Radical-Type Aziridination with [Co\textsuperscript{III}(TAML\textsuperscript{red})]\textsuperscript{−} in Water; Understanding and Preventing Epoxidation via Nitrene Hydrolysis

Eva J. Meeus,\textsuperscript{1} Caroline J. Verhoef,\textsuperscript{1} Nicolaas P. Van Leest,\textsuperscript{1} Joost N. H. Reek\textsuperscript{1,*} and Bas de Bruin\textsuperscript{1,*}

\textsuperscript{1}Homogeneous, Supramolecular and Bio-inspired Catalysis Group, van ‘t Hoff Institute for Molecular Sciences, University of Amsterdam (UvA), Science Park 904, 1098 XH Amsterdam (The Netherlands)

*Correspondence: b.debruijn@uva.nl, j.n.h.reek@uva.nl

Abstract

Base-metal catalyzed nitrene transfer reactions in water are challenging, but have the potential to broaden the range of applications. Typically, these reactions suffer from the formation of oxygen containing side-products, of which the origin is not fully understood. Therefore, we set out to investigate aqueous styrene aziridination, using a water-soluble [Co\textsuperscript{III}(TAML\textsuperscript{red})]\textsuperscript{−} catalyst known to be active in radical-type nitrene transfer in organic solvents. The cobalt-catalyzed aziridination of styrene in water (pH = 7) yielded styrene oxide as the major product, next to minor amounts of aziridine. Based on 18O-labeling studies and catalysis experiments, we show that styrene oxide formation proceeds via hydrolysis of the nitrene-radical complex [Co\textsuperscript{III}(TAML\textsuperscript{red})][N(Ts)]\textsuperscript{−}. Computational studies support that this process is facile and yields an oxyl-radical complex [Co\textsuperscript{III}(TAML\textsuperscript{red})(O•)]\textsuperscript{−}, which is active in oxygen atom transfer to styrene. Based on these mechanistic insights, the pH was adjusted to afford selective aziridination in water.

Introduction

Transition metal catalyzed (radical-type) oxo, carbene and nitrene transfer reactions enable the direct functionalization of C–H and C=C double bonds, affording valuable products.\textsuperscript{1–6} For instance, biologically active molecules often contain fragments with carbon-nitrogen bonds at specific positions,\textsuperscript{7} with aziridines among the representative examples.\textsuperscript{8,9} Although the formation of such bonds typically requires multiple steps and harsh reaction conditions, N-group transfer reactivity allows direct functionalization under mild conditions.\textsuperscript{10–12} Base metal catalyzed (radical-type) nitrene transfer reactions have therefore received considerable attention in this field. However, these reactions are typically performed in organic solvents and mostly under inert and anhydrous conditions.\textsuperscript{13–15} This is due to the air- and water sensitivity of the generally reactive intermediates involved in these reactions.\textsuperscript{10}

Nevertheless, water could be considered as an ideal reaction medium for radical-type transformations. This is because of the relatively high bond dissociation enthalpy\textsuperscript{16} (BDE) of the HO–H bond (119 kcal mol\textsuperscript{−1}). A higher BDE should prevent direct hydrogen atom transfer (HAT) from the solvent, which is commonly observed for organic solvents with weak C–H bonds such as THF, toluene or acetonitrile (C(sp\textsuperscript{3})–H BDE of 90, 92 and 97 kcal mol\textsuperscript{−1} respectively).\textsuperscript{17–20} Enabling radical-type group transfer in aqueous medium may also open-up a wider range of (novel) applications. For example, the Mascareñas group recently demonstrated the application of group transfer in the fast-growing field of \textit{in vivo} catalysis.\textsuperscript{21} They studied how mitochondrial functions can be altered by the intracellular synthesis of quinoxalines, which is enabled by N–H carbene insertions.

To date, aqueous nitrene transfer reactions prove to be challenging. Examples of base-metal catalyzed radical-type nitrene transfer reactions in water are therefore scarce and have only been successfully performed in the presence of micelles.\textsuperscript{22,23} Interestingly, the few studies that do perform these transformations ‘purely’ in water (without use of e.g. micelles or phase transfer catalysts), report the formation of oxygen containing side-products.\textsuperscript{24–27} For example, catalytic olefin aziridination with iron and manganese complexes, using hypervalent iodine reagents (iminodioxinanes) as nitrene precursors, yielded epoxides next to the desired aziridine products. Although this work acknowledges the potential role of water,\textsuperscript{28} no in-dept studies on the formation of such side-products are reported. Therefore, the overall reactivity of (radical-type) metal-nitrene complexes in water still remains rather poorly understood (Scheme 1a).
To broaden the application of (radical-type) nitrene transfer catalysis in aqueous medium, the reactivity of nitrene (radical) complexes needs to be understood to allow rational approaches to selective catalysis protocols.\textsuperscript{28} It is thereby key to investigate how these transformations yield the undesired oxygen-containing products when carried out in water. The group of Che recently reported the formation of a Ru(VI)–oxo(alkylimido) complex via a Ru(VI)–bis(alkylimido) complex when dissolved in wet organic solvent under anaerobic conditions.\textsuperscript{30} The formed oxo complex subsequently enables oxygen atom transfer (OAT) yielding styrene oxide (Scheme 1b). It may thus be hypothesized that base-metal nitrene radical complexes suffer from hydrolysis, likely affording oxyl radical complexes active in OAT. Therefore, the goal of this study is to investigate the potential role of water in the formation of oxygen-containing side-products during radical-type nitrene transfer catalysis, and to explore the mechanism of this process.

Scheme 1. The potential role of water in radical-type nitrene transfer catalysis

(A) (Radical-type) nitrene transfer in aqueous medium can yield oxygen containing side-product formation.\textsuperscript{24-27}

(B) Previous study that reports on the formation an oxo complex from a nitrene complex, when dissolved in wet organic solvent under anaerobic conditions, and subsequent OAT.\textsuperscript{30}

During our previous studies, the formation and reactivity of nitrene radical adducts of a cobalt-TAML complex (TAML = Tetra-Amino Macrocyclic Ligand) were investigated in organic media.\textsuperscript{31} Interestingly, the TAML scaffold is redox-active when coordinated to cobalt. It was also shown that upon reaction with excess iminiodiane, PPh\textsubscript{4}[Co\textsuperscript{III}(TAML\textsuperscript{red})] is selectively converted to a bis-nitrene radical complex PPh\textsubscript{4}[Co\textsuperscript{III}(TAML\textsuperscript{red})][N*R]\textsubscript{2} (red = fully reduced tetra-anion, q = doubly-oxidized di-anionic ligand, R = tosyl or nosyl). With iminiodiane as the limiting reagent, a mono-nitrene radical complex is formed: PPh\textsubscript{4}[Co\textsuperscript{III}(TAML\textsuperscript{red})][N*R] (sq = mono-oxidized tri-anionic ligand-centered radical). Both nitrene radical complexes are best described as electrophilic one-electron-reduced Fischer-type nitrene radicals. Notably, the mono-nitrene radical is believed to be the catalytically active intermediate in both sulfimidation\textsuperscript{13} and olefin aziridination\textsuperscript{15} reactions under aerobic conditions (Scheme 2a). The productive C–N bond formation during aziridination reactions was reported to proceed via an unusual asynchronous transition state.\textsuperscript{13} Specifically, C–N bond formation occurs via nucleophilic attack of the nitrene lone-pair onto a (partially) formed styrene radical cation, as a result of initial substrate-to-ligand single-electron transfer, and not via the more commonly observed attack of the nitrene radical. Altogether, the reactivity of nitrene radicals on PPh\textsubscript{4}[Co\textsuperscript{III}(TAML\textsuperscript{red})] is well understood in organic solvents.

The cobalt-TAML complex has also been investigated for its reactivity in OAT to thioanisole by the group of Nam (Scheme 2a).\textsuperscript{34} They reported a Lewis acid-stabilized cobalt-oxo complex. Interestingly, their characterization was interpreted as the TAML scaffold being innocent (TAML\textsuperscript{red}) and the cobalt center being oxidized (Co\textsuperscript{IV}), which is in contrast to our findings with nitrene precursors. Based on \textsuperscript{18}O-labeling experiments the authors were able to show that the oxygen source affording the sulfoxide product is the cobalt(IV)-oxo complex [Co\textsuperscript{IV}(TAML\textsuperscript{red})(O)(SC\textsubscript{6}H\textsubscript{5})].\textsuperscript{35}

Given the well-understood behavior of cobalt-TAML complexes in (radical-type) N- and O-group transfer in organic media, we decided to use a water soluble [Co\textsuperscript{IV}(TAML\textsuperscript{red})]\textsuperscript{–} complex\textsuperscript{36} to investigate the role of water in side-product formation during aqueous radical-type nitrene transfer. In this study, we set out to validate the hypothesis that nitrene radical complexes suffer from hydrolysis, which yields oxyl radical complexes active in OAT. Specifically, the following key findings are reported in this work (see also Scheme 2b):

1. Hydrolysis of the nitrene radical complex [Co\textsuperscript{IV}(TAML\textsuperscript{red})(N'TS)\textsuperscript{–}] yields a cobalt-oxyl complex.
In contrast to earlier interpretations, NEVPT2-CASSCF calculations show that the electronic structure of this complex is best described as a triplet spin Co(III)-oxyl radical complex: \([\text{Co}^{\text{III}}(\text{TAML}^{\text{red}})(\text{O}^{\bullet})^{-}]\), with one unpaired electron mainly on the redox-active TAML scaffold, and the other unpaired electron in the Co–O \(\pi^*\)-symmetric antibonding orbital.

The formation of styrene oxide during alkene aziridination results from OAT with the \textit{in situ} formed \([\text{Co}^{\text{III}}(\text{TAML}^{\text{red}})(\text{O}^{\bullet})^{-}]\) complex.

Hydrolysis of the nitrene radical complex \([\text{Co}^{\text{III}}(\text{TAML}^{\text{red}})(\text{N}^{\bullet}\text{Ts})]^{-}\) can be controlled by changing the pH, yielding the desired aziridine product or styrene oxide selectively.

Scheme 2. Previous work on \([\text{Co}^{\text{III}}(\text{TAML}^{\text{red}})]^{-}\) and the outline of this work

(A) Previous work on the formation and reactivity of cobalt-TAML radical nitrene and oxo complexes in organic solvent.\(^{33,34}\)

(B) Epoxide formation in aqueous alkene aziridination proceeds via competitive hydrolysis of the radical nitrene complex, yielding an oxyl radical complex active in OAT.
Results and Discussion

[Co{sup III}(TAML{sup red})]-catalyzed aziridination in aqueous media

To investigate the competence of the water-soluble Li[Co{sup III}(TAML{sup red})] catalyst in aqueous medium, the aziridination reaction of styrene with PhINTs{sup III} (Ts = tosyl) was performed in Milli-Q and D{sub 2}O (to directly analyze the water layer by \textsuperscript{1}H NMR spectroscopy, Table S1), under aerobic conditions at 37°C (unless noted otherwise). Under these conditions, with 10 mol% Li[Co{sup III}(TAML{sup red})], styrene was converted into mostly the epoxide product (1) (35% yield, with respect to PhINTs) after two hours, whereas the aziridine product (2) was formed in minor amounts (3%) (entry 1, Table 1). In the presence of 10 mol% LiCl, or without any catalyst present, no product formation was observed at all (entry 2). Without iminiodiiniane present, no product formation was observed either (entry 3). Also a control reaction with p-toluenesulfonamide (TsNH{sub 2}) as the N-source (i.e. the decomposition product of PhINTs) did not yield any product (entry 4). Performing the reaction at room temperature (instead of 37°C) gave comparable yields (entry 5), which shows a marginal effect of the reaction temperature on the product selectivity. Most important, under anaerobic conditions, epoxide product 1 is still the major product formed (entry 6). This points to water, and not oxygen, playing a significant role in the formation of styrene oxide.

PhINNs (Ns = nosyl) has been explored as an alternative nitrene precursor for PhINTs in the catalytic alkene aziridination reaction as well. Notably, this relatively more electron withdrawing iminiodiiniane increases the yield of the aziridine product 2 (13%) and reduces the amount of epoxide product 1 formed (25%) (entry 7, Table 1), in comparison to reactions carried out with PhINTs (relatively electron donating, entry 1). Furthermore, a slightly different Li[Co{sup III}(TAML{sup red})] complex, with two chlorides instead of hydrogens installed on the TAML backbone (Scheme 2a, top), was used. The product ratios achieved with this catalyst are fairly similar with respect to the standard catalyst (entry 8 versus entry 1). This implies that substitutions on the TAML scaffold do not significantly influence the formation of styrene oxide. The fact that different N-sources afford other product ratios and that substitutions on the TAML scaffold do not affect epoxide formation, strongly suggests that the formed radical nitrene species [Co{sup III}(TAML{sup red})(N{sup Ts})]{sup red} is involved in the formation of styrene oxide.

To address the involvement of the radical nitrene intermediate, the Li[Co{sup III}(TAML{sup red})] catalyzed aziridination reaction of styrene was performed in the presence of the water-soluble radical trap 5,5-dimethyl-1-pyrroline N-oxide{sup III} (DMPO) under anaerobic conditions in D{sub 2}O. Addition of 5 equivalents of DMPO with respect to PhINTs (entry 9, Table 1) completely inhibited styrene oxide formation and only traces of aziridine product 2 were observed. Given the known reactivity of DMPO as a radical scavenger, this indicates that radical-type intermediates are generated and subsequently trapped. This is supported by ESI-HRMS analysis of the reaction mixture, which afforded a signal at the m/z value corresponding to [DMPO + NTs - H]{sup -} (calcd. m/z for C{sub 13}H{sub 17}N{sub 3}O{sub 5}: 281.0960, found m/z: 281.0965, Figure S9). Additional X-band EPR spectra of the reaction mixture confirm the formation of a DMPO-trapped radical (g{sub iso} = 2.0058, A{sub iso}{sup N} = 41.12, A{sub iso}{sup iso} = 8.24, Figure S10). Given that the ESI-HRMS analysis clearly shows the NTs adduct of DMPO, we propose that the species observed in the EPR spectra is the trapped NTs radical. This confirms the initial nitrene radical formation on the cobalt complex. The absence of epoxide product 1 and the formation of only traces of aziridine product 2 confirm that the nitrene radical coordinated to cobalt is a key intermediate in both aziridine and epoxide formation. Altogether, these experiments support the hypothesis that the [Co{sup III}(TAML{sup red})(NTs)]{sup red} intermediate is formed, and reacts with water to another intermediate. The latter is most likely a cobalt-oxo or cobalt-oxyl complex, which is responsible for the formation of styrene oxide.
Table 1. Catalytic reactivity of $[\text{Co}^{\text{III}}(\text{TAML})^{\text{red}}]^{-}$ in aqueous medium and relevant control experiments

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst loading [mol%]</th>
<th>NR- or O-source</th>
<th>Yield 1 [%]$^a$</th>
<th>Yield 2 [%]$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>PhINTs</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>(b)</td>
<td>PhINTs</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>(c)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>TsNH$_2$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5$^d$</td>
<td>10</td>
<td>PhINTs</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td>6$^a$</td>
<td>10</td>
<td>PhINTs</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>PhINNs</td>
<td>25</td>
<td>13</td>
</tr>
<tr>
<td>8</td>
<td>(f)</td>
<td>PhINTs</td>
<td>31</td>
<td>4</td>
</tr>
<tr>
<td>9$^g$</td>
<td>10</td>
<td>PhINTs</td>
<td>0</td>
<td>traces</td>
</tr>
</tbody>
</table>

Ratio NR- or O-source : substrate = 1 : 5. Conditions: 2 hours, 11.5 mM NR- or O-source. $^a$Yields are quantified by $^1$H NMR with 1,3,5-tritertbutylbenzene as internal standard, upon extraction with CDCl$_3$, and are versus the NR- or O-source. Reactions (blanks excepted) were at least performed in duplicate, yields are averaged. $^b$10 mol% LiCl or no catalyst was used. $^c$No iminoiodinane was used. $^d$Experiment performed at room temperature (23 °C). $^e$Experiment performed under argon. $^f$10 mol% of a cobalt-TAML complex with a TAML$_{12}$ scaffold was used. $^g$Experiment performed in the presence of a radical trap (DMPO) in D$_2$O.

$[\text{Co}^{\text{III}}(\text{TAML})^{\text{red}}]^{-}$-catalyzed epoxide formation

To establish the role of water in epoxide formation, the $\text{Li}[\text{Co}^{\text{III}}(\text{TAML})^{\text{red}}]$ catalyzed aziridination reaction of styrene with PhINTs was reproduced in $^{18}$O-labelled water and compared to the reaction performed in Milli-Q. The formation of styrene oxide in Milli-Q was confirmed with GC-HRMS (calcd. $m/z$ for C$_8$H$_5$O: 120.0575, found $m/z$: 120.0581, Figure S8). The reaction performed in $^{18}$O-labeled water yielded styrene oxide with a $m/z$ of 122.0619, which accurately matches to styrene oxide with $^{18}$O incorporated (Figure S8). This result clearly demonstrates that water is the O-atom source for styrene oxide formation.

Besides the reaction of water with the radical nitrene intermediate – affording an oxo or oxyl radical complex – two other potential pathways that enable the formation of styrene oxide have been considered: 1) the hydrolysis of the formed aziridine product and 2) the hydrolysis of the iminoiodinane to iodosylbenzene (PhIO) as a potential O-source for styrene oxide formation.$^{28}$ To evaluate the first route, 2-(4-bromophenyl)-1-tosylaziridine (Br-Z) was synthesized (see Supporting Information). The aziridination reaction of styrene with PhINTs and $\text{Li}[\text{Co}^{\text{III}}(\text{TAML})^{\text{red}}]$ was performed in the presence of this product, under the standard conditions in Milli-Q and D$_2$O (Table S8). If the aziridine product would be hydrolyzed to styrene oxide under the catalytic conditions, formation of 4-bromostyrene oxide is expected. However, no conversion of Br-Z was observed and epoxide product 1 and aziridine product 2 were found in the expected ratios. As such we can conclude that hydrolysis of the aziridine to the epoxide does not take place under the applied catalytic conditions.

Previous work by Nam et al.$^{34}$ revealed that $\text{Li}[\text{Co}^{\text{III}}(\text{TAML})^{\text{red}}]$ is active in the sulfoxidation of thioanisole with PhIO as the O-source, which proceeds via cobalt-oxo intermediates. As such, hydrolysis of PhINTs to PhIO could well be a route to the formation of styrene oxide. To explore this possibility, we first determined the activity of the $\text{Li}[\text{Co}^{\text{III}}(\text{TAML})^{\text{red}}]$ catalyst in the styrene epoxidation reaction with PhIO in an aqueous medium under both aerobic and anaerobic conditions (Table S1, entry 9-12). We observed that the obtained styrene oxide yields with PhIO (26%) are lower than with PhINTs (35%, Table 1, entry 1). As such, the hypothetical hydrolysis of PhINTs to PhIO, under the applied reaction conditions, cannot fully explain the formation of styrene oxide when using PhINTs as the oxidant, if it plays any role at all. To investigate this further, we next explored if any significant hydrolysis of iminoiodinane takes place at 37°C (for more details see Supporting Information). These experiments show that the hydrolysis of PhINTs is only minor, and the small quantities of PhIO formed under these conditions cannot afford any significant amounts of styrene oxide (based on entry 11 in Table S1, at most 1% styrene oxide would be expected). Styrene oxide formation via hydrolysis of the iminoiodinane to iodosylbenzene is therefore highly unlikely. Altogether, the alternative routes towards styrene oxide formation have been excluded. This leaves the hydrolysis of the cobalt(III) nitrene radical complex, to form an oxo or oxyl radical complex involved in styrene epoxidation, as the most probable reaction mechanism for the observed formation of styrene oxide.
Computational mechanistic studies

The experimental results suggest that the formation of styrene oxide during alkene aziridination with [Co\(^{III}\)(TAML\(^{=})\)]\(^{-}\) may proceed via a [Co(TAML)(O)]\(^{+}\) oxo or oxyl radical intermediate that is active in OAT.\(^{47}\) This intermediate likely results from a reaction of the nitrene radical complex [Co\(^{II}\)(TAML\(^{=})\)(N\(^{+})\)Ts]\(^{-}\) with water. Given the redox-activity of the TAML scaffold and the controversial nature of cobalt(IV/V)-oxo species, which might be better described as cobalt(III/IV)-oxyl radicals, the electronic structure of the putative [Co(TAML)(O)]\(^{+}\) oxo/oxyl species is far from trivial.\(^{31, 34}\) We therefore decided to first perform an in dept study on the electronic structure of this species using multireference \(N\) electron valence state perturbation theory (NEVPT2)-corrected complete active space self-consistent field (CASSCF) calculations. To investigate the mechanism of nitrene hydrolysis and styrene oxide (versus aziridine) formation, density functional theory (DFT) calculations were performed, building on the results obtained with NEVPT2-CASSCF.

According to previous reported studies,\(^{31, 33}\) the electronic ground state wavefunctions of Co(TAML)-type complexes can be multiconfigurational. Therefore, NEVPT2-CASSCF calculations were initiated to first shine light on the electronic structure of the [Co\(^{II}\)(TAML\(^{=})\)]\(^{-}\) complex (see Supporting Information). For this complex, the electronic structure on cobalt is best described with the \(d\)-electron configuration \(d_{xy}^2(d_{yz})^2(d_{xz})^2(d_{z^2})^2\) according to NEVPT2-CASSCF\(^{(11)}\) calculations. It is therefore consistent with an intermediate spin Co\(^{III}\) center with a triplet electronic ground state \((S = 1)\), leaving the TAML scaffold in the fully reduced form (Figure S12, Figure S13).

NEVPT2-CASSCF\(^{(14, 12)}\) calculations on the [Co(TAML)(O)]\(^{+}\) species reveal an intricate electronic structure with clear multireference character of the wavefunction (see also the Supporting Information). More specifically, the ground state wavefunction is best described as having a triplet spin state, with the singlet (+14.1 kcal mol\(^{-1}\)) and quintet (+30.3 kcal mol\(^{-1}\)) spin states being substantially less stable. To account for possible solvation effects, we included implicit water solvation via the CPCM model and recalculated the ground state wavefunction in a NEVPT2-CASSCF\(^{(14, 12)}\) calculation at the triplet spin state. We observed that the ground state wavefunction is comprised of two main microstates (33.4% and 31.0%) and several other microstates each contributing <5%. A Co\(^{III}\) oxidation state was assigned on basis of the predominantly cobalt-localized and doubly filled \(d_{xy}\), \(d_{yz}\)+\(O\)\(_{xy}\) and \(d_{xz}+\sigma\)\(_{L_y}\) orbitals (occupancies of 2.00, 1.89 and 1.89, respectively. See Figure 1), and empty \(d_{z^2}\) and \(d_{xy}+\sigma\)\(_{L_z}\) orbitals (occupancies 0.18 and 0.09, respectively. Notably, the \(d_{xy}\) orbital was found to be uncorrelated and was therefore rotated into the inactive space. In both of the main microstates, one of the two unpaired electrons is localized in the nearly covalent \(O\)\(_{xy}\)–\(d_{xy}\) antibonding orbital (red label, occupancy 1.20), and has 46% \(O\) and 39% Co character. The other unpaired electron is more delocalized over the TAML scaffold (\(L\)), cobalt and \(O\)-donor, as a result of multiconfigurational filling of three electrons in the two \(O\)\(_{xy}\)–\(d_{xy}\)–\(L_y\) (green label in Figure 1) and \(L_y\)–\(d_{xy}\)–\(O\)\(_{xy}\) (blue label in Figure 1) orbitals. The former is evenly distributed over \(L\) (26%), Co (25%) and \(O\) (29%), whereas the latter is mainly \(L\) (42%) localized, with smaller contributions of Co (22%) and \(O\) (21%). This leads to a three-electrons in two-orbitals filling, with an electron occupation of 1.51 \((O\)\(_{xy}\)–\(d_{xy}\)–\(L_y)\) and 1.54 \((L_y\)–\(d_{xy}\)–\(O\)\(_{xy}\)), and the largest localization on the TAML scaffold (\(L_y\)). Overall, the electronic structure of the [Co(TAML)(O)]\(^{+}\) species is best described as [Co\(^{II}\)(TAML\(^{=})\)(O\(^{+}\))\(^{-}\)], having a triplet spin state \((S = 1)\) with one unpaired electron mainly localized on the TAML scaffold (hence; TAML\(^{=})\) and the other unpaired electron delocalized over a Co–O \(\pi^*\)-symmetric orbital. The latter orbital has a high bond covalency, but is somewhat more \(O\) localized, and hence the complex has a significant oxyl radical character. Notably, the TAML scaffold is clearly redox-active according to the NEVPT2-CASSCF\(^{(14, 12)}\) calculations. This is in contrast to previous DFT-based studies devoted to this complex, wherein this multireference character might have remained hidden in the single-reference DFT calculations (vide infra).\(^{34}\) However, from the NEVPT2-CASSCF calculations it is evident that the ground state wavefunction of the [Co\(^{II}\)(TAML\(^{=})\)(O\(^{+}\))]\(^{-}\) complex is clearly multiconfigurational and a comprehensive understanding of the exact electronic structure requires post-Hartree-Fock calculations (e.g. NEVPT2-CASSCF) as opposed to single reference methods such as DFT.
Figure 1. NEVPT2-CASSCF calculations on [Co<sup>III</sup>(TAML<sup>sq</sup>)(O•)]<sup>−</sup>

Active space, orbital assignment and graphical representation of a selection of active orbitals and occupancies in parenthesis from a NEVPT2-CASSCF(14,12) calculation with implicit (CPCM) water solvation on [Co<sup>III</sup>(TAML<sup>sq</sup>)(O•)]<sup>−</sup> in the triplet state. The grey orbital (d<sub>xy</sub>) was found to be uncorrelated and consequently located in the inactive space. The green, red and blue orbitals correlate to the colour indications describing the two major microstates contributing to the ground state wavefunction.

Since the relatively high computational costs of the multireference calculations do not allow extensive mechanistic studies, we calculated the [Co<sup>III</sup>(TAML<sup>sq</sup>)(O•)]<sup>−</sup> complex with DFT as well (see Supporting Information, BP86/def2-TZVP/disp3 level of theory). Based on a close inspection of the spin density and charge distributions, the intricate electronic structure of this intermediate is captured in a partially correct manner by the single-reference DFT wavefunction. Namely, the relative spin state energies (S = 0 (open-shell singlet), 1 (triplet) and 2 (quintet), Table S18) are correctly predicted: the [Co<sup>III</sup>(TAML<sup>sq</sup>)(O•)]<sup>−</sup> complex is described as having a triplet spin state, with the (open-shell) singlet (+12.1 kcal mol<sup>−1</sup>) and quintet (+20.6 kcal mol<sup>−1</sup>) spin states being substantially less stable, which is in accordance to the NEVPT2-CASSCF results (vide supra). However, the DFT electronic structure is best described as a cobalt(IV) oxyl radical complex (Table S17, structure AE1; triplet), and hence DFT is slightly off in predicting the relative energies of the nearly degenerate TAML and cobalt molecular orbitals (MOs). As a result, DFT predicts metal oxidation instead of TAML oxidation for this complex, while this is reversed in the NEVPT2-CASSCF calculations. Although the redox-activity of the TAML scaffold in this particular intermediate remains hidden in the DFT calculations, the obtained oxyl radical character is in accordance to the NEVPT2-CASSCF results. It is worth mentioning that next to the relative spin state energies, DFT predicts also the relative energies of the TAML scaffold and metal MOs correctly for the analogous nitrene radical [Co<sup>III</sup>(TAML<sup>sq</sup>)(N•Ts)]<sup>−</sup> and [Co<sup>III</sup>(TAML<sup>sq</sup>)(O•)]<sup>−</sup> complexes, and the electronic structures obtained with DFT are very similar to those obtained with NEVPT2-CASSCF for those compounds (except for the multireference character in the metal-ligand π-orbitals). As such, the applied DFT method gives overall acceptable results for [Co(TAML)]-systems. We therefore performed follow-up computational mechanistic studies at the same DFT level (which would not be accessible at the NEVPT2-CASSCF level).

With the electronic structure of [Co<sup>III</sup>(TAML<sup>sq</sup>)]<sup>−</sup> and [Co<sup>III</sup>(TAML<sup>sq</sup>)(O•)]<sup>−</sup> established, first the reaction of water with the radical nitrene complex was studied with DFT at the BP86/def2-TZVP/disp3 level of theory (see Supporting Information). Based on previous work and the NEVPT2-CASSCF and DFT calculations discussed above, we know that both the [Co<sup>III</sup>(TAML<sup>sq</sup>)(N•Ts)]<sup>−</sup> and [Co<sup>III</sup>(TAML<sup>sq</sup>)(O•)]<sup>−</sup> complexes have triplet (S = 1) ground states. The energy profile was therefore calculated at the triplet spin surface. A close inspection of the spin densities and charge distributions provided detailed information about the oxidation state of the TAML scaffold for the reaction intermediates (see Supporting Information). Furthermore, explicitly added water clusters have been used to stabilize the charged reaction intermediates, e.g. OH<sup>−</sup> (for computational details see Supporting Information). For the same reason, implicit corrections for water were applied in the final energy evaluation.
The computed mechanism for the epoxidation reaction catalyzed by the [Co\(^{ii}\)\{TAML\(^{4+}\)}\(^0\)] intermediate (AE1) at the triplet spin surface is depicted in Scheme 3 (cycle II, all free energies are reported with respect to reference point A). Oxo transfer to styrene proceeds via TS-AE-1 (\(\Delta G = -7.1\) kcal mol\(^{-1}\), \(\Delta \Delta G = +12.4\) kcal mol\(^{-1}\)) to afford the benzylic radical AE2 (\(\Delta G = -19.2\) kcal mol\(^{-1}\)) in an exergonic reaction. This step proceeds via a typical radical addition accompanied by an electronic reorganization of the coN substrate to intermediate spin. The subsequent ‘barrierless’ radical rebound step via TS-AE-2 (\(\Delta G = -19.1\) kcal mol\(^{-1}\), \(\Delta \Delta G = +0.1\) kcal mol\(^{-1}\)) to afford styrene oxide in AE3 (\(\Delta G = -36.4\) kcal mol\(^{-1}\)). Simultaneous with product formation, substrate-to-ligand single-electron transfer leads to reduction of the ligand to regenerate the starting complex [Co\(^{ii}\)\{TAML\(^{4+}\)}\(^0\)] \(\Delta G = -39.5\) kcal mol\(^{-1}\).}

To compare the performance of the catalyst in oxo and nitrene transfer, and to understand the ratio of product formation, the mechanism for alkene aziridination with the [Co\(^{ii}\)\{TAML\(^{4+}\)}\(^0\)] \(\Delta G = -37.9\) kcal mol\(^{-1}\). N-pyramidal inversion eventually yields the trans-aziridine (\(\Delta G = -37.9\) kcal mol\(^{-1}\)).

Notably, the calculated barriers for the reaction pathways for styrene epoxidation (Scheme 3, cycle II) and styrene aziridination (Scheme 3, cycle III) are similar and relatively low. In other words, once the [Co\(^{ii}\)\{TAML\(^{4+}\)}\(^0\)] intermediate is formed, styrene epoxidation tends to proceed as facile as styrene aziridination. The product ratio does therefore not depend on the relative rates of these reactions, but rather on the relative concentrations of the reactive intermediates. As our results suggest that the hydrolysis of the [Co\(^{ii}\)\{TAML\(^{4+}\)}\(^0\)] intermediate affords the [Co\(^{ii}\)\{TAML\(^{4+}\)}\(^0\)] intermediate, the product selectivity may be determined by the relative rates of the hydrolysis and aziridination reaction. Consequently, styrene and water most likely compete for a reaction with the radical nitrene complex. To further support this hypothesis with experimental evidence, we performed additional catalysis experiments. The standard Li[Co\(^{ii}\)\{TAML\(^{4+}\)}] catalyzed aziridination reaction was performed under aerobic conditions in D\(_2\)O, in presence of different equivalents of styrene (Table S6). Upon increasing the styrene concentration, we observed significantly more aziridine formation. More specifically, the use of 5 equivalents of styrene yields epoxide product 1 and aziridine product 2 in a 7 : 1 ratio, whereas the use of 20 equivalents of styrene affords these products in a 4 : 1 ratio (entry 1 and 3, Table S6). Based on these combined experimental and theoretical results, we propose that the experimentally observed product ratios are a result of competing rates for aziridination and nitrene hydrolysis.
Scheme 3. Proposed mechanism based on DFT calculations

Proposed mechanism for (I) the hydrolysis of $[\text{Co}^\text{III}(\text{TAML}^\text{sq})(\text{N}^\text{•Ts})]\text{–}$, (II) the epoxidation of styrene via $[\text{Co}^\text{III}(\text{TAML}^\text{sq})(\text{O}^\text{•})]\text{–}$ and (III) $[\text{Co}^\text{III}(\text{TAML}^\text{red})]\text{–}$ catalyzed styrene aziridination. Free energies ($\Delta G^\text{298K}$ in kcal mol$^{-1}$) were calculated with DFT at the BP86/def2-TZVP/disp3 (m4-grid) level of theory with implicit solvent corrections (COSMO model) at the triplet ($S = 1$) spin surface. Note that the TAML scaffold can have the following oxidation states: “red” (fully reduced tetra-anion in green), “sq” (mono-oxidized tri-anionic ligand-centered radical in red) and “q” (fully oxidized dianion in blue), see ref. 31-33 for further details.

pH-controlled aziridine formation

With the proposed mechanism in hand, we set out to explore if the reaction conditions could be modified such that we could form the desired aziridine product selectively. Based on the DFT calculations, the hydrolysis reaction proceeds via protonation of the nitrene radical followed by coordination of the formed hydroxy species to the cobalt center (Scheme 3, cycle I). Therefore, we hypothesize that this reaction may be pH sensitive and that changing the pH could be a way to control the selectivity of the overall reaction.

As such, reactions were performed under the standard conditions with PhINTs (entry 1, Table 1) at different pH in a phosphate buffered medium$^{44}$ (Table S10, Figure S11). As a control, the standard reaction (entry 1, Table 1) was also performed in phosphate buffer at pH 7. This afforded a similar epoxide product 1:aziridine product 2 ratio (entry 6, Table S10) with respect to the reaction performed in Milli-Q, which excludes any effect of the buffer salts. The reaction conditions were further optimized by increasing the catalyst, styrene and iminoiodinane concentrations (Table S11-S13). With the optimal conditions established, reactions were performed with PhINNs as well.$^{45}$ These results are presented in Table 2.
The Li[Co³(TAML)³] catalyzed aziridination reaction of styrene with PhINNs at pH 7 yielded epoxide product 1 as the major product under aerobic conditions (entry 1, Table 2). Performing the reaction under basic conditions (pH 10, entry 2 and 3) afforded the same product selectivity. Note that in absence of catalyst, no product formation was observed (entry 4). Under acidic conditions (pH 4, entry 5 and 6), aziridine product 3 is formed selectively and no product is formed in absence of catalyst (entry 7). Given that the coordination of the hydroxide and its subsequent deprotonation are key steps in the formation of [Co³(TAML)²(O)²]²⁻, this proceeds most easily at higher pH. The relatively low OH⁻ concentration in acidic media therefore explains the selectivity for aziridine product 3 at a lower pH. Overall, these results demonstrate that product formation can be controlled by changing the pH of the reaction medium, which in addition provides direct experimental evidence for the proposed mechanism for nitrene hydrolysis.

### Table 2. Catalytic reactivity of [Co³(TAML)³]⁺ in phosphate buffered medium and relevant control experiments

<table>
<thead>
<tr>
<th>Entry</th>
<th>pH</th>
<th>Yield 1 [%]⁺</th>
<th>Yield 3 [%]⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>31</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Ratio NR-source : substrate = 1 : 5. Conditions: 2 hours, 23.0 mM NR-source. Yields are quantified by ¹H NMR with 1,3,5-tritertbutylbenzene as internal standard, upon extraction with CDCl₃, and are versus PhINNs. Reactions (blanks excepted) were at least performed in duplicate, yields are averaged. All experiments are performed in phosphate buffered Milli-Q (0.1 M). Experiment performed under argon. No catalyst was used.

### Conclusions

In this work, we have investigated the role of water in side-product formation during radical-type nitrene transfer catalysis in water. More specifically, catalytic alkene aziridination of styrene with [Co³(TAML)³]⁺ and PhINNs in non-buffered solution under mild conditions (37°C, aerobic, 10 mol%), yields undesired styrene oxide as the major product. In a combined experimental and theoretical approach, we present a mechanism that explains the crucial role of water. Namely, the hydrolysis of the nitrene radical complex [Co³(TAML)⁴(N°Ts)]⁻ formed under catalytic conditions, yields an oxyl radical [Co³(TAML)⁴(O)²]⁻ intermediate that is active in oxygen atom transfer catalysis. The involvement of the nitrene radical complex is supported by the absence of product formation when the radical trap DMPO is present in solution. In addition, the corresponding NTs adduct of DMPO was observed in ESI-HRMS and X-band EPR measurements. Furthermore, the use of H₂¹⁸O as the reaction solvent affords ¹⁸O-labelled styrene oxide, unambiguously demonstrating the role of water as the oxygen donor. Based on NEVPT2-CASSCF(14,12) calculations, the electronic structure of the proposed [Co³(TAML)⁴(O)²]⁻ intermediate was established. This cobalt-oxy complex is best described as having a multireference triplet ground state, with one unpaired electron being delocalized over a nearly covalent Co–O antibonding orbital and the other unpaired electron being mainly localized on the TAML scaffold, with delocalization over cobalt and the oxyl group. Formation of styrene oxide during styrene aziridination results from oxygen atom transfer via this in situ formed [Co³(TAML)⁴(O)²]⁻ intermediate. Computational studies reveal that the epoxidation of styrene via [Co³(TAML)⁴(O)²]⁻, formed by hydrolysis of [Co³(TAML)⁴(N°Ts)]⁻, is feasible under the experimental conditions. The product selectivity of the nitrene transfer reaction is therefore dependent on the relative rates of the hydroxylation and aziridination reactions. Based on this mechanistic insight, catalytic studies at various pH were performed. These experiments provide direct evidence for the proposed mechanism, since they show that the desired aziridine product is formed selectively under acidic conditions as a result of the slower hydrolysis of the [Co³(TAML)⁴(N°Ts)]⁻ intermediate. Overall, we demonstrate that understanding the reactivity of nitrene radical complexes in water is fundamental to control and improve aqueous (radical-type) nitrene transfer catalysis.
Supplementary Information
The supplemental information that provides: experimental details, synthetic procedures, NMR spectra, HRMS data, geometries (xyz coordinates), energies of stationary points and transition states (DFT) and the description of the NEVPT2-CASSCF calculations, can be found online.

Acknowledgments
Financial support from the research priority area Sustainable Chemistry of the University of Amsterdam (RPA SusChem, UvA) is gratefully acknowledged. Ed Zuidinga (University of Amsterdam) is thanked for HRMS measurements and Nicole S. van Leeuwen is kindly acknowledged for design of the graphical abstract.

Author Contributions
E.J.M, B.d.B. and J.N.H.R. conceived the project. E.J.M. performed the initial experiments. E.J.M., C.J.V. and N.P.v.L. designed and performed further experimental investigations and theoretical calculations based on DFT. N.P.v.L. and B.d.B. performed the NEVPT2-CASSCF calculations. E.J.M and N.P.v.L. wrote the manuscript, with input from all authors, under supervision of B.d.B. and J.N.H.R.

Declaration of Interests
The authors declare no conflict of interest.

Keywords
water | nitrene radical | oxyl radical | cobalt | aziridination | epoxidation

References
[36] The following reaction conditions were adapted from ref. 34: N-source : substrate ratio, reaction time and temperature. Given that the reaction medium is water, we slightly increased the reaction temperature to 37 °C.
The aziridination reaction of styrene with PhINTs and Li[CoIII(TAMLred)] generally affords no more than 35-40% in aqueous medium. This is most likely the result of decomposition of the highly reactive intermediates – the nitrene radical or oxyl radical complex – in the presence of water, before reaction with the substrate. Further details can be found in the Supporting Information (Table S5 and Table S6).


Multiple efforts to characterize the proposed [CoIII(TAMLsq)(O•)]– intermediate formed via hydrolysis of the [CoIII(TAMLsq)(N•Ts)]– intermediate were unsuccessful. More details can be found in the Supporting Information.


A phosphate buffer (0.1 M) covers a broad pH range (1.2 – 12) which makes it ideal to screen the catalytic activity of Li[CoIII(TAMLred)] under acidic and basic conditions.

PhINNs (relatively electron withdrawing) generally affords more aziridine than obtained with PhINTs (relatively electron donating) and less epoxide product under acidic conditions, see Supporting Information (Table S13). Given that C–N bond formation in this reaction proceeds through an electronically asynchronous transition state in which electron density is donated from styrene to the nitrene radical intermediate, electron poor nitrenes facilitate this reaction more efficiently. See ref. 34 for more details.