Styrene aziridination with $[\text{Co}^{\text{III}}(\text{TAML}^{\text{red}})]^-_\text{in water}$

Understanding and preventing epoxidation via nitrene hydrolysis

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Styrene aziridination with \([\text{Co}^\text{III}(\text{TAML}^\text{red})^-]\) in water: Understanding and preventing epoxidation via nitrene hydrolysis

Nitrine transfer catalysis in water can open up a wider range of (novel) applications but remains a long-standing challenge given the formation of oxygen-containing side products. In this study, de Bruin and co-workers investigate and elucidate the hydrolysis of nitrine radical complexes to oxo/oxyl radical complexes in a combined experimental and theoretical approach. Altering the pH can suppress the formation of oxygen-containing side products via the intermediacy of oxo/oxyl radical complexes, affording selective aziridine formation in water.

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Highlights
Nitrine radical complexes can undergo hydrolysis during aqueous styrene aziridination

Experimental and theoretical investigations support oxo/oxyl radical complex formation

Oxo/oxyl radical complexes are responsible for oxygen-containing side-product formation

Hydrolysis of nitrine radical complexes is prevented or stimulated by pH changes
Styrene aziridination with [Co\textsuperscript{III}(TAML\textsuperscript{red})]\textsuperscript{−} in water: Understanding and preventing epoxidation via nitrene hydrolysis

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SUMMARY

Enabling (radical-type) nitrene transfer reactions in water can open up a wide range of (novel) applications, such as the \textit{in vivo} synthesis of medicines. However, these reactions typically suffer from oxygen-containing side-product formation, the origin of which is not fully understood. Therefore, we investigated aqueous styrene aziridination by 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 product. On the basis of \textsuperscript{18}O-labeling studies, catalysis, and mass spectrometry experiments, we demonstrated that styrene oxide formation proceeds via hydrolysis of the formed nitrene radical complexes. Computational studies support that this process is facile and yields oxyl radical complexes active in oxygen-atom transfer to styrene. On the basis of these mechanistic insights, we adjusted the pH 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{1–7} For instance, biologically active molecules often contain fragments with carbon-nitrogen bonds at specific positions,\textsuperscript{8} with aziridines among the representative examples.\textsuperscript{9,10} 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{11–13} 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{14–16} because of the air- and water-sensitive nature of the reactive intermediates involved.\textsuperscript{11}

Nonetheless, water presents an ideal reaction medium for radical-type transformations because of the relatively high bond dissociation enthalpy\textsuperscript{17} (BDE) of the HO–H bond (119 kcal mol\textsuperscript{−1}). A higher BDE can prevent direct hydrogen-atom transfer (HAT) from the solvent, which is commonly observed for organic solvents with weak C–H bonds, such as tetrahydrofuran (THF), toluene, or acetonitrile (C(sp\textsuperscript{3})–H BDE of 90, 91, and 97 kcal mol\textsuperscript{−1} respectively).\textsuperscript{18–21} Enabling (radical-type) group transfer in water could also open up a wider range of (novel) applications. For example, the Mascaréñas group recently demonstrated the application of group transfer in the fast-growing field of \textit{in vivo} catalysis.\textsuperscript{22} 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 remain 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{23,24} Interestingly, the few studies that do perform these transformations “purely” in water (without the use of, for example, micelles or phase-transfer catalysts), all report the formation of oxygen-containing side products.\textsuperscript{25–28} For example, catalytic olefin aziridination with iron and manganese complexes, using hypervalent iodine reagents (iminiodinanes) as nitrene precursors, yielded epoxides next to the desired aziridine products. Although this work acknowledges the potential role of water,\textsuperscript{29} no in-depth studies on the formation of such side products have been reported. Therefore, the overall reactivity of (radical-type) metal-nitrene complexes in water remains rather poorly understood (Scheme 1A).

Broadening the application of (radical-type) nitrene transfer catalysis in water requires a better understanding of the reactivity of nitrene (radical) complexes, as this enables rational approaches toward selective catalysis protocols in this medium.\textsuperscript{31} It is thereby crucial to investigate how these transformations yield the undesired oxygen-containing products when carried out in water. In this context, the Che group 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 enabled oxygen atom transfer (OAT) yielding styrene oxide (Scheme 1B). On the basis of this study, it can thus be hypothesized that base-metal nitrene radical complexes could likewise suffer from hydrolysis, which perhaps affords oxo/oxyl radical complexes active in OAT. Therefore, this study aims to investigate the potential role of water in forming oxygen-containing side products during radical-type nitrene transfer catalysis, and it explores the mechanism of this process to circumvent this issue in cobalt-catalyzed nitrene transfer in water.

In previous studies, we explored the formation and reactivity of nitrene radical adducts of a cobalt-TAML complex, \textit{PPh}_4[Co^{III}(TAML$^{red}$)] (TAML = tetra-amido macrocyclic ligand), in organic media.\textsuperscript{32} Interestingly, the TAML scaffold proved to be redox active when coordinated to cobalt, and we also showed that the [Co$^{III}$(TAML$^{red}$)]$^-$ complex is selectively converted to a bis-nitrene radical complex [Co$^{III}$(TAML$^{sq}$)(N$\textit{R}$)]$^-$ (red = fully reduced tetra-anion, q = doubly oxidized di-anionic ligand, R = tosyl or nosyl) upon reaction with an excess of iminoiodinane. Using iminiodinane as the limiting reagent under catalytic conditions affords a mono-nitrene radical complex: [Co$^{III}$(TAML$^{sq}$)(N$\textit{R}$)]$^-$ (sq = mono-oxidized tri-anionic ligand-centered radical) (Scheme 2A). Both nitrene radical complexes are best described as electrophilic one-electron-reduced Fischer-type nitrene radicals. Notably, the mono-nitrene radical complex is considered to be the catalytically active intermediate in both sulfimidation\textsuperscript{33} and olefin aziridination\textsuperscript{34} reactions under aerobic conditions (Scheme 2A). The productive C–N bond formation during the aziridination reactions was reported to proceed via an unusual electronically asynchronous transition state.\textsuperscript{34} Specifically, C–N bond formation occurs via nucleophilic attack of the nitrene lone-pair onto a (partially) formed styrene radical cation resulting from initial substrate-to-ligand single-electron transfer, and not via the expected pathway involving nitrene radical addition to the C=C double bond. Altogether, the reactivity of nitrene radicals on PPh$_4$[Co$^{III}$(TAML$^{red}$)] is well understood in organic solvents.

The cobalt-TAML complex has also been investigated for its reactivity in OAT to thioanisole in organic media by the group of Nam (Scheme 2A).\textsuperscript{35} A Lewis-acid-stabilized
A cobalt-oxo complex was reported, and the characterization was interpreted as the TAML scaffold being innocent (TAMLred) and the cobalt center being oxidized (Co(IV)). Interestingly, this interpretation contrasts previous findings with nitrene precursors (without Lewis acids, vide supra). Furthermore, based on 18O-labeling experiments, it was shown that the oxygen source affording the sulfoxide product is the cobalt-oxo complex [CoIV(TAMLred)(O)(Sc)]+.

Given the well-understood behavior of cobalt-TAML complexes in (radical-type) N- and O-group transfer in organic media, we employed the water-soluble Li[CoIII(TAMLred)]36 to investigate the role of water in side-product formation during aqueous radical-type nitrene transfer. Hence, this study sets out to validate the hypothesis that nitrene radical complexes suffer from hydrolysis, which might yield oxyl radical complexes active in OAT. Specifically, the following key findings are reported in this work (see also Scheme 2B).

1. In the presence of water, the nitrene radical complexes [CoIII(TAML)(N\textsuperscript{Ts})\textsubscript{n}]\textsuperscript{−} (n = 1, 2) can undergo hydrolysis, yielding cobalt-oxo/oxyl radical complexes.
2. In contrast to earlier interpretations, N-electron valence state perturbation theory (NEVPT2)-corrected complete active space self-consistent field (CASSCF) calculations show that the electronic structure of the “mono-oxo” complex [Co(TAML)(O)]\textsuperscript{−} is best described as a triplet spin (S = 1) Co(III)-oxyl radical complex, [CoIII(TAML\textsuperscript{sq})(O\textsuperscript{−},O\textsuperscript{•})\textsuperscript{−}], with one unpaired electron located mainly on the redox-active TAML scaffold and the other unpaired electron in the Co–O π\textsuperscript{*} antibonding orbital.
3. The formation of styrene oxide during styrene aziridination is the result of OAT from such in-situ-formed cobalt-oxyl radical complexes.
4. Hydrolysis of the nitrene radical complexes can be prevented or stimulated by changing the pH, yielding either the desired aziridine product (pH = 4) or styrene oxide (pH between 7 and 10) selectively.
Scheme 2. Previous work on cobalt-TAML complexes and the outline of this work

(A) Previous work on the formation and reactivity of cobalt-TAML nitrene radical and oxo complexes in organic solvent. 34, 35

(B) Epoxide formation in aqueous styrene aziridination proceeds via competitive hydrolysis of nitrene radical complexes, yielding oxyl radical complexes active in OAT.

Conditions: H₂O/D₂O, anaerobic/aerobic, 2 h, 37 °C
RESULTS AND DISCUSSION

Aqueous styrene aziridination with Li[CoIII(TAMLred)]

To investigate the competence of the Li[CoIII(TAMLred)] catalyst in water, we initially performed the aziridination reaction of styrene with PhINTs (Ts = tosyl) in Milli-Q and D2O (to directly analyze the water layer by 1H NMR spectroscopy; Table S1) under aerobic conditions at 37 °C (unless noted otherwise). Under these conditions, with 10 mol % Li[CoIII(TAMLred)], styrene was converted into mostly the epoxide product (1) (35% yield with respect to PhINTs) after 2 h. In contrast, the desired aziridine product (2) was formed in minor amounts (3%) (Table 1, entry 1). In the presence of 10 mol % LiCl, or without any catalyst present, no product formation was observed at all (entry 2). Without iminoiodinane present, no epoxide product was formed either (entry 3). Performing the reaction at room temperature (instead of 37 °C) gave comparable yields (entry 5), indicating a marginal effect of the reaction temperature on the product selectivity. Most important, under anaerobic conditions, epoxide product 1 was still the major product formed (entry 6), pointing to water rather than oxygen as being significant in the formation of styrene oxide. This hypothesis is strengthened by previous work on this catalytic system, where no epoxide formation was observed in the absence of water under aerobic conditions in organic media.

PhINNs (Ns = nosyl) has also been explored as an alternative nitrene precursor for PhINTs in the aqueous styrene aziridination reaction. Notably, this relatively more electron withdrawing iminoiodinane increased the yield of the aziridine product (31%) (entry 7).

Table 1. Catalytic reactivity of Li[CoIII(TAMLred)] in water and relevant control experiments

<table>
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<th>Entry</th>
<th>Catalyst loading (mol %)</th>
<th>NR-source</th>
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<th>Yield 2 (%)a</th>
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<td>10</td>
<td>PhINTs</td>
<td>35</td>
<td>3</td>
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<td>see footnote b</td>
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<td>9c</td>
<td>10</td>
<td>PhINTs</td>
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<td>traces</td>
</tr>
</tbody>
</table>

NR-source/substrate ratio = 1:5. Conditions: 2 h, 11.5 mM NR-source.

*Yields are quantified by 1H NMR with 1,3,5-tritertbutylbenzene as the external standard upon extraction with CDCl3 and are versus the NR-source. Reactions (blanks excepted) were at least performed in duplicate, and yields are averaged.

b10 mol % LiCl or no catalyst was used.

cNo iminoiodinane was used.

cExperiment was performed at room temperature (23 °C).

cExperiment was performed under argon.

c10 mol % of a substituted cobalt-TAML complex (TAML2+) was used.

cExperiment was performed in the presence of a radical trap (DMPO) in D2O.
product 2 (13%) and reduced the amount of epoxide product 1 formed (25%) (Table 1, entry 7) in comparison with reactions carried out with PhINTs (relatively electron donating; entry 1). Furthermore, a slightly different Li[Co<sup>III</sup>(TAML<sup>red</sup>)<sup>n</sup>] complex<sup>32,34,39</sup> with two chloride substituents on the TAML scaffold (Scheme 2A, top) was used. The product ratios achieved with this catalyst were similar to those of the standard catalyst (entry 8 versus entry 1), which implies that substitutions on the TAML scaffold do not significantly influence the formation of styrene oxide. The fact that different nitrogen sources do afford other product ratios but that substitutions on the TAML scaffold do not affect the reaction outcome strongly suggests that the nitrene radical complex(es) formed under catalytic conditions are involved in styrene oxide formation.

To address the involvement of the nitrene radical complexes, we performed the Li[Co<sup>III</sup>(TAML<sup>red</sup>)<sup>n</sup>]-catalyzed aziridination reaction of styrene in the presence of the water-soluble radical trap 5,5-dimethyl-1-pyrroline N-oxide<sup>34,40–42</sup> (DMPO) under anaerobic conditions in D<sub>2</sub>O. The addition of 5 equiv of DMPO with respect to PhINTs (Table 1, entry 9) completely inhibited styrene oxide formation, and only traces of aziridine product 2 were observed. Given the known reactivity of DMPO as a radical scavenger, the absence of product indicates that radical-type intermediates are generated and subsequently trapped. This hypothesis was validated by electrospray ionization high-resolution mass spectrometry (ESI-HRMS) analysis of the reaction mixture, which afforded a signal at the m/z value corresponding to [DMPO – H + NTs]<sup>-</sup> (calcd. m/z for C<sub>13</sub>H<sub>17</sub>N<sub>2</sub>O<sub>3</sub>S: 281.0960; found m/z: 281.0965), i.e., a NTs-containing DMPO-derivative similar to DMPOX (see Figure S15). Additionally, recorded X-band EPR spectra of the reaction mixture further support the formation of a DMPO-trapped radical (g<sub>iso</sub> = 2.0058, A<sub>Niso</sub> = 41.12 MHz, A<sub>Hiso</sub> = 8.24 MHz), albeit unidentified (Figure S16; see the supplemental information for more details). Nevertheless, the observation of a NTs-containing DMPO derivative with ESI-HRMS, in combination with the absence of product formation and the results from the catalytic control experiments described below, indicates that nitrene radical formation on the cobalt-TAML complex is a crucial intermediate in both aziridine and epoxide formation. Overall, these experiments thus support the hypothesis that the [Co<sup>III</sup>(TAML)(N<sub>Ts</sub>)<sub>n</sub>]<sup>-</sup> complexes are formed and react with water to form other reactive intermediates. The latter are most likely cobalt-oxo/oxyl radical complexes responsible for the formation of styrene oxide.<sup>35</sup>

Li[Co<sup>III</sup>(TAML<sup>red</sup>)<sup>n</sup>]-catalyzed epoxide formation

To establish the anticipated role of water in epoxide formation, we reproduced the Li[Co<sup>III</sup>(TAML<sup>red</sup>)<sup>n</sup>]-catalyzed aziridination reaction of styrene with PhINTs in <sup>18</sup>O-labeled water and compared it with the reaction performed in Milli-Q. The formation of styrene oxide in Milli-Q was confirmed by GC-HRMS (calcd. m/z for C<sub>8</sub>H<sub>8</sub>O: 120.0575; found m/z: 120.0581; Figure S14). The reaction performed in <sup>18</sup>O-labeled water yielded styrene oxide with an m/z of 122.0619, which accurately matches styrene oxide with <sup>18</sup>O incorporated (Figure S14). This result clearly demonstrates that water is the O-atom source for styrene oxide formation.

Besides the reaction of water with the nitrene radical complex—affording oxo or oxyl radical complexes—two other potential pathways that enable the formation of styrene oxide were considered: (1) hydrolysis of the formed aziridine product and (2) hydrolysis of the iminiodianine to iodosylbenzene (PhIO) as a potential oxygen source for styrene oxide formation.<sup>29</sup> To evaluate the first route, we synthesized 2-(4-bromophenyl)-1-tosylaziridine (Br-2) (see the supplemental information). The aziridination reaction of styrene with PhINTs and Li[Co<sup>III</sup>(TAML<sup>red</sup>)<sup>n</sup>] 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 is hydrolyzed to styrene oxide under the catalytic conditions, the formation of 4-bromostyrene oxide is expected. However, no conversion of Br-2 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 product does not take place under the applied catalytic conditions.

Previous work on the Li[Co$^{III}$$(TAML^{red})$] complex in organic medium revealed its activity in the sulfoxidation reaction of thioanisole with PhIO as the oxygen source, which proceeds via cobalt-oxo intermediates.\(^{35}\) Hence, hydrolysis of PhINTs to PhIO could in principle be a route to the formation of styrene oxide. To explore this possibility, we first determined the activity of the Li[Co$^{III}$$(TAML^{red})$] catalyst in the aqueous styrene epoxidation reaction with PhIO under both aerobic and anaerobic conditions (Table S1, entries 10–13). The obtained styrene oxide yields with PhIO (26%) were lower than those with PhINTs (35%; Table 1, entry 1). Hence, the hypothetical hydrolysis of PhINTs to PhIO, under the applied reaction conditions, cannot fully explain the formation of styrene oxide when PhINTs is used as the oxidant, if it plays any role at all. To investigate this further, we explored whether any significant hydrolysis of iminoiodinane occurs at all at 37 °C (for more details, see the supplemental information). These experiments show that the hydrolysis of PhINTs is only minor and that the small quantities of PhIO formed under these conditions cannot afford any significant amounts of styrene oxide (based on entry 10 in Table S1; at most 1% styrene oxide would be expected). Styrene oxide formation via hydrolysis of the iminoiodinane to iodosylbenzene is therefore improbable. Altogether, the alternative routes toward styrene oxide formation have been excluded, which leaves hydrolysis of the nitrene radical complexes—to form oxo or oxyl radical complexes involved in styrene epoxidation—as the most probable reaction mechanism for the observed formation of styrene oxide.

To further validate the above-mentioned hypothesis, we monitored the formation and reactivity of the [Co$^{III}$$(TAML)(N'Ts)_{n-}$] complexes in solution by using a flow chemistry system coupled to online (ESI) mass spectrometric detection\(^{43}\) (for more details, see the supplemental information). The reaction of Li[Co$^{III}$$(TAML^{red})$] with up to 8.7 equiv of PhINTs in acetonitrile\(^{44,45}\) was carried out in a first reactor (in the absence of other substrates; Scheme S6 and Figure S18), leading to the formation of the anticipated mono- and bis-nitrene radical complexes. In line with previous work, the relative concentration of the [Co$^{III}$$(TAML)(N'Ts)_{2-}$] complex increased with respect to [Co$^{III}$$(TAML^{red})(N'Ts)_{2-}$] when the mass spectrometry experiment was carried out in the presence of an excess of iminoiodinane and in the absence of other substrates.\(^{32,34}\) In the next experiment, the formed nitrene radical complexes were subjected to a reaction with water in a second reactor (Scheme S7 and Figure S23), which resulted in their depletion due to the formation of the oxygenated species [Co$(TAML)$(N'Ts)(O)]$^-$ and [Co$(TAML)$(O)$_2$] (Figures S25–S27). Reproduction of these experiments in $^{18}$O-labeled water afforded the same oxygenated species with consistent isotopic shifts ($\Delta m/z$ +2 or 4, respectively; Figure S28), supporting the formation of these species from a reaction between the nitrene radical complexes and water. The absence of oxygenated species when Li[Co$^{III}$$(TAML^{red})$] was combined with water in absence of PhINTs shows that hydrolysis of the nitrene radical complexes must take place (Figure S24).

If we account for previous work on analogous iron-TAML complexes, the observed oxygenated species could be identified as either cobalt-oxo/oxyl radical complexes
or the products of intra- or intermolecular ligand oxidation, i.e., complexes of which the methyl groups of the TAML scaffold are hydroxylated. The latter products can be formed via the intermediacy of oxo/oxyl radical intermediates, as was described in previous studies from the Collins group.

In the presence of D$_2$O, all hydroxyl groups are expected to undergo rapid H/D exchange—which can obviously be detected with ESI-MS—whereas such an exchange cannot take place for oxo/oxyl radical moieties. To show that cobalt-oxo/oxyl radical complexes are formed prior to ligand oxidation, we reproduced the above-mentioned experiments with D$_2$O (Figures 1A and 1B). Analysis of the obtained kinetic profiles (Figure 1C, left) suggests that hydrolysis starts predominantly from the “bis-nitrene” [Co$^{II}$](TAML$^{III}$)(NTs)$_2$– complex. This complex can be protonated with the loss of TsNH$_2$ and/or is involved in nitrene-oxo exchange reactions, thus affording the [Co(TAML)(NTs)(O)]– and [Co(TAML)(O)$_2$]– species detected with ESI-MS (Figure 1C, right). For the [Co(TAML)(O)$_2$]– species, only a slow, gradual H/D exchange was observed. This observation strongly suggests that this species is a bis-oxo/oxyl radical complex that slowly converts to another complex, such as...
that only the latter contains hydroxylated methyl groups on the TAML scaffold. Accelerating the conversion by usage of a larger D$_2$O concentration led to a steady, gradual increase in ESI-MS signals pointing to H/D exchange at one or two hydroxide moieties. These experiments confirm that the formed oxo/oxyl radical complexes are not stable and convert to Co(TAML) complexes with oxygenated ligands. In contrast, the [Co(TAML)(NTs)(O)]$^-$ species does not undergo H/D exchange. Instead, it most likely reacts faster with a second D$_2$O molecule rather than undergoing intra- or intermolecular ligand oxidation.

The above-discussed results clearly show the formation of oxo/oxyl radical complexes resulting from a reaction between the nitrene radical complexes and water. These species gradually convert to different, more stable species containing a mono- or bis-oxygenated TAML scaffold. We further substantiated these observations with supporting density functional theory (DFT) calculations (see the supplemental information and Scheme S10). However, it is important to note here that it is unknown to what extent oxidation of the TAML scaffold occurs under the applied catalytic conditions. This reaction could well be effectively suppressed in the presence of suitable oxygen-accepting substrates.

**Computational mechanistic studies**

The above-described experimental results support the hypothesis that the formation of styrene oxide during styrene aziridination with Li[Co$^{III}$(TAML$^{red}$)] might proceed via OAT from oxo or oxyl radical complexes, which result from a reaction of the nitrene radical complexes with water. Concerning the participation of these nitrene radical complexes under the applied catalytic conditions, i.e., in the presence of excess styrene, we assume that predominantly mono-nitrene [Co$^{III}$(TAML$^{red}$)(N'Ts)]$^-$ complexes are present. Under these conditions, this complex is expected to react more rapidly with styrene than with another equivalent of iminoiodinane (the latter of which is the limiting reagent), in line with previous studies. Hence, the supporting computational mechanistic studies and electronic structure calculations described below were all performed with the mono-nitrene radical complex as the anticipated reactive intermediate.

Given the redox activity of the TAML scaffold and the elusive nature of the cobalt(IV)-oxo complex (vide supra), which might be better described as a cobalt(III)-oxyl radical complex, the electronic structure of the putative [Co(TAML)(O)]$^-$ oxo/oxyl radical complex is far from trivial. Therefore, we decided to first perform an in-depth study on the electronic structure of this complex by using multireference NEVPT2-CASSCF calculations. To investigate the mechanism of nitrene hydrolysis and styrene oxide (versus aziridine) formation, we performed DFT calculations, building on the results obtained with the NEVPT2-CASSCF calculations.

According to previous studies, the electronic ground-state wavefunctions of Co(TAML)-type complexes can be multiconfigurational. Therefore, we initiated NEVPT2-CASSCF calculations to first shine light on the electronic structure of the [Co$^{III}$(TAML$^{red}$)]$^-$ complex (see the supplemental information). For this complex, the electronic structure of cobalt is best described with the d-electron configuration (d$_z^2$)(d$_x$)$^2$(d$_y$)$^2$(d$_{3z}$)$^{10}$(d$_{xy}$)$^{10}$(d$_{x^2-y^2}$)$^0$ according to the NEVPT2-CASSCF(12,11) calculations. The [Co$^{III}$(TAML$^{red}$)]$^-$ complex 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 (Figures S31 and S32).
NEVPT2-CASSCF(14,12) calculations on [Co(III)(TAML)(O)]\(^{-}\) complex revealed an intricate electronic structure with clear multireference character of the wavefunction (also see the supplemental information). More specifically, the ground-state wavefunction is best described as a triplet spin state where the singlet (+14.1 kcal mol\(^{-1}\)) and quintet (+30.3 kcal mol\(^{-1}\)) spin states are 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. The resulting ground-state wavefunction comprised two main microstates (33.4% and 31.0%) and several other microstates, each contributing <5%. A Co(III) oxidation state was assigned according to the predominantly cobalt-localized and doubly filled \(d_{xy}\), \(d_{yz}\), and \(d_{z^2}\) orbitals (occupancies of 2.00, 1.89, and 1.89, respectively; see Figure 2) and empty \(d_{x^2-y^2}\) orbitals on O. Notably, the \(d_{xy}\) orbital was found to be uncorrelated and was therefore rotated into the inactive space. In both main microstates, one of the two unpaired electrons was localized in the nearly covalent \(O_{\text{O}}-d_{xy}\) antibonding orbital (red label, occupancy 1.89) and had 46% O and 39% Co character. The other unpaired electron was more delocalized over the TAML scaffold (L), cobalt, and O donor as a result of the multiconfigurational filling of three electrons in the two \(O_{\text{O}}-d_{xy}-L\) (green label in Figure 2) and \(L-d_{xy}-O_{\text{O}}\) (blue label in Figure 2) orbitals. The former was evenly distributed over L (26%), Co (25%), and O (29%), whereas the latter was mainly L (42%) localized with smaller Co (22%) and O (21%) contributions. This led to a three-electrons-in-two-orbitals filling with an electron occupation of 1.51.

Figure 2. NEVPT2-CASSCF calculations on [Co(III)(TAML)(O)]\(^{-}\). Active space, orbital assignment, and graphical representation of a selection of active orbitals and occupancies in parentheses from a NEVPT2-CASSCF(14,12) calculation with implicit (CPCM) water solvation on [Co(III)(TAML)(O)]\(^{-}\) in the triplet state. The gray orbital (\(d_{xy}\)) was found to be uncorrelated and consequently located in the inactive space. The green, red, and blue orbitals correlate with the color indications describing the two major microstates contributing to the ground state wavefunction.
Overall, the electronic structure of the $[\text{Co}(\text{TAML})(\text{O})]^{-}$ complex is best described as $[\text{Co}^{\text{III}}(\text{TAML}^{\text{sq}})(\text{O},\text{O})]^{-}$, with a triplet spin state ($S = 1$) where one unpaired electron is mainly localized on the TAML scaffold (hence, TAML$^{\text{sq}}$) and the other unpaired electron is delocalized over a Co–O $\pi^*$ antibonding orbital. This orbital has a high bond covalency but is somewhat more O localized; hence, the complex has significant oxyl radical character. Notably, the TAML scaffold is clearly redox active according to the NEVPT2-CASSCF(14,12) calculations. This result contrasts with previous DFT-based studies devoted to this complex, wherein this multireference character might have remained hidden in the single-reference DFT calculations (vide infra). However, from the NEVPT2-CASSCF calculations, it is evident that the ground-state wavefunction of the $[\text{Co}^{\text{III}}(\text{TAML}^{\text{sq}})(\text{O})]^{-}$ complex is multiconfigurational, and a comprehensive understanding of the exact electronic structure requires post-Hartree-Fock calculations (e.g., NEVPT2-CASSCF calculations) as opposed to single-reference methods, such as DFT.

Because the relatively high computational costs of multireference calculations do not allow extensive mechanistic studies, we calculated the $[\text{Co}^{\text{III}}(\text{TAML}^{\text{sq}})(\text{O})]^{-}$ complex with DFT as well (BP86/def2-TZVP/disp3 level of theory; see the supplemental information). According to a close inspection of the spin density and charge distributions, the intricate electronic structure of this complex 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 S22) are correctly predicted: the $[\text{Co}^{\text{III}}(\text{TAML}^{\text{sq}})(\text{O})]^{-}$ complex is described as having a triplet spin state such that the (open-shell) singlet (+12.1 kcal mol$^{-1}$) and quintet (+20.6 kcal mol$^{-1}$) spin states are substantially less stable in accordance with the NEVPT2-CASSCF results (vide supra). However, the DFT electronic structure is best described as a cobalt(IV)-oxyl radical complex (Table S21, structure AE1; triplet), and hence DFT is slightly off in predicting the relative energies of the nearly degenerate TAML scaffold and cobalt molecular orbitals (MOs). As a result, DFT predicts metal oxidation instead of oxidation of the TAML scaffold for this complex, which is reversed in the NEVPT2-CASSCF calculations. Although the redox activity of the TAML scaffold in this specific complex thus remains hidden in the DFT calculations, the obtained oxyl radical character is in accordance with the NEVPT2-CASSCF results. It is worth mentioning that next to the relative spin state energies, DFT also predicts the relative energies of the TAML scaffold and metal MOs correctly for the analogous $[\text{Co}^{\text{III}}(\text{TAML}^{\text{sq}})(\text{N}^\text{Ts})]^{-}$ and $[\text{Co}^{\text{III}}(\text{TAML}^{\text{sq}})(\text{N}^\text{Ns})_2]^{-}$ complexes, and the electronic structures obtained with DFT are very similar to those obtained with the NEVPT2-CASSCF calculations for those compounds (except for the multireference character in the metal-ligand $\pi$-orbitals). As such, the applied DFT method gives overall acceptable results for the relative formation energies and overall spin states of the Co(TAML) complexes. Therefore, all follow-up computational mechanistic studies were performed with DFT (which would not be accessible with NEVPT2-CASSCF calculations anyway).

With the electronic structure of $[\text{Co}^{\text{III}}(\text{TAML}^{\text{red}})]^{-}$ and $[\text{Co}^{\text{III}}(\text{TAML}^{\text{sq}})(\text{O}^\text{O})]^{-}$ in hand, we first studied the reaction of water with the nitrene radical complex with DFT at the BP86/def2-TZVP/disp3 level of theory (see the supplemental information). On the basis of previous work and the NEVPT2-CASSCF and DFT calculations discussed above, we derived that both the $[\text{Co}^{\text{III}}(\text{TAML}^{\text{red}})(\text{N}^\text{Ts})]^{-}$ and $[\text{Co}^{\text{III}}(\text{TAML}^{\text{sq}})(\text{O}^\text{O})]^{-}$ 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 information about the oxidation states of the TAML scaffolds of the relevant reaction intermediates (see the supplemental information). Furthermore, we used explicitly added water clusters to stabilize the charged reaction intermediates, e.g., OH⁻ (for computational details, see the supplemental information). For the same reason, we applied COSMO implicit solvent corrections for water in the final energy evaluation.

We considered three potential pathways for the hydrolysis of the nitrene radical complex (Scheme S11). The most plausible pathway, in which protonation of the nitrene radical complex and coordination of OH⁻ are the least uphill, is depicted in Scheme 3 (cycle I). First, the reaction of PhlNTs with the anionic [Co^{II}(TAML^{red})]⁻ complex
(A, reference point) affords adduct A0 with $\Delta G^{298K} = +3.2$ kcal mol$^{-1}$. The barrierless ligand-to-substrate single-electron transfer affords the anionic mono-nitrene $[\text{Co}^{III}(\text{TAML})^\mathrm{red}(N'\text{T}s)]^-$ complex (A1, $\Delta G^{298K} = -19.2$ kcal mol$^{-1}$) after PhI extrusion, in accordance with a previously published DFT study on this system. 34 Protonation of $[\text{Co}^{III}(\text{TAML})^\mathrm{red}(N'\text{T}s)]^-$ by water affords A2 with $\Delta G^\circ = -13.4$ kcal mol$^{-1}$, leaving the TAML scaffold in its fully oxidized form as a result of TAML-amido single-electron transfer. The subsequent coordination of the formed hydroxy group affords A3 ($\Delta G^{298K} = -12.4$ kcal mol$^{-1}$). This step is followed by a second protonation of the amido ligand (A4, $\Delta G^{298K} = -6.5$ kcal mol$^{-1}$) and subsequent deprotonation of the hydroxy group, forming A5 ($\Delta G^{298K} = -16.9$ kcal mol$^{-1}$). Lastly, the release of TsNH$_2$ results in the proposed $[\text{Co}^{III}(\text{TAML})^\mathrm{sq}(O')]^-$ complex (AE1, $\Delta G^{298K} = -19.5$ kcal mol$^{-1}$). Despite considerable efforts, we could not locate transition states for these steps, which is typical for (de)protonation reactions. However, because the overall reaction is exergonic and takes place in water as the solvent, it seems reasonable to assume that the (de)protonation and OH$^-$ coordination elementary steps are (almost) barrierless. Overall, the calculated reaction pathway provides a feasible mechanism for the formation of $[\text{Co}^{III}(\text{TAML})^\mathrm{sq}(O')]^-$ by hydrolysis of $[\text{Co}^{III}(\text{TAML})^\mathrm{red}(N'\text{T}s)]^-$.

Next, guided by a previously reported mechanism on a biuret-amide-modified iron-TAML,49 we postulated a mechanism for the epoxidation of styrene on cobalt (Scheme 3, cycle II). On the basis of the above-described NEVPT2-CASSCF(14,12) calculations on $[\text{Co}^{III}(\text{TAML})^\mathrm{sq}(O')]^-$, we studied styrene oxide formation on the triplet spin surface. In addition, we also considered the quintet (S = 2) spin surface given that we observed high multireference character of the oxyl radical complex (see the supplemental information). These calculations demonstrate that on this spin surface, the complexes are far less stable and the barriers are significantly higher than those on the triplet surface (Table S27). Therefore, the pathway on the quintet spin surface will not be discussed further.

The computed mechanism for the epoxidation reaction catalyzed by the $[\text{Co}^{III}(\text{TAML})^\mathrm{sq}(O')]^-$ complex (AE1) at the triplet 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 ($\Delta G^{298K} = -7.1$ kcal mol$^{-1}$, $\Delta \Delta G^{298K} = +12.4$ kcal mol$^{-1}$) to afford the benzylic radical AE2 ($\Delta G^{298K} = -19.2$ kcal mol$^{-1}$) in an exergonic reaction. This step proceeds via a typical radical addition accompanied by an electronic reorganization of the cobalt center from low spin to intermediate spin. The subsequent “barrierless” radical rebound step via TS-AE-2 ($\Delta G^{298K} = -19.1$ kcal mol$^{-1}$, $\Delta \Delta G^{298K} = +0.1$ kcal mol$^{-1}$), where the TAML scaffold is not yet fully reduced, affords styrene oxide in AE3 ($\Delta G^\circ = -36.4$ kcal mol$^{-1}$). Simultaneous with product formation, substrate-to-ligand single-electron transfer leads to the reduction of the ligand to regenerate the $[\text{Co}^{III}(\text{TAML})^\mathrm{sq}(O')]^-$ complex upon product dissociation ($\Delta G^{298K} = -39.5$ kcal mol$^{-1}$).

To compare the performance of the catalyst in O- and N-group transfer and to understand the ratio of product formation, we calculated the mechanism for styrene aziridination with the $[\text{Co}^{III}(\text{TAML}^\text{red})]^-$ catalyst as well (Scheme 3, cycle III). Given that cobalt-TAML-catalyzed aziridination operates via electronically asynchronous transition states, we closely inspected the spin densities and charge distributions for this mechanism (see the supplemental information). The computed mechanism at the triplet (S = 1) spin surface for the aziridination reaction, catalyzed by the $[\text{Co}^{III}(\text{TAML}^\text{red})]^-$ complex, is depicted in Scheme 3 (cycle III; all free energies are reported with respect to reference point A). After the formation of the anionic mono-nitrene radical complex (A1), nitrene transfer to styrene...
proceeds via electronically asynchronous TS-AN-1 ($\Delta G^{\circ}{}_{298K} = -5.4 \text{ kcal mol}^{-1}$, $\Delta \Delta G^{\circ}{}_{298K} = +13.8 \text{ kcal mol}^{-1}$). This step affords benzylic radical AN1 ($\Delta G^{\circ}{}_{298K} = -19.6 \text{ kcal mol}^{-1}$) in an exergonic reaction. The subsequent radical rebound step via TS-AN-2 ($\Delta G^{\circ} = -18.1 \text{ kcal mol}^{-1}$, $\Delta \Delta G^{\circ} = +1.5 \text{ kcal mol}^{-1}$) leads to aziridine formation and is accompanied by substrate-to-ligand single-electron transfer. This step subsequently affords the coordinated cis-aziridine product in AN2 ($\Delta G^{\circ}{}_{298K} = -31.2 \text{ kcal mol}^{-1}$) and regenerates the $[\text{Co}^{\text{III}}(\text{TAMLred})]$– complex after product dissociation ($\Delta G^{\circ}{}_{298K} = -35.1 \text{ kcal mol}^{-1}$). N-pyramidal inversion eventually yields the trans-aziridine product ($\Delta G^{\circ}{}_{298K} = -37.9 \text{ kcal mol}^{-1}$).

Notably, the calculated barriers for the reaction pathways for styrene epoxidation (Scheme 3, cycle II) and styrene aziridination (Scheme 3, cycle III) are comparable and relatively low. The addition of the oxyl radical to styrene (TS-AE-1, $\Delta \Delta G^{\circ}{}_{298K} = +12.4 \text{ kcal mol}^{-1}$) and the nucleophilic attack of the nitrene radical onto styrene (TS-AN-1, $\Delta \Delta G^{\circ}{}_{298K} = +13.8 \text{ kcal mol}^{-1}$) are both rate determining and fairly similar in energy according to the calculations. Therefore, the product ratio does not depend on the relative rates of these reactions but rather on the relative concentrations of the nitrene and oxyl radical intermediates. Because our results suggest that the hydrolysis of the $[\text{Co}^{\text{III}}(\text{TAMLsq})\text{(N} \cdots \text{Ts})]$– complex affords the $[\text{Co}^{\text{III}}(\text{TAMLsq})(\text{O} \cdots \text{I})]$– complex, the product selectivity might be determined by the relative rates of the nitrene hydrolysis and aziridination reaction. Consequently, styrene and water most likely compete for a reaction with the nitrene radical complex. Hence, we performed additional catalytic experiments to further support this hypothesis. The standard Li$[\text{Co}^{\text{III}}(\text{TAMLred})]$-catalyzed aziridination reaction was performed under aerobic conditions in D$_2$O in the presence of different equivalents of styrene (Table S6). As the styrene concentration increased, significantly more aziridine formation was observed. More specifically, using 5 equiv of styrene yielded epoxide product 1 and aziridine product 2 in a 7:1 ratio, whereas using 20 equiv of styrene afforded these products in a 4:1 ratio (Table S6, entries 1 and 3). On the basis of these combined experimental and theoretical results, we propose that the experimentally observed product ratios result from competing rates for aziridination and nitrene hydrolysis.

**pH-controlled aziridine formation**

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

Initially, reactions were performed under the standard conditions with PhINTs (Table 1, entry 1) at different pH values in a phosphate-buffered medium$^{50}$ (Table S11, Figure S17). As a control, the standard reaction (Table 1, entry 1) was also performed in phosphate buffer at pH 7. This procedure afforded a similar epoxide product 1/aziridine product 2 ratio (entry 6, Table S11) with respect to the reaction performed in Milli-Q, which excludes any effect of the buffer salts. We further adjusted the reaction conditions by increasing the catalyst, styrene, and iminoiodinane concentrations (Tables S12–S14). Finally, reactions were performed with PhINNs as well.$^{51}$ These results are presented in Table 2.

The Li$[\text{Co}^{\text{III}}(\text{TAMLred})]$-catalyzed aziridination reaction of styrene with PhINNs at pH 7 yielded epoxide product 1 as the major product under aerobic conditions (Table 2,
Performing the reaction under basic conditions (pH = 10; entries 2 and 3) afforded the same product selectivity. Note that no product formation was observed in the absence of catalyst (entry 4). Under acidic conditions (pH 4; entries 5 and 6), aziridine product 3 was formed selectively, and no product was formed in the absence of catalyst (entry 7). Given that coordination of a hydroxide and its subsequent deprotonation are crucial steps in the formation of the cobalt-oxo/oxyl radical complexes, these reaction steps are expected to be easier under basic conditions where high concentrations of OH⁻ are present. Hence, styrene oxide is the major product observed under neutral and basic conditions, whereas performance of the reaction under acidic conditions (with low concentration of OH⁻) leads to the preferred formation of aziridine product 3. Overall, we observed that changing the pH of the reaction medium can control product formation. These results therefore provide additional and direct experimental evidence for the proposed mechanism for nitrene hydrolysis, affording cobalt-oxo/oxyl radical complexes as the catalytically active species involved in styrene oxide formation (Scheme 4A).

Under acidic conditions, we tentatively propose the intermediacy of a cationic cobalt nitrene complex in aziridine formation (Scheme 4A). Given the cationic charge of this species, further protonolysis of the second imido moiety is unlikely.

Using pH as a tool to achieve selective aziridine formation in water, we further optimized the reaction conditions to increase product formation (Table S15). As a result, the cobalt-catalyzed aqueous styrene aziridination was most efficient with 15 mol % of [CoIII(TAMLred)]⁻ and 20 equiv of styrene at room temperature (Scheme 4B). Although radical-type nitrene transfer is typically performed in anhydrous organic media under inert conditions, styrene was successfully converted to the desired aziridine product with respectable yields in water under aerobic conditions. Further optimization of the pH afforded product formation with >99% selectivity, i.e., no epoxide formation was observed. The selective aziridination of multiple styrene derivatives supports the application of the procedure. However, despite considerable

### Table 2. Catalytic reactivity of [CoIII(TAMLred)]⁻ in phosphate-buffered medium and the relevant control experiments

<table>
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<tr>
<th>Entry</th>
<th>pH</th>
<th>Yield 1 (%)</th>
<th>Yield 3 (%)</th>
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<td>7</td>
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NR-source/substrate ratio = 1:5. Conditions: 2 h, 23.0 mM NR-source.

*All experiments were performed in phosphate-buffered Milli-Q (0.1 M).

bYields are quantified by ¹H NMR with 1,3,5-tritertbutylbenzene as the external standard upon extraction with CDCl₃ and are versus PhI NNs. Reactions (blanks excepted) were at least performed in duplicate, and yields are averaged.

cExperiment was performed under argon.

dNo catalyst was used.
efforts, no further improvements were made, which marks the limits of this specific system. We consider catalyst stability as the bottleneck, possibly related to the observation that the ligand oxidation process (hydroxylation of the TAML scaffold from the oxyl radical and/or amination from the nitrene radical) rendered catalytically inactive intermediates (*vide supra*). Ongoing work in our lab is therefore devoted to tackling these challenges.

**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, the catalytic aziridination of styrene with Li[CoIII(TAMLred)] and PhINTs in a 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, hydrolysis of the formed nitrene radical complexes yields oxyl radical complexes active in OAT catalysis. The involvement of the nitrene radical complexes is supported by the absence of

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**Scheme 4. Styrene aziridination in buffered media**

(A) Proposed catalytic species under the acidic and basic conditions yielding styrene oxide and the desired aziridine product, respectively.

(B) Selective aqueous aziridination of styrene derivatives under acidic conditions.
product formation when the radical trap DMPO is present in the reaction mixture. Furthermore, the use of H$_2^{18}$O as the reaction solvent affords $^{18}$O-labeled styrene oxide, unambiguously demonstrating the role of water as the oxygen source. The intermediacy of water in styrene oxide formation was further supported by mass spectrometry experiments in flow. The obtained dynamic flow profiles clearly show the depletion of the [Co$^{III}$(TAML)(N$^{Ts}$)$_{n}$]$^{-}$ complexes when water is introduced, pointing to hydrolysis of these complexes, which affords reactive oxo/oxyl radical complexes. The consecutive detection of oxygenated species is the result of oxidation of the TAML scaffold (in the absence of suitable oxygen-accepting substrates) via the intermediacy of these oxo/oxyl radical complexes, providing further support for the hypothesis mentioned above. On the basis of NEVPT2-CASSCF(14,12) calculations, the electronic structure of the “mono-oxo” [Co$^{III}$(TAML$_{sq}$)(O$^{Ts}$)]$^{-}$ complex was elucidated. This cobalt-oxyl radical complex is best described as having a multireference triplet ground state such that one unpaired electron is delocalized over a nearly covalent Co–O $\pi^*$ antibonding orbital and the other unpaired electron is mainly localized on the TAML scaffold, with delocalization over cobalt and the oxyl group. Styrene oxide formation during aqueous styrene aziridination most likely results from OAT via such in-situ-formed cobalt-oxo/oxyl radical complexes, which we confirmed with supporting DFT studies. These studies showed that epoxidation of styrene via [Co$^{III}$(TAML$_{sq}$)(O$^{Ts}$)]$^{-}$—formed by hydrolysis of [Co$^{III}$(TAML$_{sq}$)(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 hydrolysis and aziridination reactions. On the basis of this mechanistic insight, catalytic experiments at different pH values were performed. These experiments provide direct evidence for the proposed mechanism because they show that the desired aziridine product is formed selectively and with respectable yields under acidic conditions. Overall, we demonstrate that understanding the reactivity of nitrene (radical) complexes in water is fundamental to controlling and improving aqueous (radical-type) nitrene transfer catalysis.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact
Requests for further information and resources should be directed to and will be fulfilled by the lead contact, Bas de Bruin (b.debruin@uva.nl).

Materials availability

This study did not generate new material/reagents.

Data and code availability

This study did not generate any datasets.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.checat.2023.100700.

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AUTHOR CONTRIBUTIONS
E.J.M., B.d.B., and J.N.H.R. conceived the project. E.J.M. performed the initial experiments and designed and performed further experimental investigations and theoretical calculations based on DFT with input and contributions from N.P.v.L. and C.J.V. N.P.v.L. and B.d.B. performed the NEVPT2-CASSCF calculations, and M.T.G.M.D. and J.R. performed the flow reactor coupled MS measurements. E.J.M. and N.P.v.L. wrote the manuscript, with input from all authors, under the supervision of B.d.B. and J.N.H.R.

DECLARATION OF INTERESTS
The authors declare no competing interests.

INCLUSION AND DIVERSITY
We support inclusive, diverse, and equitable conduct of research.

REFERENCES


50. A phosphate buffer (0.1 M) covers a broad pH range (1.2–12), which makes it ideal for screening the catalytic activity of Li[CoII(TAML)3] under acidic and basic conditions.

51. PhINNs (relatively electron withdrawing) generally affords more azidine product than PHINs (relatively electron donating) and less epoxide product under acidic conditions; see Table S14. 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 nitrines facilitate this reaction more efficiently. See van Leest et al. [54] for more details.