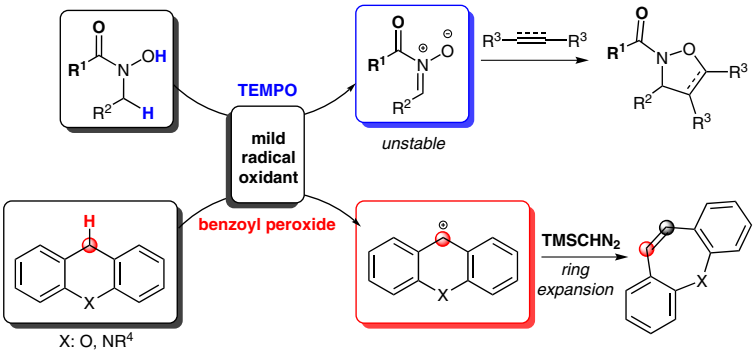
Synlett A. Gini, O. G. Mancheño Account

Mild Radical Oxidative sp³-Carbon–Hydrogen Functionalization: Innovative Construction of Isoxazoline and Dibenz[*b*,*f*]oxepine/azepine Derivatives

Andrea Gini[a,b]
Olga García Mancheño*[a,b]

[a] Institute for Organic Chemistry, University of Regensburg, Universitätsstr. 31, 93053 Regensburg, Germany
[b] Straubing Center of Science for Renewable Resources (WZS), Schulgasse 16, 94315 Straubing, Germany
olga.garcia-mancheno@chemie.uni-regensburg.de



Received: 28.08.2015
Accepted after revision: 09.10.2015
Published online: 18.01.2016
DOI: 10.1055/s-0035-1560908; Art ID: St-2015-a0680-a

Abstract Direct carbon–hydrogen bond functionalization has emerged as a powerful synthetic method for the straightforward and modular functionalization of organic molecules. In this account, we described our latest contributions in the area of oxidative sp³-carbon–hydrogen bond functionalization using mild radical oxidants for the construction of structurally important heterocycles. We have developed two new methodologies in which a new class of substrate and an uncommon nucleophilic reagent have been introduced to the existing palette of reaction partners for oxidative carbon–hydrogen functionalization. To achieve these results, the 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO) radical and a benzoyl peroxide/copper(I) system have been employed as oxidants for the dehydrogenative one-pot synthesis of *N*-alkoxycarbonyl-protected isoxazolines from hydroxylamines and for the synthesis of dibenz[*b*,*f*]oxepines, dibenzo[*b*,*f*]thiepines, and dibenz[*b*,*f*]azepines from simple xanthenes, thioxanthenes, and acridanes, respectively.

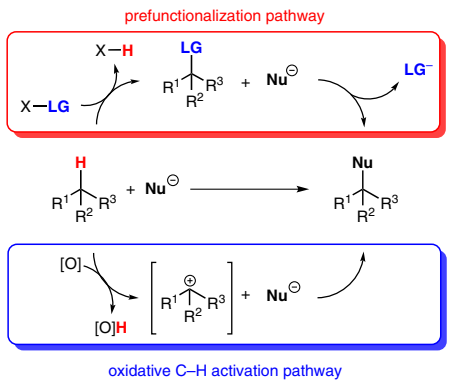
Key words carbon–hydrogen functionalization, oxidations, radicals, peroxides, heterocycles

1 Introduction

The activation and direct functionalization of carbon–hydrogen bonds, especially sp³-carbon–hydrogen, has always been a crucial topic in chemical synthesis.[1] Carbon–hydrogen bonds are ubiquitous in organic molecules, and a direct substitution of the hydrogen atom by the desired fragment or functional group is an attractive alternative to the more common multistep synthetic approaches.

In the standard methodologies (Scheme 1, top), selective functionalization at a specific sp³-carbon–hydrogen bond requires the initial installation of a common functional group (e.g., by halogenation or oxygenation). This preinstalled simple unit then acts as a leaving group (LG) for the final introduction of the desired functionality (Nu). Thus, inevitably, stoichiometric amounts of waste (H–X and LG^-) are generated.[2]

Instead, a method directly involving the carbon–hydrogen bond provides a significant reduction of synthetic steps and intrinsic waste owing to the absence of the sacrificial functional group LG (Scheme 1, bottom).[3] In this context, oxidative sp³-carbon–hydrogen functionalization reactions have become an important and valuable synthetic approach. In the last decade, practical applications of this methodology in carbon–carbon and carbon–heteroatom coupling reactions have relentlessly increased.[4]



Scheme 1 Classical and oxidative sp³-carbon–hydrogen bond functionalization approaches

However, there are some important current limitations and unsolved issues within the above-mentioned oxidative sp^3-carbon–hydrogen bond coupling methods. Among them, it is worth mentioning the *still-restricted substrate and reagent scope*.[4]

The typical substrates enrolled present the sp^3-carbon–hydrogen bond α to functional groups (such as a nitrogen, an oxygen, or an arene) able to stabilize the formal ionic intermediate and/or to an electron-withdrawing group (EWG) to make the carbon more electrophilic (Figure 1), facilitating the oxidation step. The nucleophiles employed are mostly restricted to enolizable carbonyl compounds, nitroalkanes, electron-rich aromatic compounds, (in situ generated) organometallic reagents, (activated) olefins, and small, charged nucleophiles such as cyano and trifluoromethyl anions (Figure 1).

Another crucial factor to achieve the desired reactivity and selectivity on the target substrate is the choice of appropriate oxidant. The classical oxidants in oxidative sp^3-carbon–hydrogen functionalization can be classified into three big branches: oxygen,[5] quinones such as DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone),[6] and organic peroxides such as TBHP (*tert*-butyl hydroperoxide) or DTBP (di-*tert*-butyl peroxide) (Figure 1).[7]

Molecular oxygen is the cheapest and greenest oxidant, but lacks reactivity and often needs a transition-metal cata-

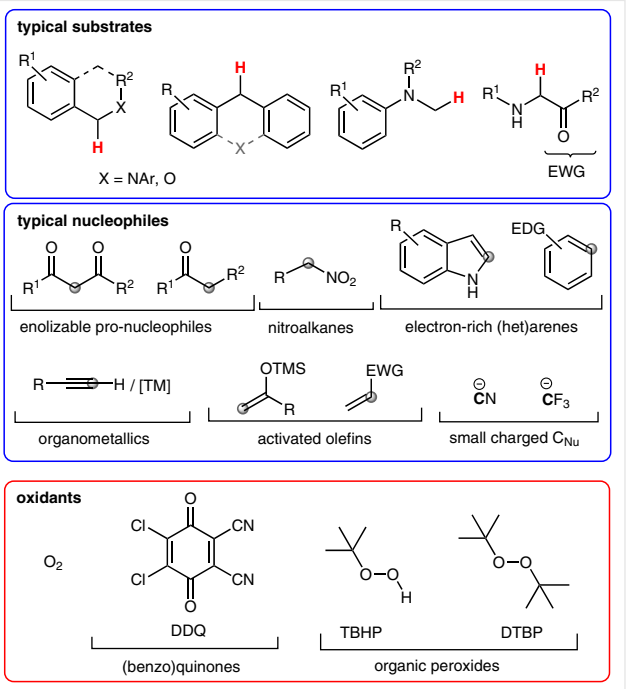
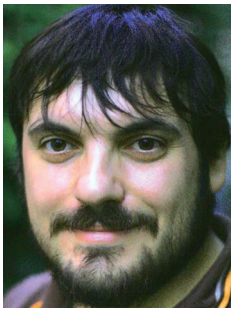


Figure 1 Most commonly used types of substrates, reagents, and oxidants

Biographical Sketches



Andrea Gini was born in Pisa in 1987. He received his bachelor's degree in chemistry in 2010 from the Università degli studi di Pisa under the supervision of Professor Dr. Fabio Bellina. In 2013, he received his master's degree in organic chemistry with *magna cum laude* from the Università degli studi di Pisa under the supervision of Professor Dr. Adriano Carpita. He joined the group of Professor Dr. Olga García Mancheño in 2014 and currently he is carrying out his Ph.D. between the University of Regensburg and the Straubing Center of Science for Renewable Resources. His current research activity focuses on the development of new carbon–hydrogen activation methods using unusual oxidants and reagents, and their application in the synthesis of highly valuable heterocycles.

Olga García Mancheño received her Ph.D. in 2005 from the Universidad Autónoma de Madrid under the supervision of Professor Juan C. Carretero. During her Ph.D., she also carried out two three-month research stays with Professor Manfred T. Reetz (Max-Planck-Institut für Kohlenforschung) and Professor Karl Anker Jørgensen (University of Aarhus). She next carried out a postdoctoral stay in the group of Professor Carsten Bolm at RWTH-Aachen University (2005–2008). At the end of 2008, she started her independent career as an assistant professor (Habilitand, mentor: Professor Frank Glorius) at the Westfälische Wilhelms University of Münster. In 2013, she was appointed as a professor of organic chemistry at the University of Regensburg and the Straubing Center of Science for Renewable Resources. Her main research interests include the development of new synthetic methods, with a special focus on catalytic approaches, and their application in the synthesis of bioactive compounds and heterocycles.

lyst as an intermediate oxidant. However, when the metal catalyst is nontoxic and cheap, such as iron (or copper), the use of molecular oxygen as a terminal oxidant can be very appealing.

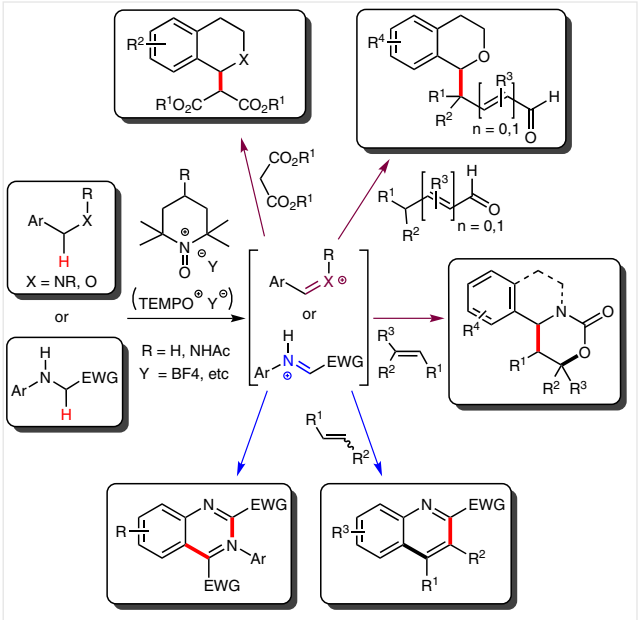
As an alternative, DDQ and the other reactive benzoquinones are widely employed as active species or secondary oxidants in dehydrogenative cross-coupling reactions.[6] However, the higher reactivity of DDQ with respect to oxygen and the nucleophilic behavior of the generated reduced hydroquinone form give some problems with sensitive substrates. In addition, the toxicity of benzoquinones discourages their use in large-scale applications.

Lastly, organic peroxides, such as TBHP,[7] are the most prominent oxidants in this type of carbon–hydrogen functionalization. Conversely, they might be considered the last choice because of their strong reactivity and therefore, in many cases, low selectivity.[8] As a result, the identification of new oxidation systems able to cover the deficiencies of the above-mentioned classical oxidants is crucial for future advances in the research area of oxidative carbon–hydrogen functionalization.

In our research program on carbon–hydrogen bond functionalization, we address the challenge of designing innovative transformations, aiming at the development of novel, mild oxidative reactions for the synthesis of valuable (bioactive) heterocycles. Since the first synthesis of the persistent 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO) radical by Lebedev and Kazarnovskii[9] in 1959, the versatility of this oxidative agent has been extensively demonstrated, both as the *N*-oxyl radical and as its *N*-oxoammonium salt derivatives (TEMPO$^+$ Y$^-$).[10] The oxidized form TEMPO$^+$ Y$^-$, in particular, presents unexplored potential as a valuable oxidant in sp^3-carbon–hydrogen functionalization. In fact, TEMPO salts are nontoxic and milder than typical organic peroxides or DDQ, probably the most used oxidants in oxidative sp^3-carbon–hydrogen functionalization.

In the last few years, our group has been dedicated to exploring further novel and valuable applications of this type of oxidant in dehydrogenative-type coupling reactions with sp^3-carbon–hydrogen bonds (Scheme 2).[11–15] We found that the tetrafluoroborate salt TEMPO$^+$ BF_4^- (R = H) or its related 4-acetamido derivative (R = NHAc) were able to easily activate isochromanes and tetrahydroisoquinolines by oxidation of the benzylic carbon–hydrogen bond α to the oxygen or nitrogen, respectively. The corresponding ionic intermediates were then able to react with enolizable pronucleophiles, such as malonates,[11] ketones, or aldehydes,[12] in the presence of a catalytic amount of an iron or copper Lewis acid species.

More interestingly, this type of oxidant also permitted the more challenging enrolment of simple, nonactivated, substituted olefins as reagent partners (Scheme 2). Thus, several oxidative carbon–hydrogen functionalization/cyclization tandem reactions with benzylic carbamates[13] and *N*-alkyl-substituted anilines[14,15] were developed in our laboratory. Despite the excellent results already obtained with this 'new generation' of oxidants, to extend further the scope of mild oxidative carbon–hydrogen functionalization, fine-tuned specific oxidation systems are still required.

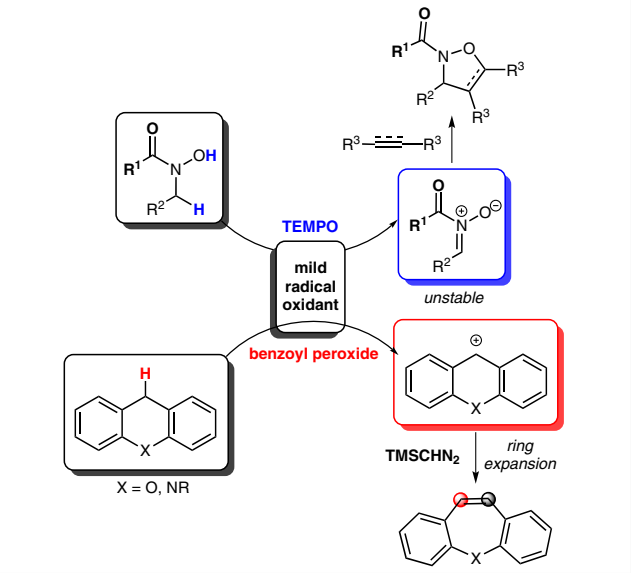


Scheme 2 Our previous achievements in oxidative sp^3-carbon–hydrogen functionalization with TEMPO$^+$ Y$^-$ oxidants

Our goal is to contribute to the development of more general and applicable oxidative carbon–hydrogen functionalization reactions by targeting the use of unexplored novel sensitive substrates and uncommon nucleophilic reagents that do not tolerate or react with the classical oxidants, but will lead to important types of heterocyclic structures. Following this aim, we initially focused our attention on two different targets: (1) the in-situ formation and trapping of unstable *N*-alkoxycarbonyl-substituted nitrones from the corresponding hydroxylamines[16] and (2) the use of trimethylsilyldiazomethane ($TMSCHN_2$) as an unusual reagent in oxidative carbon–hydrogen functionalization (Scheme 3).[17]

We found that in the first case the normal oxidants were too strong, leading to overoxidation and/or decomposition of both the substrate and the product, whereas simple TEMPO could be employed as a selective, mild radical oxidant. On the other hand, the reaction of xanthene and acridane derivatives with $TMSCHN_2$ required a more potent, but finely adjusted copper(I)/benzoyl peroxide oxidation system to promote a carbon–hydrogen functionalization/ring-expansion reaction.

In this account, these two recent contributions will be presented, including our original objectives, surprises, problems encountered, and achievements.



Scheme 3 Novel contributions with uncommon substrates and reagents

2 2,2,6,6-Tetramethylpiperidinyloxyl-Mediated Dehydrogenative Formation and Trapping of Unstable Nitrones: Synthesis of *N*-Alkoxycarbonyl-Protected Isoxazoline Derivatives

Among the five-membered heterocycles, 4-isoxazolines (2,3-dihydroisoxazoles)[18] constitute a privileged structure owing to their interesting biological activities as well as their wide applicability as building blocks for the preparation of several different functional groups (Figure 2).[19]

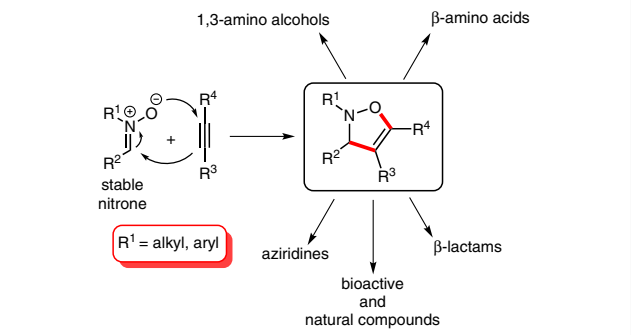
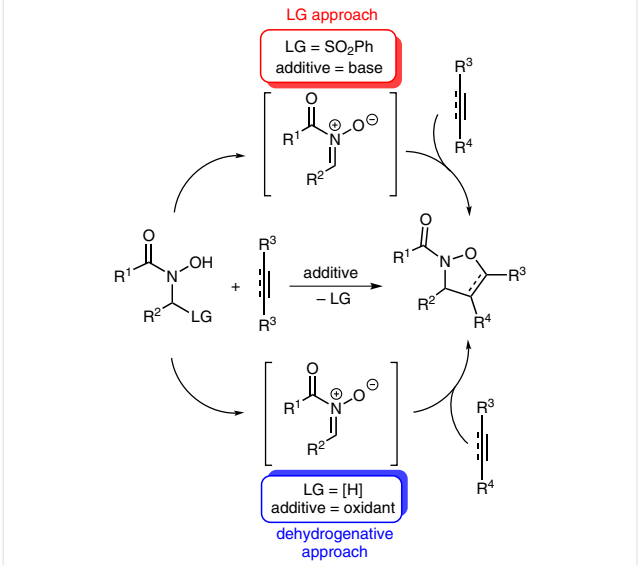


Figure 2 Versatility of 4-isoxazolines as building blocks and bioactive units

Several methods for the preparation of isoxazolines and isoxazolidines have already been described. They are mainly based on the 1,3-dipolar cycloaddition reaction (1,3-DC) between isolated, stable nitrones and a dipolarophile. However, these methodologies are essentially restricted to *N*-alkyl- and *N*-aryl-substituted nitrones (Figure 2, left).[20] This leads to isoxazolines where the protecting group is difficult to cleave or, in the worst case, it is irremovable.[21] Therefore, the synthetic scope for further applications embracing these methodologies is significantly restricted.

However, nitrones bearing removable electron-withdrawing groups, such *N*-acyl and *N*-alkoxycarbonyl moieties, are very attractive. Unfortunately, these dipole species are difficult to isolate and handle owing to their intrinsic instability. Only a few examples of 1,3-DCs as efficient methods to synthesize *N*-alkoxycarbonyl-protected isoxazolines have been reported in which the corresponding unstable nitrone intermediates are formed in situ.[22,23] However, the employed hydroxylamines must have a good leaving group, such as a sulfonyl, at the α-position to the nitrogen which can be removed under mild basic conditions (Scheme 4, top).[22a,b]

Alternatively, the procedures to directly synthesize N-protected nitrones lacking functionalization at the α-position from simple hydroxylamines generally involve condensation of an N-protected hydroxylamine with an aldehyde.[20,24] Nonetheless, the low nucleophilicity of the carbamoyl nitrogen means strong basic or acidic conditions are required to form the nitrone upon releasing an equivalent of water. Thus, the medium is not suitable for the cyclization process and the stability of the nitrone is compromised.[22,23] To solve this synthetic issue, we proposed an 'oxidative dehydrogenative' approach under mild conditions. The key strategy here was to find the right oxidant able to oxidize selectively the N-protected hydroxylamine without decomposing the in situ formed nitrone and allowing at the same time the subsequent cycloaddition reaction (Scheme 4, bottom).[16]

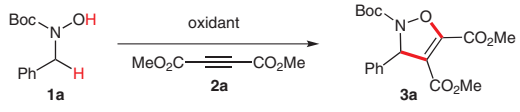


Scheme 4 Approaches for the in-situ generation and trapping of *N*-acyl- and *N*-alkoxycarbonyl-protected nitrones

Based on our experience of mild oxidative carbon–hydrogen functionalization, several oxidants were tested using the model reaction between *N*-benzyl-*N*-(*tert*-butoxycarbonyl)hydroxylamine (**1a**) and dimethyl acetylenedicarboxylate (DMAD, **2a**) as the dipolarophile at room temperature (Table 1). We first explored TEMPO$^+$ BF_4^- as the oxidant (entry 1)[11,15] which has shown large flexibility in several dehydrogenative cross-coupling reactions. However, with this type of substrate it did not provide the desired product. Other typical oxidants in dehydrogenative cross-coupling reactions, such as TBHP and DDQ, were employed, however without any success (entries 2 and 3, respectively). It is interesting to note that all of these oxidants led to full conversion of hydroxylamine **1a**. This might indicate that these reagents may be capable of the oxidation of **1a**, but not be compatible with the in situ formed nitrones.

Therefore, we next explored the possibility of employing a milder radical oxidant, since soft, nonradical conditions (e.g., with TEMPO$^+$ BF_4^- as a hydride-abstractor-type oxidant) were unsatisfactory. Thus, the TEMPO radical was chosen, although it is not a common oxidant in oxidative carbon–hydrogen functionalization.[10a–d] Gratifyingly, TEMPO provided a promising 25% yield at room temperature (entry 4). To improve the conversion the temperature was increased, leading to full conversion at 70 °C and good yield (87% yield) (entry 6).

Table 1 Optimization of the Model Reaction[a]

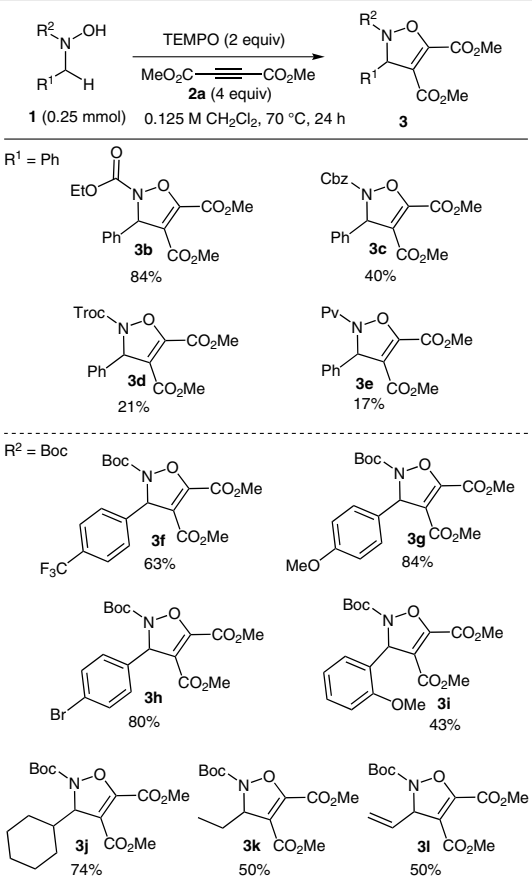


Entry	Oxidant (equiv)	Solvent	Temp (°C)	Yield[b] (%)
1	TEMPO$^+$ BF_4^- (2)	CH_2Cl_2	r.t.	<5
2	TBHP (2)	neat	r.t.	–
3	DDQ (2)	CH_2Cl_2	r.t.	<5
4	TEMPO (2)	CH_2Cl_2	r.t.	25
5	TEMPO (2)	CH_2Cl_2	50	75
6	**TEMPO (2)**	**CH_2Cl_2**	**70**	**87**

[a] **1a** (0.25 mmol, 1 equiv), **2a** (4 equiv), and oxidant in 0.125 M CH_2Cl_2 at the corresponding temperature for 24 h.
[b] Isolated yields.

Having this promising result in hand, the scope of the reaction with DMAD (**2a**) was extended to several differently substituted nitrones (Scheme 5). Initially, the effect of various acyl and alkoxycarbonyl nitrogen-protecting groups on *N*-benzylhydroxylamine was investigated. The *N*-Boc group (*N*-*tert*-butoxycarbonyl) showed a substantially better performance compared with the related acyl group *N*-pivaloyl (**3a** vs **3e**, 87 vs 17% yield, respectively) (Table 1, entry 6, and Scheme 5). Furthermore, other groups resulting in carbamate derivatives, such as ethyl carbamate **3b** (84% yield) and benzyl carbamate **3c** (40% yield), were also well tolerated (Scheme 5). However, the sterically hindered 2,2,2-trichloroethoxycarbonyl (Troc) group led to a very low yield of product **3d** (21% yield) and there were high decomposition levels under these reaction conditions.

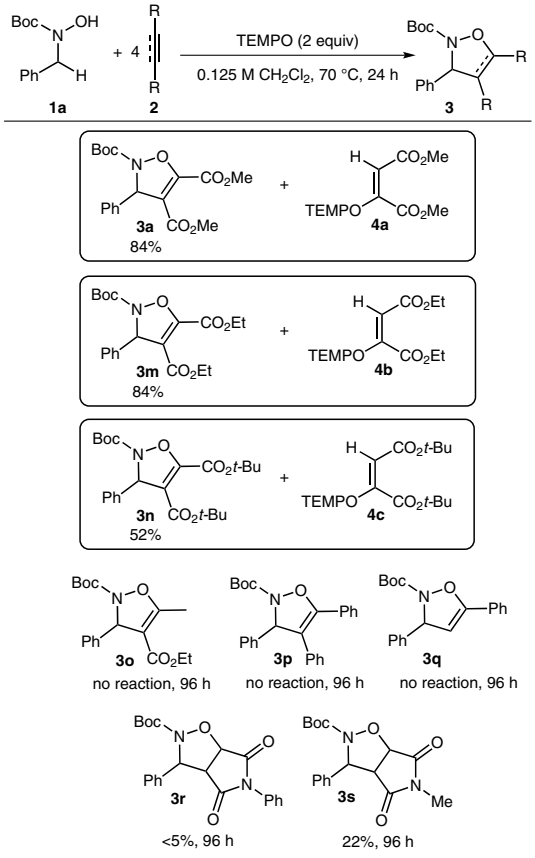
Considering the high efficiency of the Boc protecting group, a broad variety of *N*-Boc-protected substituted *N*-benzylhydroxylamines were tested next (Scheme 5). The reaction showed a broad scope, tolerating well electron-withdrawing, electron-donating, and halogen *para* substituents on the phenyl ring (63–84% yield). A more sterically demanding substrate such as an *ortho*-substituted *N*-benzylhydroxylamine also participated in the reaction, but the final isoxazoline was obtained in lower yield (e.g., **3i**, 43% yield). More interestingly, simple aliphatic and allyl-substituted hydroxylamines were also able to react under these conditions to form the desired products **3** in moderate to high yields (up to 74% yield). These are very appealing results, since in most of the previous reports on the in-situ generation and further use of this type of N-protected nitrone only the benzylic or only the aliphatic substrates were reactive.



Scheme 5 Scope of the reaction with different hydroxylamines

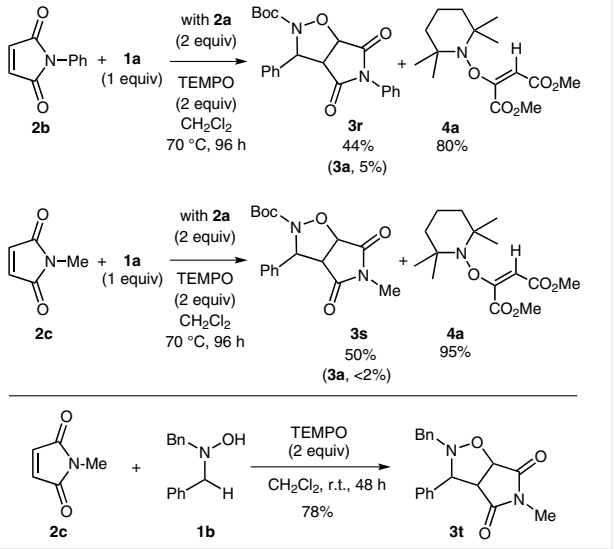
Various dipolarophiles were next investigated (Scheme 6). The reaction was not affected by the use of differently substituted acetylenedicarboxylate esters, such as the diethyl and di-*tert*-butyl derivatives giving **3m** and **3n**, respectively. However, it was found that the dipolarophile needed to have two electron-withdrawing groups to promote an efficient 1,3-DC, e.g. no reaction was observed to give products **3o**, **3p**, and **3q**. Additionally, the formation of byproducts **4a**–**c**, TEMPO–dipolarophile adducts,[25] in almost stoichiometric amounts was found when using the corresponding acetylenedicarboxylate esters as dipolarophiles.

The importance of this byproduct was recognized the first time during the screening of the different dipolarophiles. Thus, when this methodology was applied to other classes of typical dipolarophiles, such as *N*-phenyl- and *N*-methylmaleimide to give **3r** and **3s**, respectively, significant low conversions were observed and the addition byproduct was not detected. This can be explained by the better Michael acceptor nature of the acetylenedicarboxylate esters compared with maleimides, although maleimides are generally considered more efficient dipolarophile partners in 1,3-DCs.



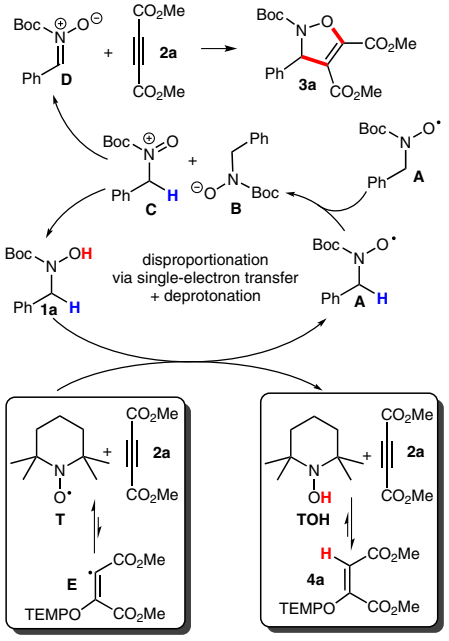
Scheme 6 Scope of the reaction with different dipolarophiles

Based on these observations, we envisioned an improvement of the conversion with the less-reactive maleimides by making use of the formation of byproduct **4a** using cheap DMAD (**2a**) as a co-reagent (Scheme 7). Thus, by adding **2a** as a sacrificial reagent in the reactions involving maleimides **2b** and **2c**, the yields of **3r** and **3s** increased up to approximately 10 or 2 times, respectively. It is interesting to note that the cycloaddition took place mostly on the maleimide, with only traces of the product with **2a** being formed (**3a**, <2–5% yield) along with byproduct **4a** in stoichiometric amounts. Unfortunately, other less-electron-deficient dipolarophiles, such as styrenes or vinyl ethers, did not provide the desired products, despite the presence of the sacrificial DMAD (**2a**) and the full consumption of hydroxylamine **1a**.



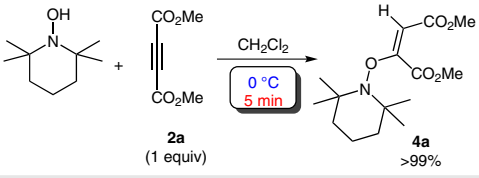
Scheme 7 Enrollment of maleimides: dimethyl acetylenedicarboxylate as a cheap sacrificial reagent

In contrast, the reaction conducted with *N*,*N*-dibenzylhydroxylamine (**1b**) and maleimide **2b** under standard conditions proceeded smoothly at room temperature providing the corresponding isoxazoline derivative in good yield (78% yield) (Scheme 7). It could be assumed then that the TEMPO radical can react easily for the formation of stable nitrones, like the *N*-benzyl derivative. Conversely, with unstable target molecules, the decomposition might be faster than the further reaction of those nitrones. Thus, to explain the good results obtained with the *N*-Boc-protected substrates, we envisioned that a transitory species and/or a more efficient radical intermediate would be involved. This radical species might be the first radical addition product between TEMPO and alkyne **2a** (intermediate **E**, Scheme 8). This hypothesis was made based on a similar radical intermediate in a radical 5-*exo*-dig cyclization postulated by König and Schreiner and co-workers.[26]



Scheme 8 The proposed mechanism

To further describe this curious behavior, a control reaction between TEMPO and **2a** in the absence of an N-protected hydroxylamine was conducted, but did not take place. On the other hand, the reaction with **2a** at 0 °C was incredibly fast using 2,2,6,6-tetramethylpiperidin-1-ol (TEMPOH), leading to near-quantitative yield of addition product **4a** (Scheme 9).[27]



Scheme 9 Addition of 2,2,6,6-tetramethylpiperidin-1-ol to the electron-poor Michael acceptor dimethyl acetylenedicarboxylate

Considering that the radical addition of TEMPO to DMAD (**2a**) is not a commonly reported easy process, a second hypothesis was then postulated: since the reduced form of the oxidant TEMPOH is a reactive nucleophilic species in the presence of Michael acceptors, a direct hydrogen radical abstraction from **1a** by TEMPO to form nitroxide intermediate **A** and TEMPOH might also be feasible (Scheme 8). With poor Michael acceptor molecules, such as ethyl methylacetylenecarboxylate or diphenylacetylene that would have produced **3o** and **3p**, respectively (see Scheme 6), the conjugate addition seems to be inefficient and the presence of free TEMPOH might assist in the decomposition of the unstable *N*-alkoxycarbonyl-protected nitroxides **A**. That could be a possible explanation for the lower performance with those substrates in the absence of DMAD (**2a**).

The course of the model reaction was followed by gas chromatography with a flame ionization detector during the first 7 hours (Figure 3). It was observed that hydroxylamine **1a** was rapidly consumed, even though the cycloaddition product arose comparably slowly. At the same time, almost two equivalents of **2a** were consumed, while the TEMPO addition byproduct **4a** formed at a similar rate. Furthermore, the nitrones could not be detected in any of the analysis conducted. Most probably the cycloaddition is a faster step of the process in comparison with the nitrone formation. Thus, it can be assumed that the nitrones would be consumed immediately after being generated. Since **1a** reacted comparably faster than the formation of **3a**, the rate-determining step of the reaction should take place after the formation of the first radical intermediate.

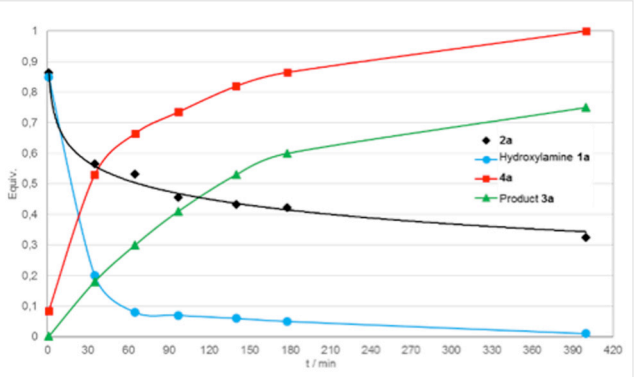


Figure 3 Kinetic study of the model reaction

With all this information, a plausible mechanism was proposed (Scheme 8). First, a hydrogen radical is removed from the hydroxylamine by TEMPO or the DMAD–TEMPO adduct to form nitroxide **A**. Unfortunately, neither of these two pathways, i.e. (1) direct hydrogen radical abstraction by TEMPO or (2) radical addition to the dipolarophile and subsequent hydrogen radical abstraction from the hydroxylamine, can be excluded. The formed radical **A** then disproportionates to anion **B** and oxoammonium species **C** via a single-electron transfer process. This is followed by deprotonation of **C** by **B** to give nitrone **D** and the substrate hydroxylamine **1a**. Finally, cycloaddition between nitrone **D** and the dipolarophile takes place to form the desired product.

To reinforce all of these assumptions, density functional theory (DFT) calculations were performed on the reaction pathway (Figure 4).[28] We were especially interested in studying the energetic differences between the two radical pathways involved in the formation of nitroxide **A**, byproduct **4a**, and nitrone **D**.

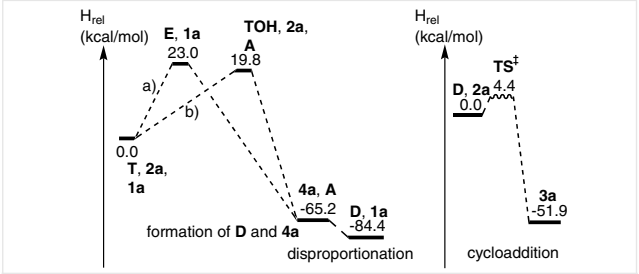


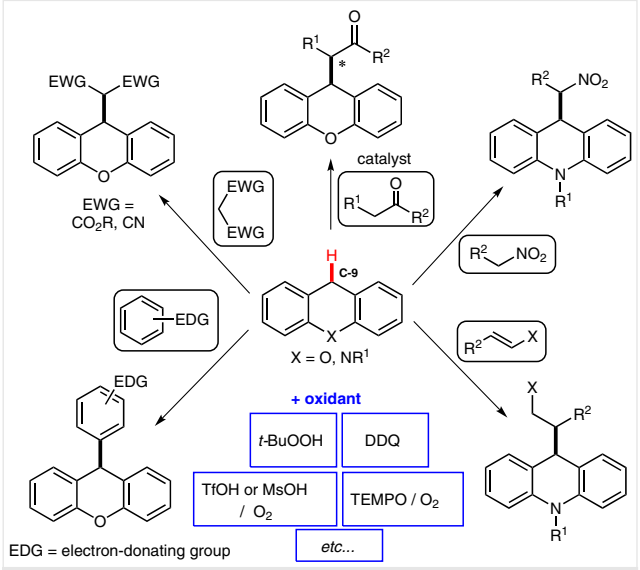
Figure 4 Density functional theory computational studies (B2PLYP-d3/TZVP//BP86-d3/TZVP) of the reaction pathways

The DFT calculations confirmed the difficulty in excluding one of the two possible endothermic routes, a and b, owing to the small difference between the relative enthalpies of the two pathways (Figure 4). Moreover no transition states could be found for the formation of radicals **A** and **E**. The DFT calculations also indicated that the disproportionation of **A** is an exothermic process. In addition, the final cycloaddition presented a low activation barrier of around 4.4 kcal/mol. Therefore, the 1,3-DC step should be fast enough to rapidly consume the nitrone and keep its concentration low during the reaction. This supports the lack of detection of nitrone **D**, upholding the kinetic studies. Moreover, the rate-determining step is likely to be one involved in the formation of the intermediate nitroxide **A** or nitrone **D**, and not the relatively favorable cycloaddition step.

3 Oxidative sp^3-Carbon–Hydrogen Bond Functionalization and Ring Expansion with Trimethylsilyldiazomethane: Synthesis of Dibenzoxepines, Dibenzothiepines, and Dibenzazepines

Oxidative cleavage of the carbon–hydrogen bond at C-9 of xanthene and acridane derivatives is an easy way to activate this position for cross-coupling reactions.[29] This carbon–hydrogen bond is quite weak (bond-dissociation energy of around 75 kcal/mol) and, consequently, the oxidation may be promoted with a wide spectrum of oxidants.[30] Despite the easy carbon–hydrogen bond cleavage in those substrates, the scope of the coupling reaction shown in Scheme 10 is still considerably limited by the nature of the nucleophile.[31]

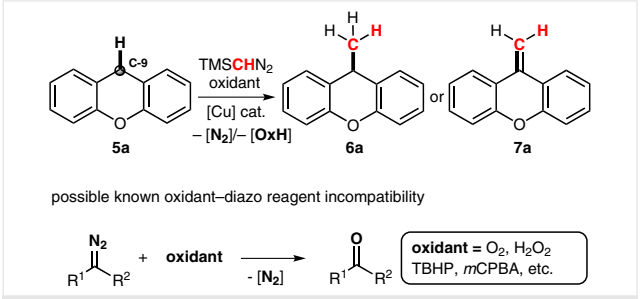
Many examples of the oxidative carbon–hydrogen functionalization of xanthenes and acridanes using enolizable nucleophiles, such as carbonyls or nitroalkanes, have been reported. However, in order to introduce different types of substituents at the C-9 position, such as alkyl or electron-poor aryl groups, in most cases it is necessary to use a Grignard or an organoboron reagent.[32] Owing to functional group incompatibilities based on the intrinsic reactivity of



Scheme 10 Oxidative carbon–hydrogen bond functionalization of xanthenes and acridanes

classical alkylating agents, 9-alkyl-substituted compounds are especially difficult to obtain and multistep approaches are usually required.[33] Thus, milder and more affordable alkylating nucleophilic agents are generally not suitable under the typical oxidative conditions used in this class of carbon–hydrogen bond functionalization. As a result, it is still very challenging to find a compromise for the reactivity between the oxidant and the nucleophilic species.[34]

We decided to tackle this problem by investigating, for the first time, the use of the less-explosive and -toxic version of diazomethane, $TMSCHN_2$, as a methylating or methylenating reagent in the carbon–hydrogen functionalization of xanthene (**5a**) (Scheme 11).[35,36]



Scheme 11 Our initial oxidative carbon–hydrogen methylation/methylenation approach and possible undesired reaction

The $TMSCHN_2$ reagent presents various attractive advantages over the less-benign and 'explosive' diazomethane while conserving the carbene reactivity. It has (1) a lower reactivity than diazomethane,[37] (2) a higher selectivity compared with classical methylating agents,[38] and (3) a sec-

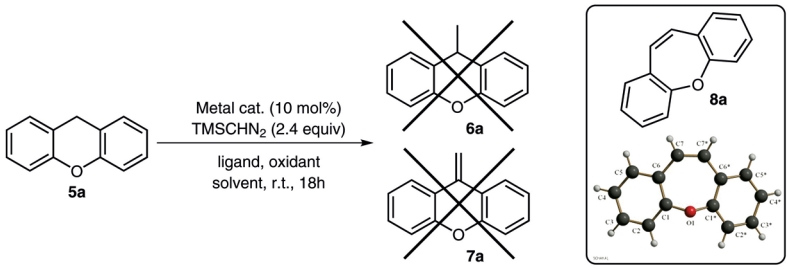
ond good leaving group, trimethylsilyl (TMS), that can be eliminated or promote further transformations. Having in mind the development of a new methylation or methylenation methodology, the use of a copper catalyst was initially explored to promote the formation of a reactive copper–carbene complex.[39,40] Thus, various oxidants were tested with xanthene (**5a**) and $TMSCHN_2$ in the presence of copper(II) triflate, which is reduced in situ by the diazo compound to copper(I) (Table 2).[40]

As expected, the typical oxidants TBHP, $TEMPO^+ BF_4^-$, and DDQ were inefficient (entries 2–4, respectively), most probably because they more readily oxidize $TMSCHN_2$ than the substrate. Nevertheless, DDQ slightly promoted the reaction, leading to 7% yield of a new product (entry 4). However, the product was something unexpected. Initially, we assumed two possibilities involving in situ TMS group elimination to give methylation product **6a** or, with standard copper–carbene chemistry, methylenation product **7a**. Mass spectrometry and NMR spectroscopic analysis confirmed the TMS elimination and the major product seemed to be **7a**. However, the NMR spectra were not in concordance with those reported in literature.[41] This led us to carry out a more accurate examination by X-ray analysis of this new product which showed that it was dibenzoxepine (**8a**). Therefore, the expansion of the inner ring took place instead of a simple nucleophilic addition to a postulated carbocation intermediate followed by TMS cleavage.

Although this result deviated from our initial targeted transformation, this synthetic approach to form dibenzoxepines that we had casually found was really appealing. These molecules are an important class of bioactive compounds[42] that lack literature-reported easy and fast synthetic methods for their preparation. The classical synthesis of dibenzoxepine, dibenzothiepine, and dibenzazepines from xanthene, thioxanthene, and acridanes, respectively, involves multistep processes to functionalize the benzylic position and introduce a CH_2LG unit (Scheme 12).[43] 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 desired product.[43]

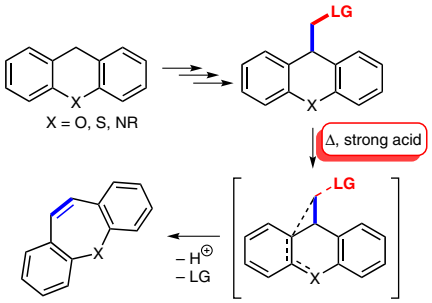
The newly discovered synthetic procedure, however, needed some improvement to make it synthetically applicable. A better performing oxidant, strong enough to activate the substrate, but at the same time mild enough to avoid the complete decomposition of $TMSCHN_2$, was required. Benzoyl peroxide was therefore tried as nonprotic, mild, stable organic peroxide. To avoid the thermal break of

Table 2 Optimization of the Reaction with Xanthene (**5a**)[a]



Entry	Catalyst	Oxidant (equiv)	Solvent	Ligand	Yield[b] (%)
1	$Cu(OTf)_2$	-	MeCN	–	–
2	$Cu(OTf)_2$	TBHP (1.2)	neat	–	trace
3	$Cu(OTf)_2$	$TEMPO^+ BF_4^-$(1.2)	MeCN	–	trace
4	$Cu(OTf)_2$	DDQ (1.2)	MeCN	–	7
5	$Cu(OTf)_2$	$(PhCO_2)_2$ (1.2)	MeCN	–	29
6	$Cu(OTf)_2$	$(PhCO_2)_2$ (1.2)	CH_2Cl_2	–	9
7	$FeCl_3$	$(PhCO_2)_2$ (1.2)	MeCN	–	12
8	$FeCl_3$	$(PhCO_2)_2$ (1.2)	CH_2Cl_2	–	24
9	$NiCl_2$	$(PhCO_2)_2$ (1.2)	MeCN	–	15
10	$RhCl_3$	$(PhCO_2)_2$ (1.2)	MeCN	–	19
11	$Cu(OTf)_2$	$(PhCO_2)_2$ (1.2)	MeCN	1,10-phenanthroline	44
12	$Cu(OTf)_2$	$(PhCO_2)_2$ (1.2)	MeCN	2,2′-bipyridine	55

[a] **5a** (0.20 mmol), $TMSCHN_2$ (0.48 mmol), oxidant, catalyst (10 mol%), and ligand in MeCN or CH_2Cl_2 (2.0 mL) at r.t. for 18 h under an argon atmosphere.
[b] Isolated yields.



Scheme 12 Dibenzoxepine, dibenzothiepine, and dibenzazepine synthesis by a multistep approach involving a Wagner–Meerwein-type rearrangement

the peroxide oxygen–oxygen bond, a metal catalyst such as copper(I), generated in situ from copper(II) triflate and $TMSCHN_2$, was employed to allow the reductive homolytic cleavage at room temperature.[44] Thus, a very promising 29% yield of ring-expansion product **8a** was obtained (Table 2, entry 5).

Other solvents and transition-metal catalysts were next tested (entries 6–10). Among these catalysts, iron(III) chloride gave a similar result to copper(II) triflate on changing the solvent to dichloromethane (entry 8). Based on the most encouraging result with $Cu(OTf)_2$ and benzoyl peroxide (entry 5), we next attempted to stabilize the copper catalyst in solution under the oxidative reaction conditions. To improve the performance of the catalyst, available, cheap, and simple *N*,*N*-bidentate ligands 1,10-phenanthroline and 2,2′-bipyridine were used (entries 11 and 12, respectively). The best result was obtained with 2,2′-bipyridine, leading to **8a** in 55% yield (entry 12). This methodology was then extended to differently substituted xanthenes and acridanes, as well as the less-reactive sulfur-derivative thioxanthene (Scheme 13).

Xanthenes provided dibenzoxepines in moderate to reasonably good yields (40–55%), whereas *N*-aryl- and *N*-alkyl-substituted acridanes led to dibenzazepines in typically higher yields (58–75%).[45] Interestingly, *N*-Boc-protected acridane also participated in this reaction, providing a dibenzazepine with an easily removable protecting group (**8e**, 41% yield). Both electron-withdrawing and -donating substituents on the aromatic rings of *N*-methylacridanes were well tolerated, providing **8i**–**k** in generally good yields.

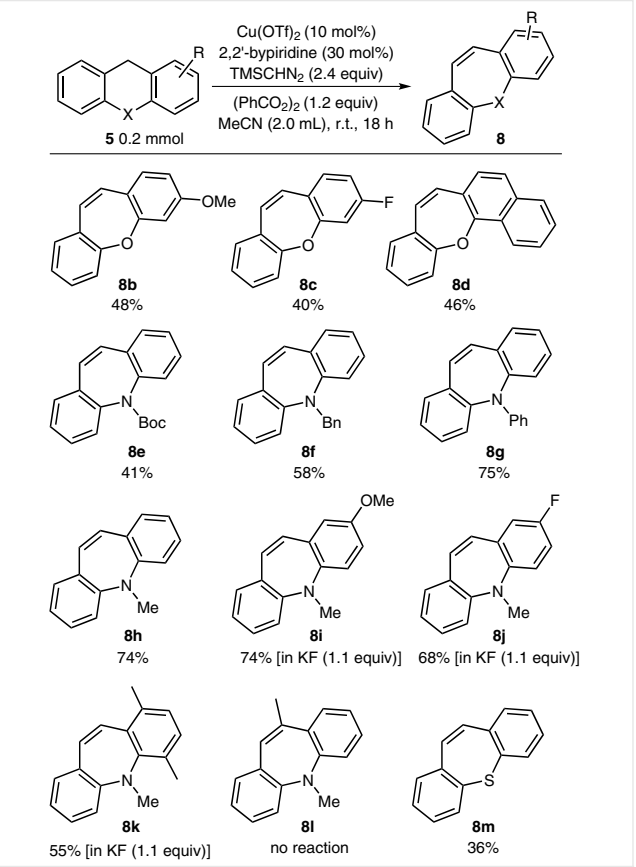
It is interesting to note that in the carbon–hydrogen functionalization of *N*-benzyl-protected acridane, complete C-9 selectivity was achieved, resulting in **8f**. Thus, no product of the reaction at the benzylic position of the protecting group was observed. On the other hand, substitution at the C-9 position was not tolerated, leading to no reaction (e.g., **8l** was not observed).

An interesting point to mention 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 dibenzazepines. Accordingly, in some cases the use of 1.1 equivalents of potassium fluoride (KF) provided higher yields of the desired product **8**. The presence of KF might help in the removal of the TMS group, especially for substrates where the elimination of this group is slow. Fortunately, the elimination problem was only observed in the case of acridanes with electron-withdrawing groups, such as that containing fluorine, providing **8j** along with the corresponding TMS-containing dibenzazepine as an inseparable mixture.

Finally, thioxanthene also reacted to give **8m** in moderate yield, despite the possible poisoning of the catalysts by coordination with the sulfur group.

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 our experimental observations, a reaction mechanism was postulated (Scheme 14). The exact role of the metal catalyst is still not fully understood, however we have excluded a carbene intermediate since similar results



Scheme 13 Scope of the reaction with differently substituted xanthenes, thioxanthene, and acridanes

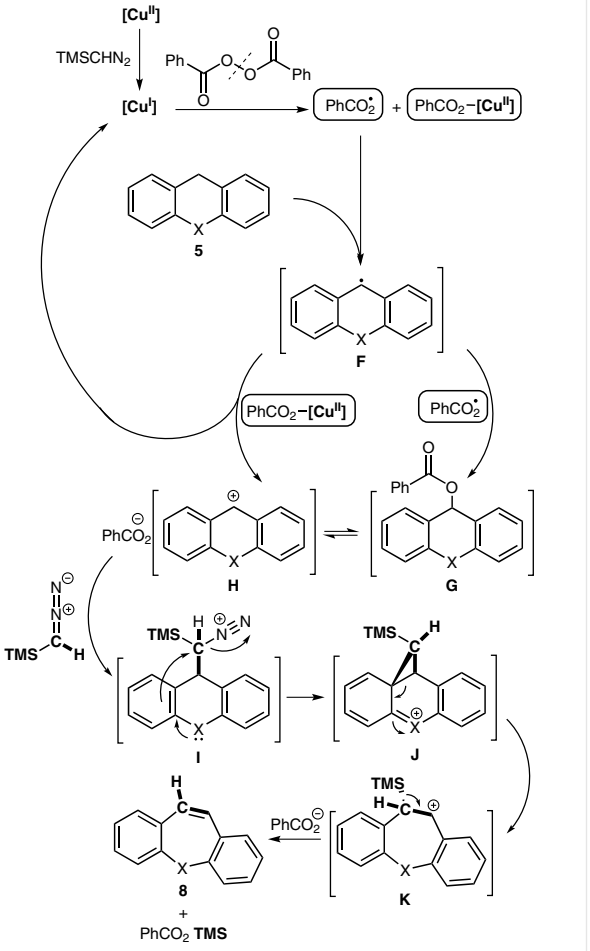
were obtained with different transition metals, including well-known and more efficient carbene precursors.

Consequently, we proposed a copper(I)-catalyzed reductive homolytic cleavage of the oxygen–oxygen bond of the benzoyl peroxide, giving a benzoyloxy radical and copper(II) benzoate. Then, the radical abstracts a hydrogen from the C-9 position of **5**, forming radical intermediate **F**. The copper(II) species then oxidizes intermediate **F** to generate carbocation **H** and regenerate the copper(I) catalyst. Besides this copper reduction step, it cannot be excluded that the excess of $TMSCHN_2$ operates as the main reducing agent, helping the metal species to return to its catalytically active oxidation state. Thus, an alternative mechanism may be involved in the formation of carbocation **H**.

This carbocation can also be formed by the reaction between the benzoyloxy radical and **F**. In this case, an unstable covalent intermediate **G** is formed which is in equilibrium with the reactive ionic form **H**.

Next the $TMSCHN_2$ reagent reacts as a nucleophile with the carbocation intermediate. After the addition, the reaction evolves to form three-membered ring system **J** promoted by the elimination of nitrogen. Ring expansion and restoration of aromaticity leads to carbocationic species **K**, which provides the final product by subsequent elimination of the silyl group with the assistance of the in situ generated phenyl carboxylate. This was supported by the formation of trimethylsilyl benzoate, the presence of which was confirmed by NMR spectroscopic analysis.

Lastly, to gain more insight into the mechanism and find out if our supposition about the unexpected ring-expansion process was reasonable, high-level DFT calculations in the gas phase were performed (Figure 5).[46]



Scheme 14 The proposed mechanism

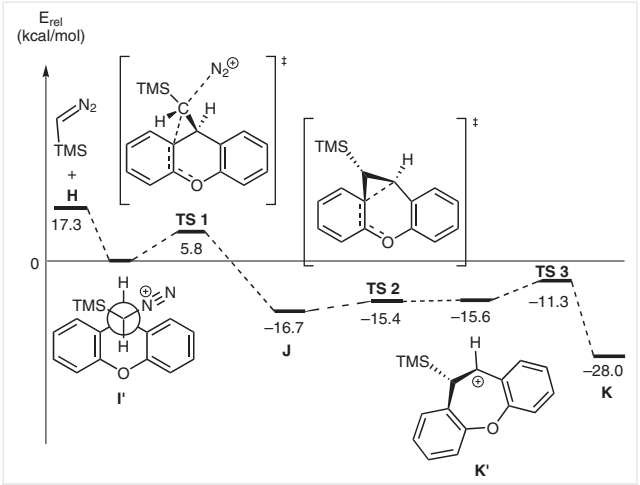


Figure 5 Density functional theory computational calculations on the reaction course

The DFT calculations further support our proposed mechanism. Thus, high-energy carbocation **H** reacts exothermically with $TMSCHN_2$ to give intermediate **I′** (the most stable conformer of **I**). This species leads to cyclopropane derivate **J** through an exothermic intramolecular S_N2-type reaction, where molecular nitrogen acts as the leaving group. The ring expansion then takes place giving a tricyclic carbocation with a strained conformation **K′**, which evolves quickly by ring inversion to give **K**.

4 Conclusions and Outlook

Important breakthroughs in the chemistry of oxidative sp^3-carbon–hydrogen bond functionalization reactions have been achieved in the last few years. However, there are still some important limitations and unsolved issues since most of the current efforts are focused only on the further use of standard oxidants to find new reaction partners. To get new substrates and reagents involved and to be able to expand this chemistry, it is crucial to explore other types of oxidants and systems.

In this account, we have presented innovative approaches dealing with this challenging issue. Two new easy one-step methods to obtain important classes of heterocycles, such as isoxazoline and dibenz[*b*,*f*]oxepine/azepine derivatives, have been achieved avoiding the classical multistep approaches. The key was the appropriate choice of oxidant for each targeted transformation, since it is essential to prevent overoxidation or undesired reactions of both the substrates and the coupling reagent partners. Moreover, we have shown within the second part of this account that this new focus can lead to further novel and/or unexpected carbon–hydrogen bond transformations.

Acknowledgment

The Deutsche Forschungsgemeinschaft is gratefully acknowledged for generous support.

References

(1) (a) *The Logic of Chemical Synthesis*; Corey, E. J.; Cheng, X. M., Eds.; John Wiley and Sons: New York, **1989**. (b) *Handbook of C–H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, **2005**.

(2) (a) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, **2004**. (b) *New Trends in Cross-Coupling: Theory and Applications*; Colacot, T., Ed.; The Royal Society of Chemistry: Cambridge, **2015**. See also: (c) Trost, B. M. *Science* **1991**, *254*, 1471. (d) Li, C.-J.; Trost, B. M. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 13197. (e) Shi, W.; Liu, C.; Lei, A. *Chem. Soc. Rev.* **2011**, *40*, 2761; and references cited therein.

(3) For example, see: (a) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010. (b) Newhouse, T.; Baran, P. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 3362. (c) Liu, C.; Liu, D.; Lei, A. *Acc. Chem. Res.* **2014**, *47*, 3459. (d) Sun, C. L.; Shi, Z. J. *Chem. Rev.* **2014**, *114*, 9219. (e) Roschangar, F.; Sheldon, R. A.; Senanayake, C. H. *Green Chem.* **2015**, *17*, 752.

(4) For selected recent reviews on oxidative carbon-hydrogen functionalization, see: (a) Scheuermann, C. J. *Chem. Asian J.* **2010**, *5*, 436. (b) Klussmann, M.; Sureshkumar, D. *Synthesis* **2011**, *3*, 353. (c) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (d) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem Rev.* **2011**, *111*, 1780. (e) Rohlmann, R.; García Mancheño, O. *Synlett* **2013**, *24*, 6. (f) Girard, S. A.; Knauber, T.; Li, C. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 74. (g) Narayan, R.; Matcha, K.; Antonchick, A. P. *Chem. Eur. J.* **2015**, *21*, 14678.

(5) For selected recent examples of carbon-hydrogen functionalization with molecular oxygen, see: (a) Vasseur, A.; Harakat, D.; Muzart, J.; Le Bras, J. *Adv. Synth. Catal.* **2013**, *355*, 59. (b) Liu, W.; Wang, S.; Zhan, H.; Lin, J.; He, P.; Jiang, Y. *Tetrahedron Lett.* **2014**, *55*, 3549. (c) Gigant, N.; Bäckvall, J.-E. *Chem. Eur. J.* **2014**, *20*, 5890. (d) Lu, Y.; Wang, H.-W.; Spangler, J. E.; Chen, K.; Cui, P.-P.; Zhao, Y.; Sun, W.-Y.; Yu, J.-Q. *Chem. Sci.* **2015**, *6*, 1923; and references cited therein. For a comprehensive overview, see: (e) Basle, O. In *From C-H to C-C Bonds: Cross-Dehydrogenative-Coupling*; Li, C.-J., Ed.; Royal Society of Chemistry: Cambridge, **2014**, RSC Green Chemistry No. 26, 197.

(6) For recent examples of carbon-hydrogen functionalization with DDQ, see: (a) Correia, C. A.; Li, C. J. *Adv. Synth. Catal.* **2010**, *352*, 1446. (b) Mitsudera, H.; Li, C. J. *Tetrahedron Lett.* **2011**, *52*, 1898. (c) Li, Y.; Cao, L.; Luo, X.; Deng, W. P. *Tetrahedron* **2014**, *70*, 5974. (d) Liu, X.; Sun, S.; Meng, Z.; Lou, H.; Liu, L. *Org. Lett.* **2015**, *17*, 2396.

(7) For selected recent examples of carbon-hydrogen functionalization with TBHP, see: (a) He, T.; Yu, L.; Zhang, L.; Wang, L.; Wang, M. *Org. Lett.* **2011**, *13*, 5016. (b) Zhou, M. B.; Song, R. J.; Ouyang, X. H.; Liu, Y.; Wei, W. T.; Denga, G. B.; Li, J. H. *Chem. Sci.* **2013**, *4*, 2690. (c) Min, C.; Sanchawala, A.; Seidel, D. *Org. Lett.* **2014**, *16*, 2756. (d) Niu, B.; Zhao, W.; Ding, Y.; Bian, Z.; Pittman, C. U.; Zhou, A.; Ge, H. *J. Org. Chem.* **2015**, *80*, 7251.

(8) Organic peroxides are not suitable for substrates with easily oxidable functional groups leading to overoxidation of the starting material or product; for example, see: (a) Kim, M.; Sharma, S.; Park, J.; Kim, M.; Choi, Y.; Jeon, Y.; Hwan, J.; In, K.; Kim, S. *Tetrahedron* **2013**, *69*, 6552. (b) Zhao, J.; Fang, H.; Han, J.; Pan, Y. *Org. Lett.* **2014**, *16*, 2530. (c) Niu, B.; Xu, L.; Xie, P.; Wang, M.; Zhao, W.; Pittman, C. U.; Zhou, A. *ACS Comb. Sci.* **2014**, *16*, 454. (d) Ali, W.; Behera, A.; Guin, S. K.; Patel, B. K. *J. Org. Chem.* **2015**, *80*, 5625.

(9) (a) Lebedev, O. L.; Kazarnovskii, S. N. *Tr. Khim. Khim. Tekhnol.* **1959**, *2*, 649; *Chem. Abstr.* **1962**, *56*, 15479f. (b) Lebedev, O. L.; Kazarnovskii, S. N. *Zh. Obshch. Khim.* **1960**, *30*, 1631; *Chem. Abstr.* **1961**, *55*, 1473.

(10) For selected reviews on TEMPO chemistry, see: (a) Sheldon, R. A.; Arends, I. W. C. E. *Adv. Synth. Catal.* **2004**, *346*, 1051. (b) Vogler, T.; Studer, A. *Synthesis* **2008**, 1979. (c) Tebben, L.; Studer, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 5034. (d) García Mancheño, O.; Stopka, T. *Synthesis* **2013**, *45*, 1602. For reviews on N-oxoammonium chemistry, see: (e) Bobbitt, J. M.; Flores, M. C. L. *Heterocycles* **1988**, *27*, 509. (f) Bobbitt, J. M.; Brückner, C.; Merbouh, N. *Oxoammonium- and nitroxide-catalyzed oxidations of alcohols*, In *Organic Reactions*; Vol. 74; Denmark, S. E., Ed.; Wiley: New York, **2009**, 103. See also: (g) Mercadante, M. A.; Kelly, C. B.; Bobbitt, J. M.; Tilley, L. J.; Leadbeater, N. E. *Nat. Protoc.* **2013**, *8*, 666.

(11) Richter, R.; García Mancheño, O. *Eur. J. Org. Chem.* **2010**, 4460.

(12) Richter, H.; Rohlmann, R.; García Mancheño, O. *Chem. Eur. J.* **2011**, *17*, 11622.

(13) Richter, R.; García Mancheño, O. *Org. Lett.* **2011**, *13*, 6066.

(14) Rohlmann, R.; Stopka, T.; Richter, H.; García Mancheño, O. *J. Org. Chem.* **2013**, *78*, 6050.

(15) Richter, H.; Fröhlich, R.; Daniliuc, C. G.; García Mancheño, O. *Angew. Chem. Int. Ed.* **2012**, *51*, 8656.

(16) Gini, A.; Segler, M.; Kellner, D.; García Mancheño, O. *Chem. Eur. J.* **2015**, *21*, 12053.

(17) Stopka, T.; Marzo, L.; Zurro, M.; Janich, S.; Würthwein, E.-U.; Daniliuc, C. G.; Alemán, J.; García Mancheño, O. *Angew. Chem. Int. Ed.* **2015**, *54*, 5049.

(18) For selected reviews, see: (a) Grünanger, P.; Vita-Finzi, P. *Isoxazolines (Dihydroisoxazoles)*, In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C.; Weissberger, A., Eds.; John Wiley and Sons: Hoboken, NJ, **1991**, Part 1, Vol. 49, 417. (b) Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2010**, 3363.

(19) For example, see: (a) Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Eur. J.* **2009**, *15*, 7808. (b) Wei, H.; Qiao, C.; Liu, G.; Yang, Z.; Li, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 620; and references cited therein.

(20) (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (b) Merino, P. In *Science of Synthesis*; Vol. 27; Padwa, A., Ed.; Thieme: Stuttgart, **2004**, 511. (c) Grigor'ev, I. A. In *Nitrile Oxides, Nitrones and Nitronates*

in Organic Synthesis: Novel Strategies in Synthesis; Feuer, H., Ed.; John Wiley and Sons: Hoboken, NJ, **2008**, 2nd ed. 129. See also: (d) Cardona, F.; Goti, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 7832; and references cited therein.

(21) For stable N-protected nitrones, such as benzyl, allyl, or glycosyl derivatives, see: (a) Confalone, P. N.; Pizzolato, G.; Lollar-Confalone, D.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1980**, *102*, 1954. (b) Vaseila, A.; Voeffray, R. *Helv. Chim. Acta* **1982**, *65*, 1953. (c) Cicchi, S.; Marradi, M.; Corsi, M.; Faggi, C.; Goti, A. *Eur. J. Org. Chem.* **2003**, 4152. (d) Ben Ayed, K.; Beauchard, A.; Poisson, J.-F.; Py, S.; Laurent, M. Y.; Martel, A.; Ammar, H.; Abid, S.; Dujardin, G. *Eur. J. Org. Chem.* **2014**, 2924.

(22) For the use of α-sulfonyl *N*-(alkoxycarbonyl)hydroxylamine precursors, see: (a) Guinchard, X.; Vallée, Y.; Denis, J.-N. *Org. Lett.* **2005**, *7*, 5147. (b) Gioia, C.; Fini, F.; Mazzanti, A.; Bernardi, L.; Ricci, A. *J. Am. Chem. Soc.* **2009**, *131*, 9614. For other in-situ approaches, see: (c) Partridge, K. M.; Anzovino, M. E.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 2920. (d) Hussain, S. A.; Sharma, A. H.; Perkins, M. J.; Griller, D. *J. Chem. Soc., Chem. Commun.* **1979**, 289.

(23) For examples of the in-situ formation of stable nitrones, see ref. 21a. For a recent photocatalytic oxidative approach, see: (a) Hou, H.; Zhu, S.; Pan, F.; Rueping, M. *Org. Lett.* **2014**, *16*, 2872. See also: (b) Morita, N.; Kono, R.; Fukui, K.; Miyazawa, A.; Masu, H.; Azumaya, I.; Ban, S.; Hashimoto, Y.; Okamoto, I.; Tamura, O. *J. Org. Chem.* **2015**, *80*, 4797. See also refs. 19 and 20.

(24) Vaalizadeh, H.; Dinparast, L. *Heteroat. Chem.* **2009**, *20*, 177; and references cited therein.

(25) For an example of the addition of hydroxyl radicals to activated olefins, see: (a) Grant, R. D.; Rizzardo, E.; Solomon, D. H. *J. Chem. Soc., Perkin Trans. 2* **1985**, 379. For related additions with TEMPO, see: (b) Babiarz, J. E.; Cunkle, G. T.; DeBellis, A. D.; Eveland, D.; Pastor, S. D.; Shum, P. *J. Org. Chem.* **2002**, *67*, 6831. (c) Coseri, S.; Ingold, K. U. *Org. Lett.* **2004**, *6*, 1641. (d) Kang, Y.-W.; Choi, Y.-J.; Jang, H.-Y. *Org. Lett.* **2014**, *16*, 4842.

(26) König, B.; Pitsch, W.; Kleon, M.; Vasold, R.; Prall, M.; Schreiner, P. R. *J. Org. Chem.* **2001**, *66*, 1742.

(27) For an example of the nucleophilic addition of secondary hydroxylamines to Michael acceptors, such as DMAD, see: Crescenzi, B.; Kinzel, O.; Muraglia, E.; Orvieto, F.; Pescatore, G.; Rowley, M.; Summa, V. WO2004058756, **2004**.

(28) Calculated relative enthalpy profiles (kcal/mol) by DFT in the gas phase (B2PLYP-D3/def2-TZVP//BP86-D3/def2-TZVP). The calculations were performed using Turbomole 6.5 within Gaussian basis sets. For an article on Turbomole, see: (a) Furche, F.; Ahlrichs, R.; Hättig, C.; Klopper, W.; Sierka, M.; Weigend, F. *WIREs Comput. Mol. Sci.* **2014**, *4*, 91. Gaussian software: (b) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A. Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Rhaghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian09 (Revision B.01)*; Gaussian Inc: Wallingford CT, **2010**.

(29) (a) Benfatti, F.; Capdevila, M. G.; Zoli, L.; Benedetto, E.; Cozzi, P. G. *Chem. Commun. (Cambridge)* **2009**, 5919. (b) Ho, X.-H.; Mho, S.-i.; Kang, H.; Jang, H.-Y. *Eur. J. Org. Chem.* **2010**, 4436. (c) Zhang, B.; Cuia, Y.; Jiao, N. *Chem. Commun.* **2012**, *48*, 4498. (d) Schweitzer-Chaput, B.; Sud, A.; Pint, R.; Dehn, S.; Schulze, P.; Klussmann, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 13228. (e) Pandey, G.; Jadhav, D.; Tiwari, S. K.; Singh, B. *Adv. Synth. Catal.* **2014**, *356*, 2813.

(30) Trumbull, K. A.; Branchaud, B. P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5544.

(31) Pintér, Á.; Klussmann, M. *Adv. Synth. Catal.* **2012**, *354*, 701.

(32) For example, see: (a) Akhavan-Tafti, H.; De Silva, R.; Sandison, M.; Handley, R. US20030232405, **2003**. (b) Chen, W.; Xie, Z.; Zheng, H.; Lou, H.; Liu, L. *Org. Lett.* **2014**, *16*, 5988. (c) Muramatsu, W. *Nakano K.* **2015**, *17*, 1549. For the alternative use of a strong base, see: (d) Sha, S. C.; Zhang, J.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2013**, *135*, 17602.

(33) For some examples implying a multistep approach, see: (a) Barton, D. H. R.; Bould, L.; Clive, D. L. J.; Magnus, P. D.; Hase, T. *J. Chem. Soc. C* **1971**, 2204. (b) Jones, G. W.; Chang, K. T.; Shechter, H. *J. Am. Chem. Soc.* **1979**, *101*, 3906. (c) Lapin, S. C.; Schuster, G. B. *J. Am. Chem. Soc.* **1985**, *107*, 4243.

(34) For an example of the undesired oxidation of diazomethane derivatives to ketones, see: Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1986**, *27*, 2005.

(35) (a) Lappert, M. F.; Lorberth, J. *Chem. Commun.* **1967**, 836. (b) Seyferth, D.; Dow, A. W.; Menzel, H.; Flood, T. C. *J. Am. Chem. Soc.* **1968**, *90*, 1080. (c) Seyferth, D.; Menzel, H.; Dow, A. W.; Flood, T. C. *J. Organomet. Chem.* **1972**, *44*, 279.

(36) For examples of carbon-hydrogen methylations with $TMSCHN_2$, see: (a) Aoyama, T.; Shioiri, T. *Synthesis* **1988**, 228. (b) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Synthesis* **1994**, 1283. For examples of methylenation-type reactions, see: (c) Lebel, H.; Paquet, V.; Proulx, C. *Angew. Chem. Int. Ed.* **2001**, *40*, 2887. (d) Dabrowski, J. A.; Moebius, D. C.; Wommack, A. J.; Kornahrens, A. F.; Kingsbury, J. S. *Org. Lett.* **2010**, *12*, 3598.

(37) For example, see: (a) Hoshimoto, N.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1980**, *21*, 46199. (b) Cesar, I.; Dolenc, M. S. *Tetrahedron Lett.* **2001**, *42*, 7099; and references cited therein.

(38) For some examples of transformations with $TMSCHN_2$, see: (a) Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1990**, *31*, 5507. (b) Kühnel, E.; Laffan, D. D. P.; Lloyd-Jones, G. C.; Martinez del Campo, T.; Shepperson, I. R.; Slaughter, J. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 7075. (c) Francais, A.; Leyva-Pérez, A.; Etxebarria-Jardi, G.; Pena, J.; Ley, S. V. *Chem. Eur. J.* **2011**, *17*, 329. (d) Cheng, J.; Qi, X.; Li, M.; Chen, P.; Liu, G. *J. Am. Chem. Soc.* **2015**, *137*, 2480.

(39) (a) Doyle, M. P.; Tamblyn, W. H.; Bagheri, V. *J. Org. Chem.* **1981**, *46*, 5094. (b) Zhao, X.; Zhang, Y.; Wang, J. *Chem. Commun.* **2012**, *48*, 10162; and references cited therein.

(40) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 3300.

(41) Okuma, K.; Nojima, A.; Matsunaga, N.; Shioji, K. *Org. Lett.* **2009**, *11*, 169.

(42) For some examples of bioactive derivatives, see: (a) Bischoff, S.; Vassout, A.; Delini-Stula, A.; Waldmeier, P. *Pharmacopsychiatry* **1986**, *19*, 306. (b) Michael-Titus, A.; Costentine, J. *Pain* **1987**, *31*, 391. (c) Bougerolle, A. M.; Dordain, G.; Berger, J. A.; Eschalier, A. *Life Sci.* **1992**, *50*, 161. (d) Möller, H.-J.; Volz, H. P.; Reimann, L. W.; Stoll, K.-D. *J. Clin. Psychopharmacol.* **2001**, *21*, 59. (e) Kalis, M. M.; Huff, N. A. *Clin. Ther.* **2001**, *23*, 680. (f) Fernández, B.;

Romero, L.; Montero, A. In *Antidepressants, Antipsychotics, Anxiolytics: From Chemistry and Pharmacology to Clinical Application*; Buschmann, H.; Díaz, J. L.; Holenz, J.; Párraga, A.; Torrens, A.; Vela, J. M., Eds.; Wiley-VCH: Weinheim, **2007**, 248.

(43) For examples based on the Wagner-Meerwein rearrangement, see: (a) Stolle, R. J. *Prakt. Chem. Naturforsch.* **1922**, *105*, 137. (b) Martinet, J.; Dansette, A. *Bull. Soc. Chim. Fr.* **1929**, *45*, 101. (c) Anet, F. A.; Bavin, P. M. G. *Can. J. Chem.* **1957**, *35*, 1084. (d) Newman, M. S.; Powell, W. H. *J. Org. Chem.* **1961**, *26*, 812. (e) Razavi, Z.; McCapra, F. *Luminescence* **2000**, *15*, 239. (f) Elliott, E.-C.; Bowkett, E. R.; Maggs, J. L.; Bacsa, J.; Park, B. K.; Regan, S. L.; O'Neill, P. M.; Stachulski, A. V. *Org. Lett.* **2011**, *13*, 5592.

(44) For examples of the copper-catalyzed homolytic cleavage of peroxide oxygen-oxygen bonds, see: (a) Kochi, J. K. *Tetrahedron* **1962**, *18*, 483. (b) Gephart, R. T. III.; McMullin, C. L.; Sapienzynski, N. G.; Jang, E. S.; Aguila, M. J. B.; Cundari, T. R.; Warren, T. H. *J. Am. Chem. Soc.* **2012**, *134*, 17350. See also: (c) Walling, C.; Zao, C. *Tetrahedron* **1982**, *38*, 1105. (d) Li, P.; Qiu, K.-Y. *Macromolecules* **2002**, *35*, 8906. (e) Cui, Z.; Shang, X.; Shao, X.-F.; Liu, Z.-Q. *Chem. Sci.* **2012**, *3*, 2853. (f) Chena, H.-H.; Wanga, G.-Z.; Hana, J.; Xua, M.-Y.; Zhaoa, Y.-O.; Xua, H.-J. *Tetrahedron* **2014**, *70*, 212.

(45) With nonsymmetrical xanthenes and acridanes, a competitive addition takes place leading to a mixture of products where the carbon atom of the nucleophile $TMSCHN_2$ ends up either at C-9 or C-10 in favor of the attack of the more electron-rich phenyl ring. This was recognized by the reaction with bis-deuterated C-9-2D **5b** providing a 1.8:1 mixture of C-9-D and C-10-D **8b**.

(46) The relative energies (kcal/mol) were calculated by DFT in the gas phase (B2PLYP-D3/def2-TZVP//B3LYP/6-311+G(d,p)) within Gaussian basis sets, see also ref. 28b.