Open-shell nitrene- and carbene-complexes of cobalt

Characterisation and reactivity

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Chapter 4

Porphyrin-Co(III)-‘nitrene radical’ catalysed synthesis of phenoxazinone and o-amino-azobenzenes

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Introduction

In the previous two chapters, we have discussed the electronic and geometric structures of nitrene-radical intermediates that are formed as a result of azide activation by cobalt(II)-porphyrins. In chapter 1 we also summarised the catalytic transformations that these systems can perform (Figure 12, chapter 1). For the porphyrin-Co(III)-nitrene radicals the reactivities were limited to intramolecular C-H insertions and aziridination reactions. For the carbene radicals, however, the current scope of reactions is much broader. Intermolecular reactions with alkynes can not only give cyclopropanes but also lead to ring compounds (see example C and E in Figure 11, chapter 1). For cobalt(III)-nitrene radicals, addition to triple bonds (alkynes, for example) are currently not reported. This limitation in reactivity of the nitrene radicals might in part be because of the high-energy azirines that are formed as products. The 1H-azirines (C–C double bond) very easily undergo rearrangements to form the more stable 2H-azirines (Figure 1). 2H-azirines are the same three membered N-heterocycles but with an N–C double-bond. The 2H-azirines also undergo follow-up reactions with electrophiles and nucleophiles alike. This is in marked contrast with the corresponding three-membered cyclopropenes which are relatively more stable (possibly due to lower ring-strain compared to azirines).

Figure 1. The three-membered N-Heterocycles called azirines. They undergo rearrangements of the double bond and can undergo ring-opening reactions with nucleophiles or electrophiles.

For the porphyrin-cobalt(III)carbene radicals, intermolecular reactions with reaction partners like acetylenes to give ring-compounds have been successful (Figure 11, chapter 1). An elegant example is that of the catalytic synthesis of 2H-Chromenes which was reported by de Bruin and co-workers in 2014. This reaction proceeds via the attack of the carbene-radical intermediate B on the alkyne functionality of phenyl acetylene. The transformation and mechanism is outlined in Scheme 1.

Scheme 1. DFT calculated mechanism of Co(II) porphyrin catalysed synthesis of 2H-Chromenes.
DFT studies on the mechanism of this system reveal the formation of the salicyl–vinyl radical intermediate C by the [Co^II(Por)] metalloradical. Unexpectedly, subsequent hydrogen atom transfer (HAT) from the hydroxyl moiety to the vinyl radical (intermediate C) leads to formation of an o-quinone methide intermediate D. This intermediate dissociates from the metal centre to undergo an endocyclic, sigmatropic ring-closing to give the 2H-chromene (Scheme 1). This was confirmed by EPR experiments and radical poisoning experiments using the 2,2,6,6-tetramethyl-1-piperidinyloxylyl (TEMPO) free radical.

This reaction inspired us to extend the chemistry to related ring-closing reactions, but this time using a nitrene precursor instead of a carbene precursor. We hypothesized that a similar substrate containing an azide functionality could also be activated by cobalt(II) porphyrins leading to N-containing heterocycles. N-containing heterocycles are interesting synthetic targets, given their ubiquity in natural products. The thus formed heterocycles in this case are called benzoxazines. They are used in polymers, resins, and as cross-linking agents due to their favourable thermal and chemical resistance and electrical properties. Many variants are also pharmaceutically active compounds. On the other hand, as these nitrene radicals are not reported in reactions with alkynes they are also mechanistically very interesting cases to study. Experimentally, however, these reactions take a different course and new pathways are discovered. The results of these investigations are disclosed in this chapter.

Results and Discussion

As an initial test reaction, o-azido phenol 1 was reacted with [Co^II(TPP)] (Figure 2) in the presence of phenyl acetylene with the expected formation of benzoxazine 2 as the product (Scheme 2). However, on analysing the crude reaction mixture the expected product 2 was not detected. Instead, new 1H-NMR peaks were observed, and the azide was fully consumed. The major product was separated from the reaction mixture by column chromatography, and proved to be the phenoxazinone 3 (Scheme 2).

![Figure 2. The two different [Co^II(Por)] complexes used as catalysts in this study.](image)

Scheme 2. Formation of phenoxazinone 3 from o-azido phenol 1 catalysed by [Co^II(TPP)].

The unexpected formation of product 3 could be rationalized if one considered HAT from the hydroxyl group in the ortho position of the cobalt(III) nitrenoid intermediate formed on activation of the azide by the catalyst [Co^II(TPP)]. This should result in the formation of the reactive ortho-iminoquinonoid
compound 4 (Scheme 3). Attack of the imine N atom of 4 at the para position (w.r.t to the carbonyl group) of another molecule of 4, followed by 1,5- sigmatropic migration of an H atom, subsequent deprotonation and oxidation would lead to formation of the phenoxazine product 3. Such a pathway using ortho-amino phenol (OAP) has also been reported before using manganese porphyrins that use H₂O₂ as the external oxidant. In our case, the deprotonation and oxidation steps probably took place in air during column chromatography.

Scheme 3. Proposed mechanism for formation of 3 from 1 mediated by [Co⁶(TPP)]

Compound 3 has anti-inflammatory and immunomodulatory properties and is, therefore, valuable for its medicinal properties. As mentioned before, other reported methods involving metalloporphyrin catalysed synthesis of 3 from OAP make use of more powerful oxidants like hydrogen peroxide, and are believed to be formed via different mechanisms. To see if formation of 3 could be avoided by using an excess of the alkyne, the reaction was also performed in neat alkyne. However, also in this case almost exclusive formation of compound 3 was observed. In addition to that, simple aziridinations of alkenes like cyclohexene and styrene were also attempted using o-azido phenol 1, which in all cases led to formation of only one identifiable and major product: phenoxazinone 3 (Table 1).
Table 1. Reaction of o-hydroxy phenyl azide 1 with different substrates under reaction conditions a and b.*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Expected product(s)</th>
<th>Obtained product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td><img src="image1" alt="Expected product" /></td>
<td><img src="image2" alt="Obtained product" /></td>
</tr>
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<td>3</td>
<td></td>
<td><img src="image5" alt="Expected product" /></td>
<td><img src="image6" alt="Obtained product" /></td>
</tr>
</tbody>
</table>

*Reaction conditions: a) 0.5 mmol of azide 1, 1mmol of substrate, 5 mol% [CoII(TPP)] (w.r.t. azide), 4 mL toluene, 50 °C, 18h. 
b) 0.6 mmol of azide 1, 15 mL of substrate, 5 mol% [CoII(TPP)], 50 °C, 18h. No nitrene transfer to the solvent (toluene) was observed in any case under the applied reaction conditions.

To be able to trap the proposed reactive intermediate 4 with a different substrate we decided to protect the phenyl ring on the 5-position, so that coupling of two iminoquinones to give products like 3 is prevented. As such, 2-azido-5-nitrophenol 5 was synthesized. As a test reaction, we tried to trap the corresponding o-quinone monoamine intermediate with 1-butoxyethene in an Inverse Electron Demand Diels-Alder (IEDDA) reaction (Scheme 4). For this transformation, however, no fruitful results were obtained when using [CoII(TPP)] as the catalyst. The crude reaction mixtures showed formation of a mixture of products containing a lot of azide starting material. This is most likely due to the inherent inability of [CoII(TPP)] to activate the azide under the applied reaction conditions. However, on switching to [CoII(TPPF20)] (Figure 2), the desired transformation could be achieved and product 6 was obtained in 80% isolated yield. Non-catalytic trapping of o-quinone monooimines has been reported earlier, but the method uses stoichiometric amounts of halogen containing oxidants, which is avoided in the reaction depicted in Scheme 4.

Scheme 4. Trapping of the o-quinone monoimine in an IEDDA reaction.

Substrate 5 was also tested in reactions with other potential reaction partners, in which we expected to be able to trap the iminoquinone intermediate with different C=C and C≡C bonds. With phenyl acetylene, no reaction involving the C≡C bond was observed. Other alkenes also proved unreactive in this process. Apparently, only electron rich alkenes like 1-butoxyethene are suitable reaction partners in this process.
Table 2. Reaction of azide 5 with different substrates*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Expected Product(s)</th>
<th>Obtained Product</th>
</tr>
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<td>2</td>
<td><img src="image4.png" alt="Image" /></td>
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<td>.....</td>
</tr>
<tr>
<td>3</td>
<td><img src="image6.png" alt="Image" /></td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /> (80 %)</td>
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</table>

*Reaction conditions: a) 0.5 mmol of azide 1, 1 mmol of substrate, 5 mol% [Co(II)(TPP)] (w.r.t. azide), 4 mL toluene, 50 °C, 18 h. b) 0.6 mmol of azide 1, 15 mL of substrate, 5 mol% [Co(TPP)], 50°C, 18 h. No nitrene transfer to the solvent (toluene) was observed in any case under the applied reaction conditions.

To investigate the generality of the observed HAT reactivity, we decided to explore the reactivity of aryl azide 7, containing an NH$_2$ substituent in the ortho-position instead of an OH substituent. The o-amino phenylazide 7 was synthesized and tested under the same reaction conditions, using [Co(II)(TPP)] as the catalyst (Scheme 5). In contrast to our expectations, however, azobenzene 8 was obtained as the major product. This observation intrigued us, as formation of azo compounds as products in reaction of azides with [Co(II)(Por)] catalysed processes has been reported only once before, and only as a minor side product.\(^7\)

![Scheme 5](image9.png)

**Scheme 5. Reaction of o-amino phenylazide 7 with [Co(II)(TPP)].**

Two mechanistic proposals for formation of azo compounds in [Co(II)(Por)] catalysed reactions have been suggested: (I) Attack of the azide starting compound on the nitrene intermediate, producing azobenzene with simultaneous N$_2$-loss, and (II) dinuclear N-N coupling involving two nitrene complexes (Scheme 6). However, formation of amines from the azides via the nitrene (radical) intermediates has also been reported, likely involving HAT from the reaction medium (solvent) to the cobalt(III) nitrene radical intermediate. The latter process, actually, also provides an alternative (and perhaps more likely) pathway for formation of azo compounds (see below).
Scheme 6. Possible side reactions in [Co\textsuperscript{II}(Por)] catalysed reactions with organic azides.

It is not so clear how the reaction conditions influence the formation of azobenzenes. One suggested possibility was that in the presence of a large excess of another reaction partner, the concentration of the nitrene intermediate cannot build-up in a sufficient manner to allow formation of azo compounds via dinuclear N-N coupling. To check this hypothesis, we repeated the reaction of azide 7 in the presence of a large excess of phenyl acetylene or styrene in refluxing toluene. However, once again the azo compound 8 was obtained as the major product. This led us to believe that there is something unique about the NH\textsubscript{2} substituent in azide 7 that relates to formation of only the azo compound. We speculate that this relates to rapid formation of o-phenylene diimine (OPDI) undergoing further reactions to form 8.

Scheme 7. Plausible mechanism for the formation of azobenzene from the reaction of azide 7 catalysed by [Co\textsuperscript{II}(TPP)].
The formation of azobenzene 8 from ortho-amino phenyl azides via the proposed phenylene diimine intermediate 9 can be reasoned in the mechanism depicted in Scheme 7. On formation of the OPDI the N atom of one of the imine moieties does a nucleophilic attack on an imine nitrogen atom of another OPDI molecule. Rearrangement of a proton then leads to the formation of the azobenzene 8 as depicted in the Scheme 7.

It is worth mentioning that this reaction of ortho-amino substituted phenyl azides to give the corresponding azobenzene compounds as the major product is one of the few catalytic examples reported so far to synthesize azo compounds in high yields. Currently, only a few examples of catalytic synthesis of azobenzenes via azides are reported. These are summarized in Scheme 8. The iron based example of Groysman and co-workers is limited in the sense that only azides with bulky substituents like mestiyl groups result in formation of azo compounds. With trifluoromethyl and methyl substituents dimers of the metal complex are obtained. The other example from Cundari and co-workers involves a nickel complex, but this system produces only stoichiometric amounts of azo compounds. An example involving a ruthenium metallo-radical system reported by Peters and co-workers proceeds via a free nitrene intermediate and works catalytically only for aryl azides with electron rich substituents like OMe and OEt. The other example by Cundari and co-workers involves a nickel complex, but this system produces only stoichiometric amounts of azo compounds.

Therefore, we decided to extend this reactivity of [CoII(TPP)] for the synthesis of other substituted o-amino azobenzenes. The reason for this is two-fold. Firstly, this catalytic method allows for a mild chemical method to synthesise azobenzenes from azides that is tolerant to primary amines to access azobenzenes via azides. The sole by-product in this key step is dinitrogen. The only other way to synthesise azobenzenes from organic azides is by thermolysis which is a very unselective reaction in general and the explosive nature of the azides is often problematic in such high temperature reactions. Secondly, as ortho substituents are known to have dramatic effects in the photochemical properties of azobenzenes the functional group tolerance of the cobalt-catalysed method here gives access to a series of o-amino-substituted azobenzenes which have thus far received limited attention with regard to their photophysical properties or as switchable molecules in general. Furthermore, the primary amine substituent can provide an easy handle for further functionalisation. This presents new possibilities for the use of azobenzenes in a variety of applications including optical switches. Overall this method allows for synthesis of new azobenzenes starting from commercially available anilines in good to excellent isolated yields.

Azide 10 (2-azido-6-(tert-butyl)aniline) was synthesised according to the method described by Jiao and co-workers. In a first test reaction, 10 (0.3 mmol) and [CoII(TPP)] (5 mol%) were dissolved in freshly
distilled toluene, and the reaction mixture was heated at 90 °C for 18 hours (Scheme ). During this time the reaction proceeded cleanly to give the corresponding azobenzene in near quantitative yield. The product was isolated by running a preparatory thin layer chromatography (prep-TLC) in pure dichloromethane (DCM). The isolated compound is a deep-red coloured solid and it could be crystallised to confirm the formation of the azobenzene product.

Scheme 9. [CoII(TPP)] catalysed reaction of 2-azido-6-(tert-butyl)aniline to give the corresponding trans-azobenzene product. (below) Crystal structure of the thus formed azobenzene.

With these results in hand we set out to optimise this reaction further. Unfortunately, lowering the catalyst loading and/or temperature was detrimental to the reaction. These results are summarised in Table 3. The reaction temperature plays a very important role in this reaction, as does the catalyst loading. Thus, while with 1 mol% catalyst loading in toluene at 90 °C the reaction proceeded, but the yields dropped (Entry 4). Lower temperatures didn’t lead to any azobenzene formation in benzene or in THF (Entry 2 and 5). Also, with no catalyst present the azide was unreactive and could be fully recovered from the reaction (Entry 6).

Table 3. Optimisation of [CoII(TPP)] catalysed synthesis of azobenzene from azide 10 as a test substrate.*

<table>
<thead>
<tr>
<th>ENTRY</th>
<th>SOLVENT</th>
<th>TEMPERATURE (°C)</th>
<th>CATALYST LOADING</th>
<th>YIELD</th>
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<tr>
<td>1</td>
<td>Toluene</td>
<td>90</td>
<td>5 mol%</td>
<td>98%</td>
</tr>
<tr>
<td>2</td>
<td>Benzene</td>
<td>60</td>
<td>5 mol%</td>
<td>----</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>60</td>
<td>5 mol%</td>
<td>----</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>90</td>
<td>1 mol%</td>
<td>60%</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>60</td>
<td>5 mol%</td>
<td>----</td>
</tr>
<tr>
<td>6</td>
<td>Toluene</td>
<td>90</td>
<td>No catalyst</td>
<td>----</td>
</tr>
</tbody>
</table>

* All reactions were carried out with 0.3 mmol of azide, [CoII(TPP)] in 4mL of Toluene. The reaction mixtures were bubbled with dinitrogen for 15 minutes prior to thermostating at mentioned temperature for 18h.

Thus with the optimised reaction conditions we proceeded towards synthesising various other substituted o-azidoanilines. These results are summarised in Table 4. The reaction proved to be quite versatile, and a variety of new substituted azobenzenes could be synthesised using the cobalt(II)-metalloradical catalysed azide-coupling methodology. Substrates with electron-donating substituents like in 10, 11, and 12 performed better in this reaction than those with electron-withdrawing groups. For example, the phenyl substitution in 13 gave 60% of the product while bromine substitution in 14 gave a 48% yield. Also with the substrate containing CF3 substituent 15 or fluorine substituent 16 the
reaction did not proceed at all. In these cases the unreacted azide was recovered pointing at the inherent inability of $[\text{Co}^{II}(\text{TPP})]$ to activate these azides in these reaction conditions.

**Table 4. Substrate screening for $[\text{Co}^{II}(\text{TPP})]$ catalysed synthesis of azobenzenes from $\alpha$-amine substituted azides.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
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<td><img src="imageA" alt="Image" /></td>
<td><img src="imageB" alt="Image" /></td>
<td>80%</td>
<td>E</td>
<td><img src="imageE" alt="Image" /></td>
<td><img src="imageF" alt="Image" /></td>
<td>60%</td>
</tr>
<tr>
<td>B</td>
<td><img src="imageB" alt="Image" /></td>
<td><img src="imageC" alt="Image" /></td>
<td>98%</td>
<td>F</td>
<td><img src="imageF" alt="Image" /></td>
<td><img src="imageG" alt="Image" /></td>
<td>48%</td>
</tr>
<tr>
<td>C</td>
<td><img src="imageC" alt="Image" /></td>
<td><img src="imageD" alt="Image" /></td>
<td>98%</td>
<td>I</td>
<td><img src="imageI" alt="Image" /></td>
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<td>...</td>
</tr>
<tr>
<td>D</td>
<td><img src="imageD" alt="Image" /></td>
<td><img src="imageK" alt="Image" /></td>
<td>90%</td>
<td>J</td>
<td><img src="imageJ" alt="Image" /></td>
<td><img src="imageL" alt="Image" /></td>
<td>...</td>
</tr>
</tbody>
</table>

* All reactions were carried out with 0.3 mmol of azide, $[\text{Co}^{II}(\text{TPP})]$ (5 mol%) in 4 mL of Toluene. The reaction mixtures were bubbled with dinitrogen for 15 minutes prior to thermostating at mentioned temperature for 18 h. Isolated yields are reported.

**Electronic properties of the synthesised $\alpha$-amino-substituted-azobenzenes**

UV-vis spectra of these compounds reveal that all synthesised products show a red shift of the $\pi-\pi^*$ and $n-\pi^*$ transitions compared to the parent azobenzene compound. Three such UV-vis spectra with electronically different substituents are shown in Figure 3 (left). The $\pi-\pi^*$ transitions are shifted to wavelengths above 450 nm and $\pi-\pi^*$ transitions between 300-350 nm are almost of equal intensity as the $n-\pi^*$ transitions. For azobenzenes with electron-donating substituents the $\pi-\pi^*$ transition is more red-shifted than of those with electron-withdrawing substituents (Figure 3, left). Time-dependent DFT (TD DFT) calculation also reasonably reproduced these experimentally observed transitions and relative intensities. For example, for the bromo-substituted compound P14 the $\pi-\pi^*$ transition value matched almost exactly ($\lambda = 323$ nm) while the $n-\pi^*$ transition was more red shifted in reality than predicted by TD DFT calculations ($\lambda = 430$ nm (TD DFT) and 463 nm (experimental)).
Figure 3. UV-vis spectra of o-amino azobenzenes $P_{11}$ ($R=i$-Pr), $P_{13}$ ($R=\text{Ph}$) and $P_{14}$ ($R=\text{Br}$) with varying electronic substituents in solvent acetonitrile (left). TD-DFT calculated (blue) and experimental UV-vis spectra (red) of compound $P_{14}$ (right).

H-bonding between the H atom of the NH$_2$ and the N atom of the azo group was also evident from the crystal structure of compound $P_{10}$. The NH···N=N hydrogen bond was found to be 2.219 Å. Such H-bonding interactions are known to hinder the isomerisation pathway between the trans- and the cis-isomers of amino-azobenzenes (Figure 4). Also in 2-hydroxy-azobenzenes, intramolecular H-bonding between the azo-nitrogen atom and the hydroxyl group is reported to lock the molecule in the trans confirmation.\textsuperscript{13} The 2-hydroxyazobenzenes provide a versatile platform for the design of reversible photoacids to generate significant pH pulses and oscillations with monochromatic light. Similar behaviour can therefore be expected for the ortho-amino-azobenzenes reported here, but is beyond the scope of this current study.

Figure 4. The NH···N=N hydrogen bonds in $P_{10}$ as revealed by X-ray diffraction studies.

DFT studies of the mechanism
To investigate the reaction barriers for the assumed facile HAT process from the ortho substituent (OH or NH$_2$) to the nitrone moiety, we investigated this process with DFT for both the OH and the NH$_2$ substituents.

Starting from the cobalt(III)-nitrone radical species the intramolecular HAT reaction of the cobalt(III)-nitrone radical of the azide 5 was found to proceed via a 6-membered transition state, further stabilized by a hydrogen bonding interaction between the transferred hydrogen atom and a pyrrole
nitrogen atom of the porphyrin (Figure 5). The barrier is very low (+1.0 kcal mol$^{-1}$), thus explaining the experimental observations. Overall, the HAT process is exergonic by $-10.8$ kcal mol$^{-1}$.

*Figure 5.* The DFT calculated barrier for HAT from the ortho hydroxyl group to the nitrene moiety. $\Delta G^{\circ}_{298K}$ in kcal mol$^{-1}$, calculated at the BP86, def2-TZVP level with dispersion corrections.

We further evaluated the changes in spin density distribution (see Figure 6 and Table 5) during the HAT process (see also Figure 5). The spin density distribution of the transition state is very similar to that in the initial cobalt(III)-nitrene radical, but after the HAT barrier and transfer of the hydrogen atom from the $–$OH group, most of the spin density moves back to cobalt (Figure 6 and Table 5). Simultaneously, the bond length of the Co-N bond elongates from 1.818 Å in the nitrene radical to 1.923 Å in the imide as depicted in Table 4.

*Figure 6.* Changes in the spin density distribution during the HAT process shown in Figure 5.
Table 5. Changes of the N, O and Co atom spin populations during the HAT shown in Figure 5

<table>
<thead>
<tr>
<th>Atom</th>
<th>2A</th>
<th>2B</th>
<th>2C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co</td>
<td>11.1%</td>
<td>8.5%</td>
<td>60.6%</td>
</tr>
<tr>
<td>N</td>
<td>39.6%</td>
<td>33.5%</td>
<td>16.1%</td>
</tr>
<tr>
<td>O</td>
<td>5.3%</td>
<td>10.0%</td>
<td>9.4%</td>
</tr>
</tbody>
</table>

Table 6. Relevant bond length (Å) changes during the HAT shown in Figure 5

<table>
<thead>
<tr>
<th>Structure</th>
<th>Co-N</th>
<th>N-C</th>
<th>C-C</th>
<th>C-O</th>
<th>N-H</th>
</tr>
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<tbody>
<tr>
<td>2A</td>
<td>1.81769</td>
<td>1.32018</td>
<td>1.47138</td>
<td>1.34208</td>
<td>1.86203</td>
</tr>
<tr>
<td>2B</td>
<td>1.81731</td>
<td>1.31667</td>
<td>1.48868</td>
<td>1.30627</td>
<td>1.33591</td>
</tr>
<tr>
<td>2C</td>
<td>1.92289</td>
<td>1.32157</td>
<td>1.50424</td>
<td>1.24441</td>
<td>1.03461</td>
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</table>

The almost barrierless abstraction of a neighbouring hydrogen atom by the otherwise highly reactive cobalt(III)-nitrene radical thus prevents any intermolecular coupling reactions of the nitrene moiety with exogenous substrates. A similar process was also calculated for the NH$_2$ substituted azide, and once again the barrier for intramolecular HAT between the NH$_2$ group and the nitrene moiety was found to be low (see Figure 7). The free energy required to reach the transition state is only +9.1 kcal mol$^{-1}$ implying that this intramolecular process is fast, even at room temperature. The overall transformation is exergonic by −3.1 kcal mol$^{-1}$.

Figure 7. The DFT calculated barrier for HAT from the ortho amino group to the nitrene moiety. $\Delta G^\circ_{298K}$ in kcal mol$^{-1}$, calculated at the BP86, def2-TZVP level with dispersion corrections.

The computed changes in the spin density distributions are once again in line with the HAT process, and similar to those computed for HAT from the OH substituent. During the HAT process the spin population shifts from the nitrene radical in 3A to cobalt in 3C, and after the HAT process the spin
density is mostly concentrated at the cobalt atom. The bond distance analysis of the relevant bonds are shown in Table 8. Here once again, the Co-N bond in the final structure elongates from 1.8521 Å in the TS 3B to 1.9604 Å in the final structure 3C. Interestingly, the adduct remains coordinated to the cobalt complex, as is evident from the bond distances.

![Figure 8](image_url)  
**Figure 8.** Changes in spin density distribution for HAT depicted in Figure 7.

**Table 7.** Changes of the N, O and Co atom spin populations during the HAT shown in Figure 7.

<table>
<thead>
<tr>
<th>Atom</th>
<th>3A</th>
<th>3B</th>
<th>3C</th>
</tr>
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<tbody>
<tr>
<td>Co</td>
<td>8%</td>
<td>11%</td>
<td>63%</td>
</tr>
<tr>
<td>N</td>
<td>36%</td>
<td>24%</td>
<td>10%</td>
</tr>
<tr>
<td>O</td>
<td>10%</td>
<td>20%</td>
<td>9%</td>
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**Table 8.** Relevant bond length (Å) changes during the HAT process shown in Figure 7.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Co-N</th>
<th>N-C</th>
<th>C-C</th>
<th>C-N</th>
<th>N-H</th>
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<tbody>
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While the barrier for the HAT process depicted in Figure 5 is low, it is not barrierless. Hence, to exclude the possibility of intermolecular coupling of the nitrene radical to phenyl acetylene (see Scheme 2b) being in competition with the intramolecular HAT process (Figure 7), we decided to make a direct computational comparison of the two processes. Attack of the porphyrin cobalt(III)-nitrene radical on the alkyne to form the γ-radical species C’ (see also Scheme 2b) was computed at the same DFT level (see Figure 9). The latter process is exergonic (−10.8 kcal mol⁻¹), but has a computed barrier of +13.4 kcal mol⁻¹. This barrier is almost 4 kcal mol⁻¹ higher than the barrier for intramolecular HAT (see Figure 7), and hence this process cannot efficiently compete with the intramolecular HAT reaction. Formation of the OPDI intermediate by HAT is expected under all reaction conditions.
Figure 9. DFT computed reaction barrier for attack of the cobalt(III) nitrene radical on phenyl acetylene leading to formation of a γ-alkyl radical intermediate. $\Delta G^\circ_{298K}$ in kcal mol$^{-1}$ computed at the BP86, def2-TZVP level with dispersion corrections.

The spin density distribution changes were once again calculated for the structures 4A, 4B and 4C. Interestingly, in contrast to the structures shown in Figures 6 and 8, the spin density in structure 4C is strongly delocalized over the carbon atoms of the γ-alkyl radical and the adjacent phenyl ring, with barely any spin density at the cobalt atom (see Figure 10).

Figure 10. Changes in spin density distributions during the HAT depicted in Figure 9.

Summary and conclusions

While trying to evaluate the effectiveness of ortho-substituted phenyl azides (OH/NH$_2$ substitution) in ring-closing reactions catalysed by [Co$^0$(Por)], we discovered that the hydrogen atom of the ortho-substituent is readily abstracted by the nitrene radical intermediate. This leads to formation of reactive intermediates like o-quinone monoimines (OQMI; for OH) and o-phenylenediimines (OPDI; for NH$_2$). These reactive compounds rapidly undergo follow-up reactions, thus preventing any direct (radical-type) coupling reactions of the nitrene radical intermediate with C=C or C≡C bonds of other substrates to give ring-compounds. The o-quinone monoimines (Y = OH) easily dimerize and produce...
phenoxizinone 3 under aerobic conditions. In the presence of 1-butoxyethene the o-quinone monooimine can also be trapped in an IEDDA reaction, producing benzoxazine 6. Formation of orthophenylene-diimine (OPDI) from ortho-NH₂-phenylazide is also associated with H atom abstraction of the Co(III) nitrene radical from the NH₂ substituent in the ortho position. As a result, azo compound 8 is obtained. Attempts to react ortho substituted azides with other reaction partners by altering the reaction conditions were not successful. DFT computations are in agreement with the experiments; HAT from the ortho-YH substituent (Y= O or NH) to the nitrene moiety has a (very) low barrier in both cases. These transformations are summarised in Figure 11.

Figure 11. Transformations observed in this study.

On one hand, the observed facile HAT from the ortho-substituent (OH or NH₂) to the nitrene moiety prevents the initially anticipated radical-type coupling of the cobalt(III) nitrene radical intermediate to C=C and C≡C bonds of other substrates. On the other hand, it does provide a mild route to prepare highly reactive o-iminoquinonoids and o-phenylenediimines which can be employed in several follow up reactions. Having said that, the possibility of further reactivity of these intermediates occurring in the coordination sphere of the catalyst cannot yet be ruled out and might even be plausible based on the bond distance data that we obtained from the DFT optimized structures of these compounds after HAT. The other way in which this transformation is unique is that this is the only chemical pathway towards substituted o-aminooazobenzenes directly from azides. The cobalt(III) porphyrins catalysed pathway is, therefore, a functional group tolerant system to synthesise azobenzenes from azides which in turn are prepared in one step from commercially available amines. The synthesised azobenzenes are bathochromically shifted compared to the unsubstituted azobenzenes. Based on the crystal structure, the ortho-amine substituent is seen to participate in H-bonding interactions with the azo N atom. This can be expected to have consequences on the trans-cis isomerisation of these compounds but is currently beyond the scope of this study. At the same time, the amine functionality in these compounds can also act as a point of functionalisation for future applications.

Supporting information experimental and computational details

General information

All manipulations were performed under N₂ atmosphere by standard Schlenk techniques or in a glovebox. Methanol and acetonitrile were distilled under nitrogen from CaH₂. THF, toluene and pentane were distilled under nitrogen from Na wire.

All NMR spectra for these experiments were recorded at 293 K.
H NMR: A Bruker Avance 400 (400 MHz) or Mercury 300 (300 MHz) machine was used. These spectra were referenced internally to residual solvent resonance of CDCl$_3$ ($\delta = 7.26$ ppm) or DMSO-d$_6$ ($\delta = 2.50$).

$^{13}$C($^1$H) NMR: A Bruker Avance 400 (101 MHz) or Bruker Avance 500 (126 MHz) machine was used. These spectra were referenced internally to residual solvent resonance of CDCl$_3$ ($\delta = 77.2$ ppm) or DMSO-d$_6$ ($\delta = 39.5$).

**Synthetic details**

Details of the newly synthesized compounds and catalytic reactions are listed

- **Synthesis of compound 5**

2-amino-5-nitrophenol (72.4 mmol) was added to aqueous HCl (6 M, 100 mL) at 0 $^\circ$C in a three neck round bottom flask. To the latter a solution of NaNO$_2$ (96.5 mmol) in 20 mL water was added dropwise. After stirring this mixture for 5 minutes NaN$_3$ (96.5 mmol) that was predissolved in 60 mL of water was added dropwise and stirred for 45 minutes. The precipitate was extracted with chloroform and then washed with water. The organic layer was dried over MgSO$_4$. On evaporation of the solvent a dark pink solid was obtained. This was purified further by flash chromatography over silica (EtOAc:Hex = 1:1) to give a dark pink solid in 80% yield.

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ 7.87 (dd, $J = 8.7$, 2.5 Hz, 1H), 7.80 (d, $J = 2.5$ Hz, 1H), 7.19 (d, $J = 8.7$ Hz, 1H), 5.65 (s, 1H).

$^{13}$C NMR (75 MHz, Chloroform-d) $\delta$ 147.46, 145.53, 133.08, 118.25, 116.92, 111.66

- **Catalytic reaction of compound 1 to give product 3**

In a flame dried Schlenk flask loaded with a stirrer 1 mmol of 1 was added followed by 0.05 mmol of [Co$^{II}$(TPP)$_{20}$]. The Schlenk flask was then evacuated and refilled with nitrogen (three times). Subsequently 4 mL of dry chlorobenzene was added, and the reaction was thermostatted at 50 $^\circ$C for 18 h. After evaporating the solvent the mixture was directly loaded on a silica gel column. The product was eluted with Hex:EtOAc (1:1) to give product 3 in 80% isolated yield.

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ 7.79 $-$ 7.72 (m, 1H), 7.45 (ddd, $J = 8.3$, 6.9, 1.6 Hz, 1H), 7.42 $-$ 7.32 (m, 2H), 6.48 (s, 1H), 6.42 (s, 1H), 5.11 (s, 2H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 180.00, 149.72, 142.25, 133.23, 129.59, 128.29, 125.05, 115.56, 114.24, 103.61.

For the other reactions of compound 1 with other substrates, the same stoichiometry was used (also see the footnote in Table 1).

- **Catalytic reaction of compound 5 to give product 6**

In a flame dried Schlenk flask loaded with a stirrer 1 mmol of 5 was added followed by 0.05 mmol of [Co$^{II}$(TPP)$_{20}$]. The Schlenk flask was then evacuated and refilled with nitrogen (three times). Subsequently 4 mL of chlorobenzene was added, and the reaction was thermostatted at 50 $^\circ$C for 18 h.
After evaporating the solvent, the mixture was directly loaded on a silica gel column. The product was eluted with Hex:EtOAc (1:1) to give product 6 in 80% yield.

$^1$H NMR (300 MHz, Chloroform-$d$) $\delta$ 7.82 – 7.65 (m, 2H), 6.53 (d, $J = 8.7$ Hz, 1H), 5.27 (t, $J = 2.4$ Hz, 1H), 4.57 (s, 1H), 3.85 (dt, $J = 9.7, 6.7$ Hz, 1H), 3.62 (dt, $J = 9.7, 6.6$ Hz, 1H), 3.58 – 3.46 (m, 1H), 3.51 – 3.38 (m, 1H), 1.54 (dq, $J = 8.6, 6.8$ Hz, 2H), 1.29 (dt, $J = 14.9, 7.4$ Hz, 3H), 0.86 (t, $J = 7.4$ Hz, 4H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 140.14, 139.16, 138.81, 119.53, 113.78, 112.78, 93.85, 68.60, 44.42, 31.54, 19.25, 13.86.

For the other reactions of compound 5 with other substrates, the same stoichiometry was used (also see footnote in Table 2).

- **Catalytic reaction of 7 to give compound 8**

In a flame dried Schlenk flask loaded with a stirrer compound 7 (67 mg, 0.5 mmol) and [Co$^{II}$ (TPP)] (17 mg, 0.025 mmol) was added and the flask was evacuated and backfilled with dinitrogen (three times). Subsequently 4 mL of PhCl was added, and the reaction mixture was thermostatted at 50 °C for 18 h. The reaction mixture was then subjected to preparative TLC (DCM as eluent) and a bright orange band was obtained which was analyzed and found to be compound 8.

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.68 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.23 – 7.06 (m, 1H), 6.93 – 6.63 (m, 2H), 5.48 (s, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 143.11, 137.73, 131.37, 124.29, 117.66, 117.04.

**Synthesis of the azides**

**Caution:** All azides were synthesized in 1 mmol scale reactions in separate Schlenk tubes. After the reactions were complete, they were combined together before work-up and column separation.

Compound 10 was synthesized according to the reported procedure of Jiao$^{12}$ and the spectral data matched with those reported.

**Compound 11** (2-azido-6-iso-propylaniline)

1 mmol of isopropylaniline was added to a flame dried Schlenk tube that contained 0.1 mmol CuBr. Then trimethyl silyl azide (2 mmol) was added followed by addition of 4 mL of freshly distilled acetonitrile. Finally 2 mmol of tetrabutyl hydroperoxide (TBHP) (5.0-6.0 M in decane) was added and the reaction was thermostatted at 30 °C for 6h. After this 15 mL of ethyl acetate was added the reaction mixture concentrated on a rotary evaporator. This was then directly loaded on to a silica column and eluted with pet ether: ethylacetate (60:1).

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.04 – 6.87 (m, 2H), 6.81 (t, $J = 7.8$ Hz, 1H), 3.84 (s, 3H), 2.98 – 2.66 (m, 1H), 1.25 (d, $J = 6.8$ Hz, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 135.71, 134.34, 125.79, 122.40, 121.29, 116.19, 28.42, 22.69.

**Compound 12** (2-azido-6-methylaniline)

1 mmol of o-toluidine was added to a flame dried Schlenk that contained 0.10 mmol of CuBr. Then trimethyl silyl azide (2 mmol) was added followed by addition of 4mL of freshly distilled acetonitrile. Finally 2 mmol of TBHP (5.0-6.0 M in decane) was added and the reaction thermostatted at 30 °C for 6h. After this 15mL of ethyl acetate was added the reaction mixture concentrated on a rotary evaporator. This was then directly loaded on to a silica column and eluted with pet ether:ethylacetate (60:1).
$^1$H NMR (300 MHz, Chloroform-d) δ 6.94 (d, J = 7.9, 1H), 6.87 (d, J = 7.4 Hz, 1H), 6.73 (t, J = 7.7 Hz, 1H), 3.77 (s, 2H), 2.17 (s, 3H).

$^1$C NMR (75 MHz, CDCl$_3$) δ 136.31, 126.74, 124.83, 123.46, 118.36, 115.96, 17.35.

**Compound 13** (3-azido-[1,1'-biphenyl]-2-amine)

2-Phenylaniline (1 mmol) was added to a flame dried Schlenk tube that contained 0.10 mmol of CuBr. Then TMSN$_3$ (2 mmol) was added followed by addition of 4 mL of freshly distilled acetonitrile. Finally 2 mmol of TBHP (5.0-6.0 M in decane) was added and the reaction was heated at 30°C for 6 hours. Then 15 mL of ethyl acetate was added, reaction mixture evaporated. It was then directly loaded on silica (Petroleum ether: ethylacetate (60:10)) to give the desired product in 60% isolated yield. Analytical data matched literature.$^{1}$

$^1$H NMR (400 MHz, Chloroform-d) δ 7.48 – 7.34 (m, 5H), 7.05 (dd, J = 7.8, 1.5 Hz, 1H), 6.94 (dd, J = 7.6, 1.5 Hz, 1H), 6.85 (t, J = 7.7 Hz, 1H), 3.94 (s, 2H).

**Compound 14** (2-azido-6-bromoaniline)

2-Bromoaniline (1 mmol) was added to a flame dried Schlenk tube that contained 0.10 mmol of CuBr. Then TMSN$_3$ (2 mmol) was added followed by addition of 4 mL of freshly distilled acetonitrile. Finally 2 mmol of TBHP (5.0-6.0 M in decane) was added and the reaction was heated at 30°C for 6 hours. Then 15 mL of ethyl acetate was added, reaction mixture evaporated. It was then directly loaded on silica (Hexane: ethylacetate (90:10)) to give the desired product in 23% isolated yield.

$^1$H NMR (400 MHz, Chloroform-d) δ 7.21 (dd, J = 8.0, 1.3 Hz, 1H), 6.98 (dd, J = 7.9, 1.3 Hz, 1H), 6.65 (t, J = 8.0 Hz, 1H), 4.25 (s, 2H).

$^{13}$C NMR (101 MHz, Chloroform-d) δ 136.51, 128.72, 125.97, 118.89, 117.31, 109.55.

HRMS calcd. 211.96976 for C$_6$H$_5$BrN$_4$ found 211.96964.

**Catalytic reactions to give azobenzenes**

For the catalytic reactions the following general procedure was followed.

All reactions were carried out with 0.3 mmol of azide. $[\text{Co}^{II}(\text{TPP})]$ (5 mol%) was transferred to a flame dried Schlenk tube after which the Schlenk was evacuated and back-filled with dinitrogen three times. In a separate Schlenk tube containing 0.3 mmol of the azide, 4 mL of toluene was added to dissolve the azide. Using a syringe this solution was transferred to the Schlenk tube containing the $[\text{Co}^{II}(\text{TPP})]$. The reaction mixture was then bubbled with dinitrogen for 15 minutes after which it was heated at 90°C for 18 h.

The reaction mixture was concentrated and was directly loaded to a glass baked silica plate and ran using suitable solvent (or solvent mixtures). The desired compound always gave a characteristic bright orange/red band on the silica plate.

**9-(E)-2,2'-(diazene-1,2-diyl)dianiline**

Using the general procedure (Prep-TLC using pure DCM), 80% isolated yield. Analytical data matched literature.$^{14}$

$^1$H NMR (400 MHz, Chloroform-d) δ 7.68 (dd, J = 8.0, 1.6 Hz, 1H), 7.23 – 7.06 (m, 1H), 6.93 – 6.63 (m, 2H), 5.48 (s, 2H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 143.11, 137.73, 131.37, 124.29, 117.66, 117.04.
**P10- (E)-6,6'-(diazen-1,2-diyl)bis(2-(tert-butyl)aniline)**

Using the general procedure (Prep-TLC using DCM), 98 % isolated yield.

$^1$H NMR (300 MHz, Chloroform-$d$) $\delta$ 7.50 (dd, $J = 8.1$, 1.4 Hz, 1H), 7.40 – 7.24 (d, 7.8 1H), 6.70 (t, $J = 7.9$ Hz, 1H), 1.49 (s, 9H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 145.00, 140.29, 135.73, 129.74, 117.76, 115.97, 35.10, 30.25.

HRMS calcd. 324.23140 for $C_{20}H_{28}N_4$ found: 324.2310.

**P11- (E)-6,6'-(diazen-1,2-diyl)bis(2-isopropylaniline)**

Using the general procedure (Prep-TLC using DCM), 98% isolated yield.

$^1$H NMR (300 MHz, Chloroform-$d$) $\delta$ 7.52 (dd, $J = 8.1$, 1.5 Hz, 1H), 7.19 (dd, $J = 7.6$, 1.4 Hz, 1H), 6.77 (t, $J = 7.8$ Hz, 1H), 5.24 (s, 2H), 3.10 – 2.83 (m, 1H), 1.32 (d, $J = 6.8$ Hz, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 142.53, 138.65, 134.21, 117.61, 117.30, 27.67, 22.34.

HRMS calcd. 296.20010 for $C_{18}H_{24}N_4$, found 296.2005.

**P13- (E)-3,3''-(diazen-1,2-diyl)bis([(1,1''-biphenyl)-2-amine])**

Using the general procedure (Prep-TLC using DCM: hexane= 1:1), 60% isolated yield.

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.70 (dd, $J = 8.1$, 1.6 Hz, 1H), 7.60 – 7.48 (m, 5H), 7.19 (dd, $J = 7.2$, 1.6 Hz, 1H), 6.86 (t, $J = 7.7$ Hz, 1H), 5.55 (s, 2H).

$^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 143.00, 141.4, 135.73, 130.64, 115.72, 114.87

HRMS calcd. 364.16880 for $C_{24}H_{20}N_4$ found 364.1687.

**P14- (E)-6,6'-(diazen-1,2-diyl)bis(2-bromoaniline)**

Using the general procedure (Prep-TLC using DCM: hexane= 1:1), 48% isolated yield.

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.64 (dd, $J = 8.1$, 1.5 Hz, 1H), 7.48 (dd, $J = 7.8$, 1.5 Hz, 1H), 6.70 (t, $J = 7.9$ Hz, 1H), 6.09 (s, 2H).

$^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 141.75, 138.80, 138.09, 132.64, 129.45, 129.35, 129.17, 129.11, 127.72, 121.42, 117.32.

HRMS calcd. 367.92722 for $C_{12}H_{10}Br_2N_4$ found 367.9276.

**Computational details**

Geometry optimizations were carried out with the Turbomole program package\textsuperscript{15} coupled to the PQS Baker optimizer\textsuperscript{16} via the BOpt package\textsuperscript{17} at the DFT level using the b3-lyp functional\textsuperscript{18} and def(2)-TZVP basis set\textsuperscript{19} for the geometry optimizations of all stationary points. All minima (no imaginary frequencies) and transition states (one imaginary frequency) were characterized by numerically calculating the Hessian matrix. ZPE and gas-phase thermal corrections (entropy and enthalpy, 298 K, 1 bar) from these analyses were calculated.
Table 7. SCF energies, enthalpies and free energies of the compounds involved in the HAT step described in Figure 3 in the main text in Hartree (BP86, def2-TZVP, disp3).

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Table 8. SCF energies, enthalpies and free energies of the compounds involved in the HAT step described in Figure 5 in the main text in Hartree (BP86, def2-TZVP, disp3).

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Table 9. SCF energies, enthalpies and free energies of the compounds involved in the HAT step described in Figure 7 in the main text in Hartree (BP86, def2-TZVP, disp3).

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Acknowledgements

We thank Dr. W.I Dzik (HIMS, UvA) for assistance with X-ray Diffraction studies and Ed Zuidinga (HIMS, UvA) for mass measurements.
References


(a) PQS version 2.4, 2001, Parallel Quantum Solutions, Fayetteville, Arkansas, USA (the Baker optimizer is available separately from PQS upon request); (b) Baker, J. J. Comput. Chem. 1986, 7, 385.

