Ground-state dioxygen undergoes metal-free [3 + 2]-annulations with allenes and nitrosoarenes under ambient conditions†

Jinxian Liu,‡a,b Manisha Skaria,‡a Pankaj Sharma,‡a Yun-Wei Chiang‡a and Rai-Shung Liu†‡a

The cycloadditions of molecular dioxygen with neutral π-bond motifs rely heavily on singlet-state \(^{1}\text{O}_2\), whereas ground state \(^{3}\text{O}_2\) is chemically inactive. Here we report novel [3 + 2]-annulations among ground state \(^{3}\text{O}_2\) (1 bar), allenes, and nitrosoarenes at low temperatures, efficiently yielding dioxygen-containing oxacycles. With less hindered 1-aryllallene derivatives, these dioxygen species undergo skeletal rearrangement to 3-hydroxy-1-ketonyl-2-imine oxides. These cycloadditions represent valuable one-pot \(O,O,O\)-trifunctionalizations of allenes. Our EPR experiments confirm the presence of 1,4-diradical intermediates from an allene/nitrosoarene mixture, which manifest the hidden diradical properties of nitrosoarenes.

Introduction

Cycloadditions of two or three π-bond molecules are powerful tools to access carbocyclic or heterocyclic scaffolds. Ground-state \(^{3}\text{O}_2\) has low-lying LUMO orbitals, but its triplet state greatly reduces its chemical reactivity toward neutral molecules unless a metal catalyst is present. The cycloadditions of \(^{3}\text{O}_2\) dioxygen rely nearly exclusively on prior photo-activation to form singlet-state \(^{1}\text{O}_2\) (ref. 1) that reacts with dienes, olefins or even arenes in \([n + 2]\)-cycloadditions (\(n = 2\) and 4, Scheme 1, eqn (1)). This photolytic process requires a sensitizer in cold bath (\(-40 ^\circ\text{C}\)) over a protracted period (\(-12\) h) because highly energetic \(^{1}\text{O}_2\) might produce byproducts from the oxygen-ene reactions and oxidative C–C cleavage reactions.\(^{6}\) In the case of allenes, singlet dioxygen afforded a complicated mixture of undesired compounds.\(^{7,a,b}\)

As ground-state \(^{3}\text{O}_2\) is a free π-molecule and is available everywhere; its metal-free \([n + 2]\)-cycloadditions with commonly used unsaturated hydrocarbons would provide a clean and cheap synthesis of valuable 1,\(\pi\)-diols, although there is no literature precedence. As far as we are aware, only 1,4-diradical precursors such as \(o\)-benzocyclobutanes,\(^{8}\) 1,2,6,7-octatetraenones,\(^{9}\) 2,3-dimethylenebicyclo[2.2.0]hexane\(^{10}\) and other 1,4-diazo species\(^{11}\) reacted with ground-state \(^{3}\text{O}_2\) in thermal \([4 + 2]\)-cycloadditions; these precursors are too uncommon to show general utility. We recently achieved metal-catalyzed annulations of \(N\)-hydroxy allenylamines with nitrosoarenes via a single radical process.\(^{12}\) In search of a breakthrough in dioxygen chemistry, we developed facile \([3 + 2]\)-cycloadditions among nitrosoarenes, allenes and ground-state \(^{3}\text{O}_2\) to efficiently afford \(N\)-(1,2-dioxolan-4-ylidene)aniline oxides (eqn (2)). Particularly notable are the ambient conditions: \(-15\) to \(0 ^\circ\text{C}\), \(^{3}\text{O}_2\) (1 bar), no light, no catalyst and no additive. Importantly, these facile spin-forbidden dioxygen annulations reveal a new role of nitrosoarenes as effective diradical precursors that is synthetically significant in nitroso chemistry.\(^{13}\) In the context of nitrosoalkene and nitroso/alkyne reactions,\(^{11}\) theoretical calculations by Houk\(^{13,c,f}\) suggested the intermediacy of the diradical species, but these transient species could not be trapped with dioxygen or other small molecules.

![Scheme 1](image)

Current reactions: \([2+2]\) and \([4+2]\)-cycloadditions with singlet oxygen

This work: \([3+2]\)-annulations involving \(^{3}\text{O}_2\)

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2-Amino-1,3-diols are present in numerous natural products with diverse biological activity (Fig. 1).14 Catalytic O₅N₃O-trifunctionalization of allenes is a new appealing tool to assess these motifs, as noted by the work of Schomaker, who reported Rh-catalyzed intramolecular cyclizations of homo-allylenysulfamate esters via a two-step sequence.3,m In contrast, our one-pot intermolecular O₅N₃O-functionalizations employ common and cheap nitrosoarenes, allenes and oxygen.

### Results and discussion

Table 1 presents the optimized yields of a O₅N₃O-trifunctionalized molecule 3a from a mixture of allene 1a, nitrosobenzene 2a (n equiv.) and O₂ (1 bar). When 1.5 equiv. of nitrosobenzene 2a was used in cold THF (−15 °C), the yield was 43% (entry 1). The yield of 3a increased to 63% with nitrosobenzene in three fold proportions (entry 2). In other solvents, the yields of 3a were 50% in toluene, 54% in CH₃CN, and 58% in DCM (entries 3–5). The yield of 3a decreased substantially to 10% in THF at 25 °C (entry 6). The reaction under N₂ failed to yield the desired product 3a in a traceable amount (entry 7).16 Compound 3a assumes an E-configuration with its hydroxyl cis to the nitrene oxygen to form a hydrogen bond. This structure was inferred from X-ray diffraction measurements of its relative molecular structure of compound 4a, armed by its X-ray cation using a silica column.

Table 1  Optimization of reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Gas</th>
<th>n</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>O₂</td>
<td>1.5</td>
<td>−15</td>
<td>2</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>O₂</td>
<td>3</td>
<td>−15</td>
<td>2</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>O₂</td>
<td>3</td>
<td>−15</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>MeCN</td>
<td>O₂</td>
<td>3</td>
<td>−15</td>
<td>2</td>
<td>54</td>
</tr>
<tr>
<td>5</td>
<td>DCM</td>
<td>O₂</td>
<td>3</td>
<td>−15</td>
<td>2</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>O₂</td>
<td>3</td>
<td>25</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>THF</td>
<td>N₂</td>
<td>3</td>
<td>−15</td>
<td>10</td>
<td>—</td>
</tr>
</tbody>
</table>

1 [1a] = 0.1 M. b Product yields are reported after purification using a silica column.

Table 2  O₅N₃O-Trifunctionalizations of allenes with O₂ and ArNO<sub>a</sub>b

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>THF, O₂ (1 bar)</td>
<td>43</td>
</tr>
<tr>
<td>3b</td>
<td>THF, O₂ (1 bar)</td>
<td>50</td>
</tr>
<tr>
<td>3c</td>
<td>THF, O₂ (1 bar)</td>
<td>68</td>
</tr>
<tr>
<td>3d</td>
<td>THF, O₂ (1 bar)</td>
<td>63</td>
</tr>
<tr>
<td>3e</td>
<td>THF, O₂ (1 bar)</td>
<td>45</td>
</tr>
<tr>
<td>3f</td>
<td>THF, O₂ (1 bar)</td>
<td>28</td>
</tr>
</tbody>
</table>

To assess the reaction scope, we applied these optimized conditions to additional mono- and 1,3-disubstituted allenes 1b–1q; Table 2 summarizes the results. For phenylallene 1a, its corresponding reactions with 4-methyl-, 4-methoxy- and 3,5-dimethylphenylnitroso species afforded 3-hydroxy-1-ketonyl-2-imine oxides 3b–3d in 54–68% yields (entries 1–3). Varied arylallenes 1b–1e (Ar = 4-MeC₆H₄, 4-ClC₆H₄, 4-BrC₆H₄ and 3-thienyl) yielded desired compounds 3e–3h in satisfactory yields (50–74%, entries 4–6). 3-Substituted phenyllallenes 1f and 1g (R = n-Bu and Ph) were also effective substrates for these cycloadditions (entries 7–8).

Notably, the reaction of sterically hindered 3-cyclohexyl-1-phenyllallene 1i with 4-methoxyphenylnitroso 2c and O₂ (1 bar) afforded dioxygen-containing oxacycle 4a together with desired product 3i; the yields were 45% and 28%, respectively. Species 4a assumes an anti-configuration (dr > 20 : 1) according to its <sup>3</sup>H NOE spectra; this new compound was efficiently converted to compound 3j in hot THF (eqn (3)), via a Kornblum–DeLaMare rearrangement.22

The kinetic stability of dioxygen-containing oxacycle 4a is enhanced with a suitable steric environment. We further tested the reactions on various 1-aryl-1-methylallenes 1j–1m with 4-methoxyphenylnitroso 2c and O₂ (1 bar) in THF (0 °C), generating dioxygen-containing compounds 4b–4e (Ar = 4-RC₆H₄, R = H, Me, MeO, Br) in satisfactory yields (Table 3, entries 1–4). The molecular structure of compound 4b was confirmed by its X-ray...
Various 1-aryl-3,3-dimethylallenes (Ar = 4-RC₆H₄, R = H, Me, MeO, Br), electron-rich nitrosoarenes and O₂ were also amenable to such cycloadditions, yielding desired compounds 4f–4m in satisfactory yields (60–72%, entries 5–12) except 4k in only 38% yield. This dioxygen cycloaddition was applicable to cyclohexylidene-derived phenylallene 1r, affording compound 4n in 66% yield (entry 13). Compounds 4 serve as the first examples of the cycloadditions of ground-state O₂ with unsaturated hydrocarbons at low temperatures.

An electron-deficient nitrosoarene is an inapplicable substrate, as shown by eqn (4). Under O₂, the reaction of trisubstituted allene 1p with 4-chlorophenyl nitroso species 2f in cold THF (0 °C) afforded nitroso-containing cycloadduct 5a in 53% yield; the dioxygen-containing product, ca. 5%, was unstable for isolation (eqn (4)). In contrast, the same allene 1p could deliver dioxygen-containing species 4j and 4k using electron-rich nitrosoarenes under the same conditions (entries 9–10, Table 3).

Under nitrogen, trisubstituted allene 1p reacted with 4-methylphenyl nitroso 2b in cold THF to form nitroso-containing cycloadduct 5b in 60% yield (eqn (5)). The stereochemistry and its E-conformation of this new compound was confirmed by its X-ray diffraction pattern. Such a new reaction represents a new and useful O,N,N-functionalization of allenes. A preliminary survey of the reaction scope is summarized in Table 4. We tested the reactions on 1,3-di- and 1,1,3-trisubstituted allenes 1g and 1t that reacted with nitroso-arenes (R = H, Cl, CO₂Et) to afford nitroso-containing cycloadducts 5c–5g in reasonable yields (58–83%). Furthermore, the anti-conformation of compound 5c was determined by X-ray diffraction.

Dioxygen-containing heterocycles 4 are readily reduced with Pd/C, H₂ (1 atm) in MeOH (23 °C) to cleave their O–O bonds, satisfactorily yielding desired 1,3-dihydroxy-2-imine oxides 6. These reductions highlight the utility of molecular oxygen to afford 1,3-dihydroxy-2-amino derivatives. Several instances of affording tertiary 1,3-alcohol derivatives are illustrated in eqn (6) and (7); their chemical yields exceed 65%. Under these reductions, the valuable nitrone functionalities of these acyclic 1,3-diols remain intact as indicated by their HRMS and ¹³C-NMR spectra.
The facile cycloadditions among allenes, nitrones and ground-state O₂ are very astonishing because an intersystem crossing (ISC) must be involved for one key intermediate. To investigate the mechanism, we examined the reaction of 1-phenyl-3-cyclopropylallene 1s with 4-methylphenylnitroso species 2b under O₂, yielding compound 3m in 71% yield; this transformation did not induce cyclopropane cleavage because of the stability of the phenylallylic radical A (eqn (8)).¹⁹ We thus exclude the intermediacy of the dicarbon radical A, although analogous carbon radicals were postulated for the α-quinodimethine species. We isolated compound 7 in 13% yield from the reaction of 1-phenylallene 1a with PhNO (1.2 equiv.) and TEMPO (2 equiv.) under N₂, indicating the formation of diradical intermediates (eqn (9)). We employed EPR to characterize the diradical species from a mixture of 3,3-dimethyl-1-phenylallene 1n and nitrosobenzene 2a in THF at 0 °C (0.5 h). Fig. 2 (top) shows the EPR signal of the diradical species; the intensity of this signal remains unchanged for 5 h under N₂. The simulation analysis was performed using the EasySpin program. The satisfactory fit was achieved with a two-component simulation (bottom). The abundant component (70%) corresponds to nitrogen-centered diradicals (g = 2.00616, ðN = 10.7 G and 3.0 G) respectively. The minor component corresponds to a monoradical nitroso with ðN = 10.7 G. Notably, when recorded at T < 130 K, the spectrum exhibits a well-known nitroso rigid-limit lineshape in accordance with the above simulation result; the coupling of unpaired electrons with the nitrogen center is evident.

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\text{Scheme 2 depicts a plausible mechanism to rationalize the remarkable facility of such dioxygen annulations. We postulate that allene 1 reacts initially with nitrosobenzene to form 1,4-diradical species A, which is expected to couple with nitrogen in two magnitudes, i.e. ðN = 10.7 G and 3.0 G respectively. The capture of molecular dioxygen O₂ by 1,4-diradical species A forms peroxy diradical B in a triplet state, as the two radical centers of species B are remote from each other, rendering an intersystem crossing (ISC) feasible. After a change of spin state, singlet-state diradical B' is expected to form primary 1,2-oxaziridine diradical C through a 3-exo-trig cyclization that is more feasible than an alternative 5-endo-trig cyclization. A final radical–radical coupling of resulting species C forms precursor D, and ultimately yields desired 1,2-dioxolanes 4. This proposed path rationalizes the formation of compound 7 from the TEMPO experiment (eqn [9]) well. The trapping of the 1,4-biradical generates single radical species F that undergoes a rapid 3-exo-trig cyclization to form benzyl radical G. A second trapping of this species with the TEMPO radical is expected to yield species I that is prone to hydrolysis on a silica column to yield observed product 7.}

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\text{Scheme 2 A plausible mechanism.}
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\[
\text{Conclusions}
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Prior to this work, singlet-state oxygen O₂ failed to react with allenes to give useful oxygenated products. This study reports the first examples of metal-free [3 + 2]-cycloadditions among allenes, nitrosoarenes and ground-state O₂ (1 bar) at low temperatures, efficiently yielding dioxygen-containing oxacycles. With less hindered 1-aryllallene derivatives, the resulting oxacycles undergo skeletal rearrangement to 3-hydroxy-1-ketonyl-2-imine oxides. These transformations highlight a cheap, efficient and clean synthesis of 1,3-dihydroxy-2-amino derivatives. Our experimental data indicate that an initial attack of a nitrosoarene at an allene generates a diradical species that is detectable with EPR. We envisage that the concept of nitrosoarenes as diradical precursors will inspire new synthetic concepts.
Acknowledgements

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Notes and references


17 Crystallographic data of 3b, 4b, 5b and 5e were deposited at the Cambridge Crystallographic Data Centre (3b CCDC 1507478, 4b CCDC 1507477, 5b CCDC 1510902, 5e CCDC 1540299).


19 The rearrangement of cyclopropylmethyl radicals to homoallylic radicals is seriously affected by the radical substituents; this process is reversible. Previous studies by Bowry indicate that stable cyclopropylbenzyl radicals are reluctant to form the corresponding homoallylic radicals. In our system, key intermediate A is a very stable phenylallylic radical that has many resonance forms. The equilibrium of this rearrangement is expected to be favourable for initial radicals A that can be trapped by O₂ to yield the observed product 3m. For the nature of this radical rearrangement, see the leading reference, A. J. Beckwith and V. W. Bowry, J. Am. Chem. Soc., 1994, 116, 2710–2716.

\[ \text{Ch}^{3}\text{O}_2^+ + \text{A} \rightarrow \text{3m} \]


