 – 7.22 (m, 1H), 7.11 (d,  $J = 8.1$  Hz, 1H), 7.03 – 6.98 (m, 1H), 6.95 – 6.91 (m, 1H), 6.84 (d,  $J = 8.6$  Hz, 1H), 6.68 (d,  $J = 2.5$  Hz, 1H), 6.60 (dd,  $J = 8.5, 2.6$  Hz, 1H), 4.92 (s, 1H), 4.07 (tt,  $J = 12.1, 3.1$  Hz, 1H), 3.80 (s, 3H), 1.88 – 1.74 (m, 2H), 1.70 – 1.61 (m, 2H), 1.54 – 1.41 (m, 3H), 1.18 – 0.99 (m, 3H).  **$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ ): 176.3, 175.2, 160.3, 153.1, 152.1, 137.2, 133.5, 129.5, 129.4, 129.0, 128.9, 128.4, 123.2, 119.8, 119.7, 117.1, 111.7, 111.6, 110.2, 102.0, 59.6, 55.5, 48.4, 29.8, 26.2, 25.2. **HRMS** (ESI-MS): Mass calc. for  $[\text{C}_{28}\text{H}_{27}\text{NO}_4]^+$ :  $m/z = 442.2013$ , found:  $m/z = 442.2022$ . *Deuterated portion*. Mass calc. for  $[\text{C}_{28}\text{H}_{26}\text{DNO}_4]^+$ :  $m/z = 443.2076$ , found:  $m/z = 443.2076$

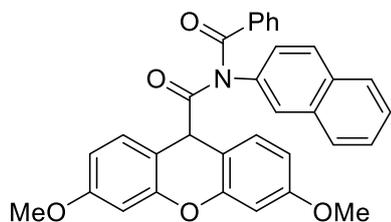
### N-Benzoyl-N-cyclohexyl-3,6-dimethoxy-xanthene-9-carboxamide (3pa)



According to the general procedure, using xanthene **1p** (48.5 mg, 0.2 mmol, 1 equiv.) dry  $\text{Cu}(\text{OTf})_2$  (7.2 mg, 0.02 mmol, 10 mol %), 2,2'-bipyridyne (9.4 mg, 0.06 mmol, 30 mol%), MeCN (2 mL), cyclohexyl isocyanide **2a** (49.7  $\mu\text{L}$ , 0.40 mmol, 2.0 equiv.), benzoyl peroxide (58.1 mg, 0.24 mmol, 1.2 equiv.) the title compound was obtained after 18 h by flash column chromatography (hexane/EtOAc, 4:1) as a white solid (63.3 mg, 0.134 mmol, 67%).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ): 7.88 – 7.76 (m, 2H), 7.72 – 7.65 (m, 1H), 7.63 – 7.50 (m, 2H), 6.82 (d,  $J = 8.5$  Hz, 2H), 6.66 (d,  $J = 2.6$  Hz, 2H), 6.60 (d,  $J = 2.5$  Hz, 1H), 6.58 (d,  $J = 2.6$  Hz, 1H), 4.84 (s, 1H), 4.07 (tt,  $J = 12.0, 3.6$  Hz, 1H), 1.88 – 1.74 (m, 2H), 1.69 – 1.62 (m, 2H), 1.53 – 1.42 (m, 3H), 1.19 – 1.01 (m, 3H).  **$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ ): 176.7, 175.3, 160.3, 153.0, 137.3, 133.5, 129.5, 129.5, 129.0, 111.91, 110.1, 102.0, 59.7, 55.6, 47.8, 29.9, 26.3, 25.2. **HRMS** (ESI-MS): Mass calc. for  $[\text{C}_{29}\text{H}_{29}\text{NO}_5]^+$ :  $m/z = 472.2118$ , found:  $m/z = 472.2126$ .

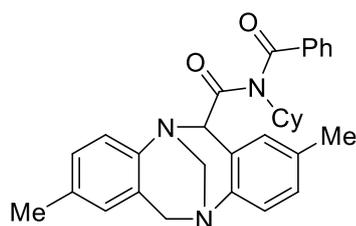
### N-Benzoyl-N-(naphthalen-2-yl)-3,6-dimethoxy-xanthene-9-carboxamide (3pf)



According to the general procedure, using xanthene **1p** (48.5 mg, 0.2 mmol, 1 equiv.) dry  $\text{Cu}(\text{OTf})_2$  (7.2 mg, 0.02 mmol, 10 mol %), 2,2'-bipyridyne (9.4 mg, 0.06 mmol, 30 mol%), MeCN (2 mL), 2-naphthalen-2-yl isocyanide **2f** (49.7  $\mu\text{L}$ , 0.40 mmol, 2.0 equiv.), benzoyl peroxide (58.1 mg, 0.24 mmol, 1.2 equiv.) the title compound was obtained after 18 h by flash column chromatography (hexane/EtOAc, 4:1) as a white solid (49.6 mg,

0.097 mmol, 49%).  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ ): 7.79 – 7.75 (m, 1H), 7.73 (d, 1H), 7.65 – 7.59 (m, 3H), 7.49 – 7.42 (m, 3H), 7.40 – 7.32 (m, 4H), 7.30 – 7.26 (m, 2H), 6.71 (dd,  $J = 8.5, 2.6$  Hz, 2H), 6.59 (d,  $J = 2.5$  Hz, 2H), 3.81 (s, 6H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ ): 170.8, 160.4, 152.7, 133.8, 130.3, 130.0, 129.5, 129.3, 129.1, 128.6, 128.5, 128.1, 128.1, 127.8, 127.8, 127.3, 126.7, 125.8, 123.2, 111.8, 110.3, 102.0, 55.6, 45.5.

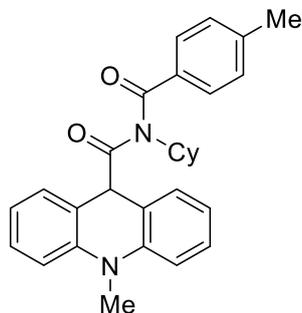
## N-Benzoyl-N-cyclohexyl-2,8-dimethyl-6H,12H-5,11-methanodibenzo[*b,f*][1,5]diazocine-6-carboxamide



According to the general procedure, using Tröger's base **1p** (48.5 mg, 0.2 mmol, 1 equiv.) dry Cu(OTf)<sub>2</sub> (7.2 mg, 0.02 mmol, 10 mol %), 2,2'-bipyridyne (9.4 mg, 0.06 mmol, 30 mol%), MeCN (2 mL), cyclohexyl isocyanide **2a** (49.7 μL, 0.40 mmol, 2.0 equiv.), benzoyl peroxide (58.1 mg, 0.24 mmol, 1.2 equiv.) the title compound was obtained after 18 h by flash column chromatography (hexane/EtOAc, 4:1) as a white solid (27.8 mg, 0.058 mmol, 29%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.84 – 7.78 (m, 2H), 7.50 – 7.41 (m, 3H), 7.05 (d, *J* = 8.2 Hz, 1H), 7.00 – 6.96 (m, 1H), 6.93 – 6.88 (m, 2H), 6.65 (s, 1H), 6.51 (s, 1H), 4.86 (d, *J* = 17.3 Hz, 1H), 4.30 – 4.16 (m, 2H), 3.94 (d, *J* = 17.3 Hz, 1H), 3.80 (d, *J* = 16.6 Hz, 1H), 3.62 (d, *J* = 16.5 Hz, 1H), 2.21 (s, 3H), 2.14 (s, 3H), 1.75 – 1.64 (m, 3H), 1.56 – 1.49 (m, 2H), 1.38 – 1.31 (m, 1H), 1.23 – 1.11 (m, 3H), 1.09 – 1.00 (m, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 171.2, 170.4, 146.7, 140.7, 137.2, 134.8, 134.0, 132.3, 128.9, 128.8, 128.5, 128.3, 127.8, 127.4, 126.9, 126.8, 125.5, 125.0, 74.5, 58.2, 58.0, 53.7, 31.1, 28.8, 26.4, 25.4, 21.1. HRMS (ESI-MS): Mass calc. for [C<sub>31</sub>H<sub>33</sub>N<sub>3</sub>O<sub>2</sub>]<sup>+</sup>: *m/z* = 480.2646, found: *m/z* = 480.2651.

### Reactivity and Mechanistic studies.

### Ugi-type reaction with the acridinium salt intermediate (**1a'**)<sup>1c</sup>: synthesis of N-*p*-toluyl-N-cyclohexyl-10-methyl-acridane-9-carboxamide (**6aa**)



In an oven-dried screw cap schlenk dry **1a'** (58.6 mg, 0.2 mmol, 1 equiv.) was dissolved in dry MeCN (2 mL). Then cyclohexyl isocyanide **2** (49.7 μL, 0.4 mmol, 2 equiv.) and sodium *p*-toluate (34.5, 0.48 mmol, 2.4 equiv.) were added and the obtained mixture was stirred at room temperature for 4 h. After evaporating the solvent, the crude product was purified by by flash column chromatography (hexane/EtOAc, 9:1) obtain **6aa** as a white solid (27.8 mg, 0.058 mmol, 29%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): (300 MHz, CDCl<sub>3</sub>): □ 7.73 – 7.60 (m, 2H), 7.40 – 7.29 (m, 2H), 7.25 – 7.19 (m, 2H), 6.97 – 6.90 (m, 2H), 6.90 – 6.82 (m, 2H), 6.81 – 6.73 (m, 2H), 4.97 (s, 1H), 4.03 (tt, *J* = 12.0, 3.6 Hz, 1H), 3.41 (s, 3H), 2.51 (s, 3H), 1.76 – 1.57 (m, 4H), 1.52 – 1.44 (m, 1H), 1.30 – 1.25 (m, 2H), 1.14 – 0.99 (m, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): □ 176.0, 174.7, 144.0, 142.7, 135.0, 130.1, 129.5, 128.6, 128.4, 120.9, 120.5, 112.8, 59.3, 53.19, 33.3, 29.8, 26.3, 25.3, 21.9. HRMS (ESI-MS): Mass calc. for [C<sub>29</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>]<sup>+</sup>: *m/z* = 439.2380, found: *m/z* = 439.2381.

### Competition experiment

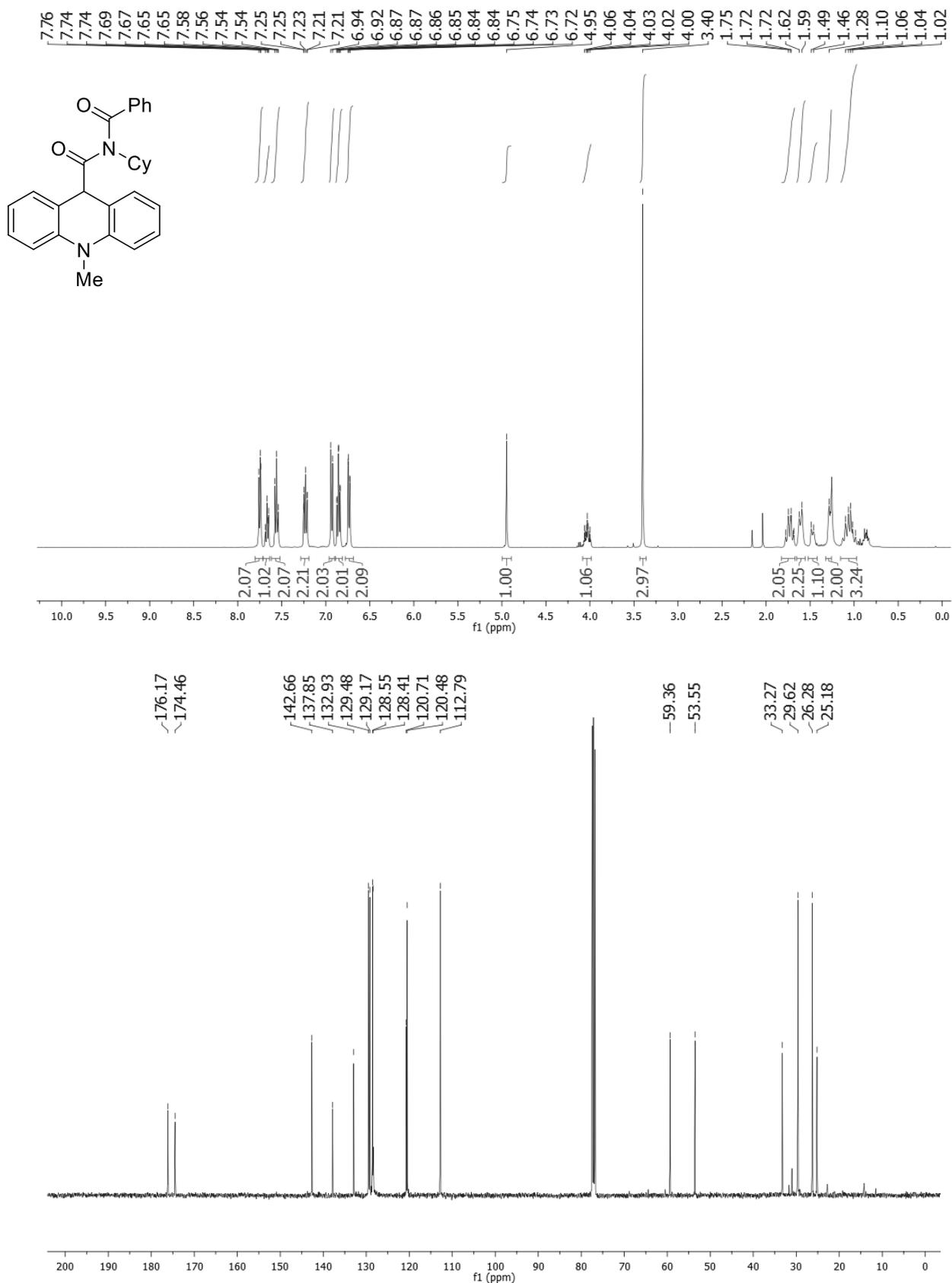
In an oven-dried screw cap schlenk dry Cu(OTf)<sub>2</sub> (5.4 mg, 0.015 mmol, 10 mol %), 2,2'-bipyridyne (7 mg, 0.045 mmol, 30 mol%), acridane **1a** (29.3 mg, 0.15 mmol, 1 equiv.) and *p*-toluic acid (24.5 mg, 0.18 mmol, 1.2 equiv.) were added following this order. The solid mixture was dissolved in acetonitrile (1.5 mL), then the cyclohexyl isocyanide **2a** (37.2 μL, 0.30, 2 equiv.) and benzoyl peroxide (43.1 mg, 0.18 mmol, 1.2 equiv.) were added following this order. The obtained mixture was stirred at room temperature for 4 h. After evaporating the solvent, the crude product was purified by by flash column chromatography (hexane/EtOAc, 9:1) obtain a mixture of **3aa** and **6aa** as a white solid (**3aa** + **6aa** 66:33, 29.1 mg, 29%)

## References

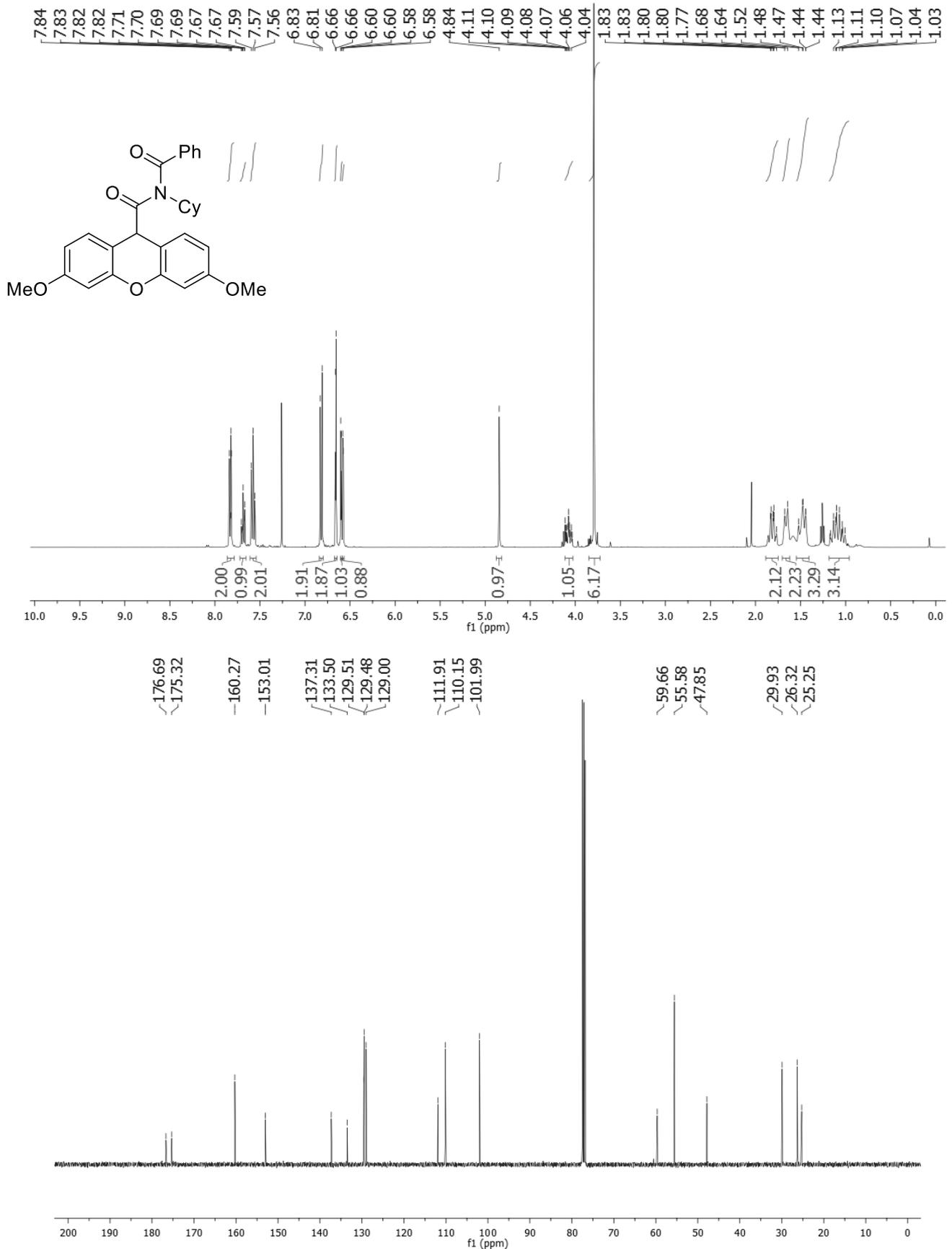
- 1 (a) C. Pal, M. K. Kundu, U. Bandyopadhyay and S. Adhikari, *Bioorg. & Med. Chem. Lett.*, 2011, **21**, 3563. (b) Á. Pintér and M. Klusmann, *Adv. Synth. Catal.*, 2012, 354, 701. (c) T. Stopka, L. Marzo, M. Zurro, S. Janich, E.-U. Würthwein, C. G. Daniliuc, J. Alemán and O. García Mancheño, *Angew. Chem. Int. Ed.*, 2015, **54**, 5049.
- 2 C. Zhang, S. Murarka and D. Seidel, *J. Org. Chem.*, 2009, **74**, 419.

Selected NMR examples

N-benzoyl-N-cyclohexyl-10-methyl-acridane-9-carboxamide (3aa)



# N-benzoyl-N-cyclohexyl-3,6-dimethoxy-xanthene-9-carboxamide (3pa)



# 5

## Summary / Zusammenfassung

Csp<sup>3</sup>-H bonds are ubiquitous in natural and synthetic molecules, but chemists are still struggling to develop general and convenient methodologies for a gentle and direct activation of such bonds. Indeed, new mild and regioselective processes involving the oxidative functionalization of high energetic Csp<sup>3</sup>-H bonds are highly desirable, especially when valuable heterocyclic scaffolds are involved. Following this perspective, in this thesis are presented my results on the mild Csp<sup>3</sup>-H bond oxidative activation involved in the synthesis, ring expansion and functionalization of heterocycles.

In **Chapter 2**, two different approaches in which the oxidative C-H functionalization is applied on the formation of reactive dipolar species trapped *in-situ* by dipolar cycloaddition are shown. In this context, the TEMPO mediated formal “dehydrogenation” of N-carbamoyl protected hydroxylamines, and the consequent trapping of the generated unstable nitrones were proposed. This methodology resulted as a very efficient approach for the synthesis of several N-acyl and N-carbamoyl isoxazolines, allowing also the reaction with more challenging substrate, such as alkyl and allyl hydroxylamine. Furthermore, a two-step one-pot azide formation/click-reaction preliminary study was displayed. The reaction consisted in a copper/hydroxylperoxide mediated Csp<sup>3</sup>-H activation, addition of trimethylsilyl-azide and the consecutive click-reaction step. This strategy, in its simplicity, resulted very versatile, and it allowed the formation of poly-heterocycles from unstable azide substituted systems.

In **Chapter 3**, applications of diazocompounds in expansion ring reaction of heterocycles *via* Csp<sup>3</sup>-H oxidative functionalization were further explored. Following the experience grown in the García's group, a novel methodology for the synthesis of demanding benzoazepine scaffold *via* TEMPO salt mediated Csp<sup>3</sup>-H oxidative functionalization/ring expansion of common tetrahydroisoquinoline was developed. Furthermore, a new synthetic pathway for a high value anti-obesity drug, so called Lorcaserin was proposed. Finally, a preliminary study for the achievement of a one-step Csp<sup>3</sup>-H bond functionalization/N-based expansion ring were displayed.

In **Chapter 4**, a novel oxidative activation/Ugi-type reaction was proposed. This strategy allowed for the first time the functionalization of benzylic Csp<sup>3</sup>-H bonds following a Ugi-type approach. In this way, several 9-imide acridanes and xanthenes were prepared, and the acridane scaffolds resulted a precursor of a novel and potent class of organo-photocatalyst. In addition, the proposed approach was also efficiently enrolled in the functionalization of other classes of substrate.

Csp<sup>3</sup>-H Bindungen sind sowohl in der Natur, als auch in synthetischen Molekülen allgegenwärtig. Chemikern ist es bis jetzt allerdings nicht gelungen, eine allgemein geeignete Methode zu entwickeln, um diese Art von Bindung mild und direkt zu aktivieren. Tatsächlich ist die Funktionalisierung von hoch energetischen Csp<sup>3</sup>-H Bindungen von sehr großen Interesse, besonders wenn heterozyklische Strukturen involviert sind. In diesem Zusammenhang, befasst sich meine Arbeit mit der milden oxidativen Csp<sup>3</sup>-H Bindungsaktivierung in der Synthese, Ringerweiterung und der Funktionalisierung von Heterozyklen.

In **Kapitel 2** werden zwei verschiedene Konzepte der oxidativen C-H Funktionalisierung gezeigt, bei der die Bildung reaktiver bipolarer Spezies, die dann *in situ* durch eine bipolare Zykladdition abgefangen werden, präsentiert. Vor diesem Hintergrund, wurde die durch TEMPO vermittelte formale „Dehydrogenierung“ von N-Carbamoyl geschützten Hydroxylaminen und das Abfangen der so gebildeten instabilen Nitrone entwickelt. Diese Methode zeigte sich sehr effizient in der Synthese verschiedener N-Acyl und N-Carbamoyl Isoxazoline, als auch bei der Umsetzung anspruchsvoller Substrate, wie Alkyl- und Allyl-substituierte Hydroxylamine. Des Weiteren, wurde eine vorläufige Studie einer zweistufigen Eintopf Azid-Bildungs- und Klick-Reaktion gezeigt. Die Reaktion basiert auf einer Kupfer/Hydroxylperoxid unterstützten Csp<sup>3</sup>-H Aktivierung, der Addition von Trimethylsilylazid und der konsekutiven Klick-Reaktion. Diese Strategie, in ihrer Einfachheit, ist ein vielseitiges Konzept für die Bildung von Polyheterozyklen ausgehend von labilen Azid-substituierten Systemen.

In **Kapitel 3** wurden die Anwendungen von Diazoverbindungen, an Ringerweiterungsreaktionen von Heterozyklen, *via* einer Csp<sup>3</sup>-H oxidative Funktionalisierung erforscht. Eine neue Methode für die Synthese anspruchsvoller Benzazepinderivate durch die TEMPO-Salz vermittelte Csp<sup>3</sup>-H oxidative Funktionalisierung/Ringerweiterung üblicher Tetrahydroisoquinoline wurde entwickelt. Des Weiteren, wurde ein neuer Syntheseweg für das Arzneimittel Lorcaserin vorgeschlagen. Schließlich wurde eine vorläufige Studie über das Erlangen einer einstufigen Csp<sup>3</sup>-H Bindungsfunktionalisierung/N-basierte Ringerweiterung vorgestellt.

In **Kapitel 4** wurde eine neue oxidative Aktivierung/Ugi-artige Reaktion vorgestellt. Durch diese Strategie war zum ersten Mal eine Funktionalisierung benzylicher Csp<sup>3</sup>-H Bindungen über eine Ugi-artige Reaktion möglich. Verschiedene 9-Imide, Acridane und Xantheme wurden hergestellt, wovon die Acridanverbindungen eine neue und vielversprechende Klasse von Organo-Photokatalysatoren darstellt. Außerdem konnte das vorgeschlagene Konzept auch in der Funktionalisierung anderer Substanzklassen verwendet werden.

# 6

## Abbreviations

1,3-DC	1,3-dipolar cycloaddition
4-NHAc-T <sup>+</sup>	4-Acetoamido-2,2,6,6-tetramethyl-1-oxopiperidin-1-ium
4-NHAc-TEMPO	(4-Acetoamido-2,2,6,6-tetramethylpiperidin-1-yl)oxyl
4-OH-TEMPO	(4-hydroxy-2,2,6,6-tetramethylpiperidin-1-yl)oxyl
AcOEt	Ethyl Acetate
Ad	Adamantyl
BDE	Bond-dissociation energy
Bn	Benzyl
BOC	<i>tert</i> -Butyloxycarbonyl
BPO	Benzoyl Peroxide
bpy	2,2-Bipyridine
BTF	Trifluorotoluene
Bu	<i>n</i> -Butane
Cy	Cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DCE	Dichloroethane
DCM	Dichloromethane
DCP	Dicumyl Peroxide
DFT	Density functional theory
DMAD	Dimethyl acetylenedicarboxylate
DME	Dimethoxyethane
DMF	N,N-Dimethylformamide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DTBP	Di- <i>tert</i> -butyl peroxide
EDG	Electron-donating group
Et	Ethyl
EWG	Electron-withdrawing group

GC-MS	Gas chromatography – mass spectrometry
HAT	Hydrogen atom transfer
HPLC	High performance liquid chromatography
IBX	2-iodobenzoic acid
MeCN	Acetonitrile
Me	Methyl
MsOH	Methanesulfonic acid
MTBE	Methyl <i>tert</i> -butyl ether
N <sub>3</sub>	Azide
NMR	Nuclear magnetic resonance
OMe	Methoxy
Ph	Phenyl
PIDA	(Diacetoxyiodo)benzene
PIFA	(Bis(trifluoroacetoxy)iodo)benzene
Piv	Pivaoyl
SET	Single electron transfer
T <sup>+</sup>	2,2,6,6-tetramethyl-1-oxopiperidin-1-ium
<i>t</i> Bu	<i>tert</i> -Butyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
TFE	Tetrafluoroethylene
TfO	Triflate
TfOH	Triflic Acid
THBP	<i>tert</i> -Butyl hydroxy peroxide
THIQ	tetrahydroisoquinoline
TIPS	triisopropylsilyl
TMS	Trimethylsilyl

TMSCHN <sub>2</sub>	Trimethylsilyl diazomethane
TMSN <sub>3</sub>	Trimethylsilyl azide
TPTA	tris(4-bromophenyl)aminium hexachloroantimonate
Troc	2,2,2-Trichlorethoxycarbonyl
Tol	<i>p</i> -Tolyl