Hypovalent substrates in transition metal catalysis: C-H bond functionalisation, ring-closing reactions & polymer synthesis

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Citation for published version (APA):

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Chapter 3

Mechanism of Cobalt(II) Porphyrin-Catalysed C–H Amination with Organic Azides: Radical Nature and H–Atom Abstraction Ability of the Key Cobalt(III)-Nitrene Intermediates

Abstract:

The mechanism of the Co$^{II}$ porphyrin-catalysed benzylic C–H bond amination of ethylbenzene, toluene and 1,2,3,4-tetrahydronaphthalene (tetralin) with a series of different organic azides ($N_3C(O)OMe$, $N_3SO_2Ph$, $N_3C(O)Ph$ and $N_3P(O)(OMe)_2$) as nitrene sources was studied by means of DFT calculations and EPR spectroscopy. The DFT studies reveal a stepwise radical formation of the ‘nitrene radical’ intermediates (por)Co$^{III}$–N•R (R = –C(O)OMe, –SO_2Ph, –C(O)Ph, –P(O)(OMe)_2). The formation of ‘nitrene radical complexes’ is predicted by DFT to be exothermic, and hence these species should be detectable in absence of other reacting substrates. In good agreement, solution EPR studies show signals with $g$-values characteristic for ligand radical complexes and provide, for the first time, the experimental characterisation of these ‘nitrene radical’ intermediates. These complexes are best described as nitrene radical anion ligand complexes [(por)Co$^{III}${N•R−}], with the unpaired spin density almost entirely located at the nitrogen atom of the nitrene moiety. The Co$^{III}$-nitrene radical complexes were demonstrated to be key intermediates in C–H amination reactions, and readily abstract a hydrogen atom from benzylic positions of the organic substrates to form close-contact pairs of the formed organic radicals R’• and the Co$^{III}$-amido complexes (por)Co$^{III}$–NHR ({$R'$• … (por)Co$^{III}$–NHR}). These close-contact pairs readily collapse, via a virtually barrierless pathway, to produce the Co$^{II}$-amine complexes (por)Co$^{II}$–NHR’. Additionally, studies of electronically different porphyrin ligands demonstrated that the groups at the meso position influence the electronic properties of the metal centre, which can be used to control the formation and reactivity of the nitrene intermediate. This study further includes mechanistic studies to understand the catalyst deactivation pathways, and explains the formation of side-products observed experimentally.
3.1 Introduction.

Direct functionalisation of C–H bonds is of outstanding importance due to its far-reaching practical applications as atom-, time- and cost-efficient alternatives to traditional hydrocarbon functionalisation approaches, which involve stepwise stoichiometric modifications. This has led to the development of prominent methodologies for hydrocarbon transformations such as palladium-catalysed cross-coupling of C–H bonds, C–H insertion of carbenoid and nitrenoid species as well as a number of efficient protocols for selective modification of non-activated alkanes. Numerous applications of amines have stimulated an intensive exploration of direct C–H amination methods. These reactions typically employ iminoiodanes (i.e. PhI=NTs), haloamines-T, carbamates or azides as the nitrene sources. Among several catalysts that have been tested, the most successful ones are still based on expensive Rh and Ru complexes, but less costly Mn, Cu and Fe-based catalysts have also been reported. Organic azides are among the most promising and environmentally friendly nitrene sources for these reactions, for which a large substrate scope is available. However, while most of the known catalysts are quite effective with iminoiodanes, currently only a limited number of catalysts are capable of employing organic azides for C–H amination, which are much more desirable nitrene sources.

CoII porphyrin catalysts (Figure 1) have attracted considerable attention as a result of their unique reactivity in carbene transfer reactions. They are also efficient catalysts for olefin aziridination employing organic azides as the nitrene source. In line with this chapter, CoII catalysts have also been reported as efficient catalysts for amination of benzylic C–H bonds with organic azides (Scheme 1). This reaction proved to be quite sensitive to the structure and nature of the employed organic azides, C–H substrates and the catalyst. Whereas 2,2,2-trichloroethoxycarbonyl azide (CCl3CH2OC(O)N3; TrocN3) was found to be an excellent nitrene source (or amination reagent) to produce target amines in high yields, tosyl azide (TsN3) demonstrated only modest reactivity; and benzoyl azide (BzN3) and dimethyl azidophosphate ((MeO)2P(O)N3) showed no reactivity. In addition, the activity of the CoII–
based catalysts was rather unexpected. For example, the catalysts Co(TPFPP) (1c) and Co(TDCIPP) (1d), which had previously proven to be efficient in C–H amination reactions employing bromamine-T as the nitrene source, were inactive with organic azides. On the other hand, Co(TPP) (1b), which showed only rather poor catalytic reactivity with bromamine-T, turned out to be a quite effective catalyst for amination employing organic azides.

Cenini and co-workers reported a kinetic study of Co(por)-catalysed C–H amination reaction of benzylic derivatives with aryl azides. The reaction was found to exhibit overall third-order reaction kinetics (first-order in the catalyst, first-order in the azide, and first-order in the benzylic substrate).

A detailed mechanistic investigation is indispensable to gain a better understanding of the CoII-catalysed C–H amination reactions, and should assist in addressing further selectivity issues. Insight into the key active species of these reactions is of crucial importance to understand the influence of the different steric and electronic factors on the rate and outcome of these processes, and should aid future investigations to expand the substrate scope and design of new efficient catalysts. To the best of our knowledge, the quite specific mechanism of amination of alkenyl and aryl C–H bonds is the only example that has been studied computationally, that undergoes a different intramolecular pathway than that proposed for benzylic C–H amination. Additionally, amination of allylic C–H bonds with the azide PhN₃ (which gives rather poor yields and poor selectivity in nitrene transfer/insertion reactions) was recently studied in the context of Co(por)-catalysed aziridination reactions. Thus, we sought for detailed theoretical and experimental mechanistic information about Co(por) catalysed C–H amination with organic azides in order to identify the factors that play a role during these catalytic reactions. Herein, we present an EPR spectroscopic and detailed computational study on the mechanism of the Co(por)-catalysed amination of benzylic C–H bonds by a series of different organic azides. The computational investigations include an examination on the effect of the electronic properties that the porphyrin ligand of the Co(por) catalyst have on the rate-limiting step (via transition states TS1 and TS2) of the catalytic reactions. Remarkably, the mechanism we propose herein appears to be rather general, since an analogous pathway had also been suggested, although without computational support, for non-heme iron-catalysed aliphatic C–H hydroxylation and amination reactions.
3.2 Results and Discussion

Below, we will first discuss the detailed catalytic C–H amination mechanism based on our DFT computational studies and validate the obtained results with the experimental information available to date. On the basis of these DFT results, we will then focus on our experimental detection of the proposed key nitrene radical intermediates using EPR spectroscopy. The obtained EPR data are reported at the final account of this chapter.

Computational studies

Calculations were performed by employing the non-hybrid BP86 level of theory, which is shown to give reliable and satisfactory results for related systems.\textsuperscript{14c,18} As a simplified model of the Troc-group, we used the methyl formate substituent (MeOC(O)–). The benzylic C–H substrates were modeled with ethylbenzene, which can also be used as a representative model for tetralin (1,2,3,4–tetrahydronaphthalene), since the calculated barriers of the rate-limiting steps appeared to be very similar for both substrates (see below). Experimentally, yields for C–H amination of ethylbenzene and tetralin were reported to be comparable.\textsuperscript{9d} We initially used the non-substituted Co(por) (1a, Figure ) complex as a smaller model for Co(TPP) (1b), which has been reported to be an efficient catalyst for the amination of benzylic C–H bonds.\textsuperscript{9d} We further expanded our study to include electronically different porphyrin ligands (variation of the substituent at the meso-phenyl groups) for a selection of the key steps of the mechanism (\textit{vide infra}).

We will first discuss the amination of ethylbenzene with methyl azidoformate, a model of the TrocN\textsubscript{3}, which was experimentally shown to be an effective nitrene source for C–H amination. We will then present the computational pathways with phenylsulfonyl azide, benzoyl azide and dimethyl azidophosphate, which were found experimentally to be less effective nitrene sources. Finally, we will present the influence of different porphyrin ligands on the catalytic activity of Co(por)-based systems in the C–H amination reaction.

\textit{Nitrene insertion into C–H benzylic bond of ethylbenzene.} The activation step of methyl azidoformate (2a) by Co complex 1a involves coordination of the \textalpha{}–nitrogen of 2a to the Co\textsuperscript{II} centre (Scheme 2). This process is exothermic by about –1.8 kcal mol\textsuperscript{-1} (Figure 2). The formed azide complex 3a undergoes dinitrogen elimination, leading to formation of the ‘nitrene’ complex 4a. The activation enthalpy $\Delta H^{\ddagger}(TS1a)$ for this step is +12.3 kcal mol\textsuperscript{-1}
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(Figure 2), which agrees well with the observed rates under typical reaction conditions (40–80 °C).

The electronic structure of 4a is noteworthy. It is found that the ‘nitrene’ complex is actually a species with a ‘nitrene radical ligand’, very similar to the ‘nitrene radical species’ that were recently reported to be the key intermediates in olefin aziridination reactions.16,18a This feature underlines the general importance of redox non-innocent ligands in catalysis.20 As illustrated in Figure 3, the unpaired electron resides mainly on the ‘nitrene’ nitrogen, i.e. the nitrogen of the NC(O)OMe moiety, and is slightly delocalised over the neighbouring cobalt and carbonyl oxygen atoms. Accordingly, the ‘nitrene ligand’ is best described as a nitrogen-centred ligand radical (RN•)− (‘nitrene radical anion ligand’).

This gives rise to clear radical-type reactivity at its nitrogen atom, resulting in effective hydrogen-atom abstraction from the benzylic position of ethylbenzene (TS2a, Figure 4). This leads to a close-contact (interaction) catalyst–radical pair (5a) of the thus formed benzylic radical PhCH•CH3 (R’•) and the CoIII-amido complex (por)CoIII–N\textsubscript{H}C(O)OMe. Intermediate 5a provides a decent, but simplified model for the solvent-caged catalyst–radical pair {R’• …
Mechanism of CoII Porphyrin-Catalysed C–H Amination with Organic Azides

(por)CoIII–NHC(O)OMe}, which is expected to play a crucial role in solution (Figure 4). Although the computed activation enthalpy for TS2a (ΔH‡ = +6.3 kcal mol⁻¹) is lower than the activation energy for formation of the nitrene radical 4a (TS1a = +12.3 kcal mol⁻¹), both reactions have quite comparable ΔG‡ values (ΔG‡ (TS1a) = +20.6, ΔG‡ (TS2a) = +17.0 kcal mol⁻¹). The energy profile therefore corresponds well with the observed first order kinetics in the catalyst, azide and benzylic/allylic substrate reported by Cenini and co-workers for related systems in C–H amination of cyclohexene, α-methylstyrene and toluene with p-NO₂-C₆H₄N₃ as the nitrene source, wherein formation of the nitrene and its subsequent C–H bond activation reactivity should both be rate limiting processes. The experimental kinetic profile for the exact reactions based on the TrocN₃ nitrene source has not yet been determined.

Replacing ethylbenzene with tetralin as the benzylic C–H substrate in the calculations results in similar TS2 barrier (ΔH‡ (TS2) = +6.2 kcal mol⁻¹; ΔG‡ (TS2) = +16.7 kcal mol⁻¹). As expected, the TS2 barrier for activation of toluene (ΔH‡ (TS2) = +7.4 kcal mol⁻¹; and ΔG‡ (TS2) = +18.2 kcal mol⁻¹) is higher than for ethylbenzene and tetralin. This correlates with the experimental observation that amination of tetralin is possible using toluene as the solvent. The energies of the intermediates and the TS3 barrier for the following steps with toluene are very similar to those of ethylbenzene, and do not constitute any additional rate limiting barriers.

The catalyst-radical pair {R’• … (por)CoIII–NHC(O)OMe} 5a undergoes a very facile radical substitution (rebound-type reaction), in which the ‘free’ benzylic radical back-attacks the nitrogen atom of the (por)CoIII–NHC(O)OMe species to form the target amide product 6a (Figure 4). This step is essentially barrierless at the enthalpy surface (a small barrier transition state (TS3a) was located at the SCF surface; ΔE‡ = +0.1 kcal mol⁻¹). The carbamate 6a is found to be very weakly coordinated to the Co centre and its dissociation occurred already

Figure 4. Reaction profile (ΔH in kcal mol⁻¹) for the nitrene insertion reaction into the benzylic C–H bond of ethylbenzene.
during the geometry optimisation steps.

**Formation of byproducts.** Experimentally, TrocNH$_2$ is formed as a main side product under the applied reaction conditions.$^9$d Initially, we assumed that this side product would be formed as a result of homolysis of the Co–N bond in the intermediate 5a.$^9$d However, this seems rather unlikely on the basis of the DFT calculations. Although the Co–N bond dissociation enthalpy (BDE = +39.4 kcal mol$^{-1}$) is perhaps not particularly high as an absolute value,$^{23}$ it is much higher than the TS$_1$ and TS$_2$ barriers. Therefore, the barriers for side reactions proceeding via direct homolytic bond splitting of the Co–N bond of 5a should be at least equal to or perhaps even higher than this BDE value, and thus, these side reactions should compete poorly. However, hydrogen-atom transfer from a C–H bond at the beta-position of the ‘free’ benzylic radical to the amido nitrogen atom in the {R’$^\cdot$ ... (por)Co$^{III}$-NHC(O)OMe} catalyst-radical pair 5a (a reaction bearing some similarity with radical disproportionation by free radicals bearing β-hydrogens) is well supported by the DFT calculations (Figure 5). For the radical-rebound step in Figure 4, this reaction is essentially barrierless at the enthalpy surface (a small barrier transition state TS$_{4a}$ was located at the SCF surface; $\Delta E = +1.8$ kcal mol$^{-1}$). The productive rebound-steps in Figure 4 and the steps leading to byproducts in Figure 5 therefore compete, which is in good agreement with the experiments. Even though the processes leading to the target insertion product (TS$_{3a}$) and to the byproduct (TS$_{4a}$) have similar activation enthalpies, the former is exergonically favoured ($\Delta G^\ddagger$ (TS$_{3a}$) of +1.2 kcal mol$^{-1}$ vs. $\Delta G^\ddagger$ (TS$_{4a}$) of +3.8 kcal mol$^{-1}$). This explains the fact that the insertion product is experimentally the major compound in most cases.$^9$d

The formation of TrocNH$_2$ via β-hydrogen abstraction from the benzylic organic radical should lead to the formation of an alkene byproduct. Indeed, experimental reinvestigation of the catalytic C–H amination of ethylbenzene with GC–MS revealed the formation of styrene as a byproduct.

It is noted that a large amount of TrocNH$_2$ was also observed in the amination reaction of ethyl phenylacetate.
Mechanism of CoII Porphyrin-Catalysed C–H Amination with Organic Azides (PhCH₂C(O)OEt), which has no C–H bonds at the β-position of its reactive benzylic moiety.⁹d This indicates the existence of another pathway for formation of TrocNH₂ byproduct, because the pathway depicted in Figure 5 requires the presence of β-hydrogen atoms. In this case, we assumed that the formation of the byproduct is due to a subsequent hydrogen-atom abstraction from the amine product.

We modelled this possibility using 6a as the substrate. HAA from the benzylic position of 6a by the nitrene radical complex 4a, followed by hydrogen atom transfer from the intermediate radical to the Co–NHCOOMe intermediate 5’a would lead to the imine 8a (Figure 6). The latter most likely decomposes to MeOC(O)NH₂ and a corresponding carbonyl compound during purification by column chromatography on silica under the applied experimental conditions. The abstraction of the hydrogen atom from the benzylic position of the amine 6a proceeds with a small TS₅ₕ barrier of +4.9 kcal mol⁻¹ leading to the intermediate 5’a, which is a close-contact catalyst-radical pair {R’•…(por)CoIII–NHC(O)OMe} wherein R’• is the corresponding benzyl radical MeOC(O)NHCH•(Ph)Me (Figure 6). This step is also thermodynamically favourable with ΔH° = −16.2 kcal mol⁻¹. Since the alternative abstraction of a hydrogen atom from the NH group has a rather high barrier (+11.9 kcal mol⁻¹), it is considered to be much less probable²⁴ (Figure 6; for the whole reaction profile of the NH–hydrogen abstraction). Moreover, the intermediate 9a is found to be rather unstable, and should undergo a rapid reverse interconversion into the starting species 4a and 6a.

In the formed intermediate 5’a, hydrogen atom transfer from the amine NH

![Figure 6](image-url)
moiety at the β–hydrogen position of the benzylic radical to the cobalt-amido nitrogen atom then leads to the formation of the MeOC(O)NH₂ byproduct and the imine 8a. This process is again essentially barrierless (a small barrier transition state TS6a was located at the SCF surface; ΔE = +0.7 kcal mol⁻¹).

As shown in Figure 6, the formation of the TrocNH₂ byproduct by hydrogen abstraction from the final amide 6a has a higher kinetic barrier and is energetically less favorable than the β-hydrogen atom transfer pathway in Figure 5. Therefore, the pathway in Figure 5 should prevail for substrates containing hydrogen atoms at the β-position with respect to the benzylic radical. Nonetheless, the alternative mechanism in Figure 6 is a viable pathway for TrocNH₂ byproduct formation in reactions featuring substrates lacking such β-hydrogen atoms.

**Influence of different organic azides.** The successful experimental use of TrocN₃ as a nitrene source raises the question why the other tested azides showed either a rather poor reactivity (e.g. TsN₃ gave only 32% yield of the target amide) or no reactivity at all (e.g. (EtO)₂P(O)N₃ and PhCON₃).⁹d To shed some light on this issue, we carried out quantum chemical calculations of the two rate-limiting steps (TS1 and TS2) for phenylsulfonyl azide 2b, benzyol azide 2c and dimethyl azidophosphate 2d (Figure 7).

While coordination of the azide to Co(por) proceeds as a slightly exothermic reaction for phenylsulfonyl azide 2b (ΔH° = −2.2 kcal mol⁻¹) and dimethyl azido-phosphate 2d (ΔH° = −0.8 kcal mol⁻¹), it is endothermic for benzyol azide 2c (ΔH° = +4.3 kcal mol⁻¹) (Figure 7).

The elimination of dinitrogen to form the nitrene radical species 4b–d (Figure 7) is in all cases associated with a higher barrier than the analogous reaction with methyl azidoformate 2a (ΔH°F (TS1a) = +12.3 kcal mol⁻¹; see Figure 2). The spin density at the nitrogen atom in

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**Figure 7.** Reaction profile (ΔH in kcal mol⁻¹) for C–H bond amination employing phenylsulfonyl-, benzyol- and dimethoxy-phosphoryl azide as the nitrene sources.
species 4a–d depends slightly on the nature of the R group, resulting in somewhat more localised radical density at the ‘nitrene’ nitrogen nucleus for species 2a and 2d.\textsuperscript{19}

Whereas the energy barrier (\(\Delta H^\ddagger\)) of the first step (TS1) is only slightly higher in case of phenylsulfonyl azide (\(\Delta H^\ddagger (TS1b) = +12.5\) kcal mol\(^{-1}\)), TS1 is substantially higher for benzoyl azide (\(\Delta H^\ddagger (TS1c) = +16.4\) kcal mol\(^{-1}\)) and azidophosphate (\(\Delta H^\ddagger (TS1d) = +19.3\) kcal mol\(^{-1}\)). Thermodynamically, however, all reactions are exothermic with \(\Delta H^\circ\) of –21.4 kcal mol\(^{-1}\) for the formation of phenylsulfonyl derivative 4b, –12.4 kcal mol\(^{-1}\) for benzoyl nitrene 4c and –9.6 kcal mol\(^{-1}\) for azidophosphate species 4d, respectively. Interestingly, the TS1 barrier seems to correlate with the N(\(\alpha\))–N(\(\beta\)) bond length in the azide (N\(\alpha\)–N\(\beta\) bond lengths: 1.243 Å (2a); 1.239 Å (2b); 1.240 Å (2c); and 1.236 Å (2d)). Only arylsulfonyl-derivative 2b is slightly out of this general trend. A longer N\(\alpha\)–N\(\beta\) bond distance typically indicates a lower bond energy, which in turn should lead to a lower TS1 barrier.

The activation energy of the second step also differs quite substantially for the studied azides (Figure 7). Thus, phenylsulfonyl and benzoyl derivatives have relatively high \(\Delta H^\ddagger (TS2)\) barriers of +12.7 kcal mol\(^{-1}\) and +11.0 kcal mol\(^{-1}\), whereas dimethoxy phosphoryl nitrene shows a moderate barrier of +6.5 kcal mol\(^{-1}\). While the formation of the benzylic radical is exothermic by –5.2 and –7.6 kcal mol\(^{-1}\) for the benzoyl and phosphoryl derivatives, respectively, it is slightly endothermic by +1.2 kcal mol\(^{-1}\) for the phenylsulfonyl derivative. For the phenylsulfonyl derivative, the combination of a higher TS1 barrier and the substantially increased TS2 barrier should make the nitrene insertion reaction quite slow, in line with the lower yields observed experimentally. For the benzoyl and phosphate azides, the TS2 barriers (second step: H–atom abstraction) are quite low, but the TS1 barriers for nitrene radical formation (first step: dinitrogen elimination) are much higher, which explains the poor reactivity of these substrates in the C–H insertion reactions. This fact may be attributed to a

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**Table 1.** Mulliken spin density distributions of the nitrene radical species 4a–d.

<table>
<thead>
<tr>
<th>(por)Co(N•R) species</th>
<th>BP86/def-TZVP</th>
<th>b3-lyp/def-TZVP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>4a MeOC(O)-</td>
<td>74%</td>
<td>18%</td>
</tr>
<tr>
<td>4b PhSO2-</td>
<td>65%</td>
<td>27%</td>
</tr>
<tr>
<td>4c PhC(O)-</td>
<td>58%</td>
<td>26%</td>
</tr>
<tr>
<td>4d (MeO)2PO-</td>
<td>66%</td>
<td>27%</td>
</tr>
</tbody>
</table>
comparatively high Na–Nβ bond energy of the two latter azides. These data are in excellent agreement with the experimental observations.$^d$

**Co(por) catalysts with different substituents.** Intrigued by the variable activity of different catalysts, we also carried out a computational study of the two rate-limiting steps (TS1 and TS2) for the catalysts 1c and 1d (Figure 4 and Figure 8). As clearly shown in Figure 8, substitution of the meso-hydrogens of the porphyrin ring by electron-withdrawing perfluorophenyl and 2,6-dichlorophenyl groups leads to an increase in the TS1 activation barrier for nitrene radical formation from +12.3 kcal mol$^{-1}$ for the unsubstituted Co(por) complex 1a to +13.1 and +14.1 kcal mol$^{-1}$ for 1c and 1d, respectively (Figure 4 and Figure 8). This effect is even more evident for the comparative DFT calculations using the experimentally most successful Co(TPP) catalyst 1b, which has remarkably low ΔH$^\ddagger$ (TS1c') of only +10.2 kcal mol$^{-1}$ (Figure 8). Thermodynamically, all reactions are exothermic processes with ΔH$^\circ$ values of −12.7 kcal mol$^{-1}$ for the formation of 4a', −12.4 kcal mol$^{-1}$ for formation of 4b' and −16.4 kcal mol$^{-1}$ for formation of 4c', respectively.

The energies of the second hydrogen-atom abstraction step (TS2) are comparable for all the catalysts (Figure 4 and Figure 8) with a ΔH$^\ddagger$ (TS2) barrier of +6.3 kcal mol$^{-1}$ for both Co(TPP) and Co(por) catalysts, and +6.1 kcal mol$^{-1}$ and +7.6 kcal mol$^{-1}$ for the

![Figure 8. Reaction profile (ΔH in kcal mol$^{-1}$) for C–H amination employing catalysts 1b–d (see Figure 1 for the structure of the catalysts).](image)
Mechanism of Co\textsuperscript{II} Porphyrin-Catalysed C–H Amination with Organic Azides

perfluorophenyl- and 2,6-dichlorophenyl-substituted porphyrin complexes \(4a'\) and \(4b'\), respectively. Hence, the electronic influence of the meso-substituents has a much bigger influence on the first TS1 step of the catalytic reaction.

For efficient formation of the nitrene intermediates 4, it seems apparent that a catalyst should bear groups with rather mild electron-withdrawing properties at the meso-positions of the porphyrin ring. Groups that are too strongly electron-withdrawing (i.e. \(C_6F_5-\) and \(2,6-Cl_2C_6H_3-\)) would be ineffective, whereas no substituent at the meso-position at all (as in catalyst 1a) would also lead to a decrease in catalytic activity. On one hand, electron-withdrawing groups are beneficial for the reaction because they enhance the formation of the Co–N bond in the azide adducts 3 and thereby weaken the Na–Nβ bond of the azide, but on the other hand elimination of nitrogen in the transition states TS1 involves a considerable oxidation of the metal centre by electron transfer to the nitrene nitrogen. For example, in the transition states TS1a’–c’, about 20% of the unpaired electron has already been transferred to the ‘nitrene’ nitrogen (Figure 9).\textsuperscript{25} As strongly electron-withdrawing groups at the meso-porphyrin position of the catalyst raise the redox potential of cobalt in the corresponding complexes, this hampers the internal electron transfer from cobalt to nitrogen, resulting in higher activation energies for nitrogen elimination. Therefore the optimal Co(por) catalysts for this reaction must have subtly balanced electronic properties.

**Implications for (optimising) the catalytic reactions.** The above computational study provides rather detailed answers to central mechanistic questions concerning (por)Co catalysed C–H bond amination reactions using organic azides as the nitrene source. These insights hint to a window of opportunities in exploring the substrate scope, and seeking for the optimal reaction conditions and the best catalysts. These catalytic implications are shortly summarised in this section.

Elimination of dinitrogen from the azide adduct to form the ‘nitrene radical’ intermediate (TS1) and subsequent benzylic hydrogen abstraction by this intermediate (TS2) are both kinetically important. The effectiveness of an azide as nitrene source is mainly determined by the activation energies of these two steps. The poor reactivity of the benzoyl- and dimethoxy-
phosphoryl azides can be attributed to the high $\text{TS1}$ activation barriers for dinitrogen elimination. In case of phenylsulfonyl azide, a rather high barrier of the hydrogen abstraction step ($\text{TS2}$) is likely responsible for its low reactivity. The lowest combined $\text{TS1}$ and $\text{TS2}$ barriers for the $\text{N}_3\text{C}(\text{O})\text{OMe}$–based amination are in good agreement with the fact that $\text{N}_3\text{C}(\text{O})\text{OCH}_2\text{CCl}_3$ (TrocN$_3$) is the optimal nitrene source in this series. Differences in the $\text{TS2}$ barriers further determine largely the substrate-, regio- and product selectivities.

The initial dinitrogen elimination $\text{TS1}$ can be considered as the most challenging step of the entire catalytic process. Changes in the structure of the azide as well as the catalyst have a large influence on the activation energies of this step. Electron-withdrawing groups at the meso-position of the porphyrin ligand of the catalyst enhance the formation of the Co–N bond in the azide adducts and thus lower the barrier for $\text{N}_2$ loss. However, as elimination of dinitrogen gas from the azide adducts effectively involves a partial electron transfer from the metal to the ‘nitrene’ nitrogen, the use of groups that are too strongly electron-withdrawing at the porphyrin meso-position of the catalyst have a detrimental effect by raising the redox potential of cobalt in the corresponding complexes. Cobalt complexes of porphyrins with rather mild electron-withdrawing properties thus appear to be the most effective catalysts. Further catalyst improvements should mainly be focused on the facilitation of this step, in which the redox non-innocence of the nitrene moiety plays a crucial role. Metal complexes that enable effective dinitrogen elimination from the azides to generate a nitrogen-centred radical are essential. Complexes appended with H–bond donors (e.g. Co(3,5-DiBu-ChenPhyrin; see Figure 10) are particularly interesting in this respect, and should lower the $\text{TS1}$ barriers significantly, as they do in case of related aziridination reactions. We expect much from catalytic amination reactions with such complexes in the near future.

**EPR spectroscopy**

The above DFT studies, as well as our previous computational investigations, reveal that the formation of nitrene radical complexes of the type (por)Co(N•R) upon reaction of (por)Co species with organic azides is exothermic. Hence (in absence of other reacting substrates), these species should be detectable. Quite remarkably, however, they have never been detected before, despite their interesting electronic structure. Therefore we decided to study the reaction of the porphyrin complexes Co(TPP) and Co(3,5-DiBu-ChenPhyrin) with the organic azides $p$-$\text{O}_2\text{N}\text{C}_6\text{H}_4\text{SO}_2\text{N}_3$ and TrocN$_3$ with solution EPR spectroscopy (Figure 10). As discussed above, Co(TPP) is an active catalyst for nitrene insertion reactions in C–H bonds,
Mechanism of Co$^{II}$ Porphyrin-Catalysed C–H Amination with Organic Azides

while Co(por) complexes appended with amido H-bond donors such as Co(3,5-Di’tBu-ChenPhyrin) are the most active catalysts for olefin aziridination reactions.$^{15}$ These reactions proceed via similar nitrene radical ligand complexes as the key intermediates in the catalytic cycle.$^{18a}$

Excess of $p$-NO$_2$C$_6$H$_4$SO$_2$N$_3$ and TrocN$_3$ was added to solutions of Co(TPP) and Co(3,5-Di’tBu-ChenPhyrin) in D$_6$-benzene, respectively, and the solutions were shaken for 10–30 min at room temperature under an inert nitrogen atmosphere. Isotropic solution EPR spectra were recorded on a standard X-band EPR spectrometer. Clear and well-resolved EPR signals were detected that are characteristic for the nitrene radical ligand complexes (Figure 11). While the isotropic $g$ values are clearly characteristic of an $S = 1/2$ organic ligand-based radical, the signals do show well-resolved hyperfine coupling patterns with cobalt ($I = 7/2$). Hyperfine couplings with a single nitrogen nucleus are apparent from line shape analysis by spectral simulations. Satisfactory simulations were obtained,$^{26}$ yielding the cobalt and nitrogen hyperfine couplings listed in Table 2.

Figure 10. Organic azides and cobalt(II) porphyrin complexes used in EPR studies.

Figure 11. (left) Experimental and simulated isotropic EPR spectrum (benzene solution) of (TPP)Co(N•p-SO$_2$C$_6$H$_4$NO$_2$) at RT (frequency = 9.38056 GHz; modulation amplitude = 1 G; microwave power = 0.2 mW). (right) Experimental and simulated isotropic EPR spectrum (benzene solution) of (3,5-DitBu-ChenPhyrin)Co(N•Troc) measured at RT (frequency = 9.3791 GHz; modulation amplitude = 0.5 G; microwave power: 0.2 mW).
Chapter 3

Table 2. Experimental\textsuperscript{a} and DFT calculated\textsuperscript{b} EPR parameters.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$g_{iso}$</th>
<th>$A_{iso}$\textsuperscript{c}</th>
<th>$\rho$ (%)\textsuperscript{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>(TPP)Co(N•SO$_2$C$_6$H$_4$NO$_2$)\textsuperscript{a}</td>
<td>2.004</td>
<td>24.8</td>
<td>11.0</td>
</tr>
<tr>
<td>I \textsuperscript{b}</td>
<td>2.008</td>
<td>20.0</td>
<td>14.8</td>
</tr>
<tr>
<td>(3,5-Di‘Bu-ChenPhyrin)Co(N•Troc)\textsuperscript{a}</td>
<td>2.005</td>
<td>19.0</td>
<td>6.0</td>
</tr>
<tr>
<td>II \textsuperscript{b}</td>
<td>2.000</td>
<td>26.8</td>
<td>22.1</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Parameters from spectral simulations. \textsuperscript{b} Orca, B3LYP/def2-TZVP. \textsuperscript{c} Hyperfine couplings in MHz. \textsuperscript{d} Mulliken spin density (Orca, B3LYP/def2-TZVP).

The EPR parameters of (TPP)Co(N•SO$_2$C$_6$H$_4$NO$_2$) and (3,5-Di‘Bu-ChenPhyrin)Co(N•Troc) were also calculated with DFT, based on the simplified models I and II shown in Figure 12. The computed EPR data are in qualitative agreement with the experimental data (Table 2). Table 2 also includes the computed spin density distribution at the B3-LYP/def2-TZVP level of theory. The nitrogen hyperfine couplings derived from the spectral simulations are smaller than those calculated with DFT (especially for II). However, considering the use of these simplified gas phase models results are in good agreement.\textsuperscript{27}

The obtained EPR results are quite relevant, considering the fact that the Co(por)-based nitrogen-centred ligand radicals were never detected before, but frequently proposed as key intermediates in nitrene transfer chemistry with Co(por) catalysts. We take these EPR data as the first direct experimental evidence for the formation of Co$^{III}$–nitrene radical complexes upon reaction of Co(por) species with organic azides. The spin density of these species is clearly centred on the nitrene ligand (see also Figure 3), which is of crucial importance to understand the reactivity of the key nitrene intermediates in the above described C–H amination reactions (vide supra) as well as those in related olefin aziridination reactions.\textsuperscript{18a}

3.3 Summary and Conclusions.

The Co$^{II}$ porphyrin-catalysed amination of aliphatic C–H bonds with organic azides has been shown to proceed via a multistep radical-type mechanism. Coordination of organic azides to the cobalt centre,
followed by elimination of dinitrogen (TS1), produces unusual ‘nitrene radical’ intermediates (por)Co\textsuperscript{III}–N•Y that have most of their unpaired spin density localised at the ‘nitrene’ nitrogen atom. Formation of these nitrene ligand radical complexes is an exothermic process, and hence the DFT calculations predict that nitrene ligand radical complexes should be detectable species in absence of other reacting substrates. In good agreement, experimental detection of isotropic solution EPR signals with g-values characteristic for ligand radical complexes revealing hyperfine coupling with cobalt and a nitrogen nucleus were detected in the spectra obtained from (por)Co complexes in the presence of an excess of organic azides. The ‘nitrene radical’ intermediates are capable of abstracting a hydrogen atom from benzylic positions of the aromatic substrates (TS2) to form close-contact pairs of the thus formed organic radicals R’• and the cobalt(III)-amido species (por)Co\textsuperscript{III}–NHR ({{R’ • … (por)Co\textsuperscript{III}–NHR}}). These close-contact pairs easily collapse in a virtually barrierless fashion (TS3) to produce the desired NHRR’ amine products with regeneration of the Co(por) catalyst. Formation of the observed R–NH\textsubscript{2} byproducts most likely involves β-hydrogen atom abstraction from the benzylic radical R’• in the close-contact radical-catalyst pair {{R’ •… (por)Co\textsuperscript{III}–NHR}} intermediates to form an olefin and (por)Co\textsuperscript{III}–NH\textsubscript{2}Y. This olefin byproduct forming process is also essentially barrierless and should compete with the desirable collapse of {{R’ • … (por)Co\textsuperscript{III}–NHR}} to form the amine products. Olefin formation via this radical-type β-hydrogen elimination has been confirmed experimentally. Elimination of dinitrogen from the azide adduct to form the ‘nitrene radical’ intermediate (TS1) and subsequent benzylic hydrogen abstraction by this intermediate (TS2) are both kinetically important.

The herein reported combined computational and experimental study provides valuable information about the intimate reaction mechanism of these intriguing C–H amination reactions and shed new light on how to address selectivity issues in catalytic C–H amination reactions. This should aid future developments to expand the substrate scope and the design of new catalytic systems.

3.4 Experimental details.

Computational methods. Geometry optimisations were carried out with the Turbomole program package\textsuperscript{28} coupled to the PQS Baker optimizer\textsuperscript{29} via the BOpt package,\textsuperscript{30} at the ri-DFT level using the BP86 functional and the resolution-of-identity (ri) method.\textsuperscript{31} We used the SV(P) basis set\textsuperscript{32} for the geometry optimisations of all stationary points. All minima (no imaginary frequencies) and transition states (one imaginary frequency) were characterised by numerically calculating the Hessian matrix. ZPE and gas-phase thermal corrections (entropy
and enthalpy, 298 K, 1 bar) from these analyses were calculated. Improved energies were obtained with single point calculations at the DFT/BP86 level using the Turbomole def-TZVP basis set.\textsuperscript{33} Estimated condensed phase (1 L mol\textsuperscript{-1}) free energies and entropies were obtained from these data by neglecting the enthalpy RT term and subsequent correction for the condensed phase reference volume (S\textsubscript{CP} = S\textsubscript{GP} + R\text{ln}(1/24.5)) for all steps involving a change in the number of species, except for steps involving gaseous N\textsubscript{2}.

**EPR spectroscopy.** Sample preparation: Co(3,5-Di'Bu-ChenPhyrin)\textsuperscript{34} and Co(TPP)\textsuperscript{35} were prepared according to published procedures. They were dissolved in dry benzene-d\textsubscript{6} and an excess of the organic azide was added in a in a N\textsubscript{2}-filled glovebox, after which the solution was transferred into a EPR tube. The samples were shaken for 10–30 minutes before measurements. Experimental X-band EPR spectra of these mixtures were recorded on a Bruker EMX spectrometer at room temperature located in Nijmegen. The spectra were simulated by iteration of the isotropic $g$ values, hyperfine coupling constants and line widths. We thank Prof. F. Neese for a copy of his EPR simulation program. Calculated EPR spectra were obtained at the DFT B3-LYP/def2-TZVP level with Turbomole-optimised geometries using Orca.\textsuperscript{36}

### 3.5 Acknowledgments.

We thank H. Lu, H. Jiang and Prof. X. P. Zhang for the provision of the Co(3,5-Di'Bu-ChenPhyrin) and for their contribution to this chapter. We also thank dr. V. Lyaskovskyy for the fruitful collaboration in this chapter.

### 3.6 Notes and References.


See Table 1 in the computational methods section for a distribution of the Mulliken spin densities values over the cobalt and nitrogen atoms.


In a recent DFT-OLYP study employing $p$-NO$_2$-PhN$_3$ as the nitrene source, Ghosh and coworkers reported very similar barriers for nitrene radical formation (+31 kcal mol$^{-1}$) and subsequent allylic hydrogen atom abstraction from 2-methyl-1-butene (+27.4 kcal mol$^{-1}$). See ref. 16.

Complex 5a is found to have a closed-shell singlet ground state at the b3-lyp level of theory. The triplet species is ~2 kcal mol$^{-1}$ higher in energy. Attempts to locate an open-shell singlet (singlet biradical) electronic state in all cases led to transformation into a closed-shell species during the geometry optimisations.


Intermediate 9a is 1.4 kcal mol$^{-1}$ more stable than the transition state TS7a if ZPE is not taken into account. The transition state geometry optimisation of the TS7a failed, since the calculations led to the more stable intermediate 7a. We report here the energy of the TS7a as a maximum on the potential energy surface, obtained by constrained geometry optimisation. For the whole reaction profile see the Supporting Information.

According to Mulliken population analysis at the BP86/def-TZVP level.

The experimental spectrum of (TPP)Co(N•$p$-SO$_2$C$_6$H$_4$NO$_2$) also reveals a sharp signal stemming from a small amount (~ 1% of the total spectral intensity) of a free organic radical. The hyperfine couplings of this species with nitrogen (~ 30 Mhz) and possibly a deuterium (~ 7 MHz) nucleus suggests that this is perhaps the free $p$-NO$_2$PhSO$_2$–ND$^\bullet$ radical. This species could be generated from (TPP)Co(N•$p$-SO$_2$C$_6$H$_4$NO$_2$) upon reaction with trace amounts of D$_2$O in the solvent.

Isotropic $A_{iso}$ values are averaged values of the anisotropic $A_x$, $A_y$ and $A_z$ values. Since the computed anisotropic hyperfine couplings have both positive and negative values, small deviations can have a relatively large influence on the computed $A_{iso}$ values. Nonetheless, the agreement between the experimental and computed values is decent.

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