Cobalt Catalysis | Very Important Paper |

Cobalt-Porphyrin-Catalysed Intramolecular Ring-Closing C–H Amination of Aliphatic Azides: A Nitrene-Radical Approach to Saturated Heterocycles

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Abstract: Cobalt-porphyrin-catalysed intramolecular ring-closing C–H bond amination enables direct synthesis of various N-heterocycles from aliphatic azides. Pyrrolidines, oxazolidines, imidazolidines, isoindolines and tetrahydroisoquinolines can be obtained in good to excellent yields in a single reaction step with an air- and moisture-stable catalyst. Kinetic studies of the reaction in combination with DFT calculations reveal a metallo-radical-type mechanism involving rate-limiting azide activation to form the key cobalt(III)-nitrene radical intermediate. A subsequent low barrier intramolecular hydrogen-atom transfer from a benzylic C–H bond to the nitrene-radical intermediate followed by a redox rebound step leads to formation of the desired N-heterocyclic ring-products. Kinetic isotope competition experiments are in agreement with a radical-type C–H bond-activation step (intramolecular KIE = 7), which occurs after the rate-limiting azide activation step. The use of di-tert-butyl dicarbonate (Boc₂O) significantly enhances the reaction rate by preventing competitive binding of the formed amine product. Under these conditions, the reaction shows clean first-order kinetics in both the [catalyst] and the [azide substrate], and is zero-order in [Boc₂O]. Modest enantioselectivities (29–46 % ee in the temperature range of 100–80°C) could be achieved in the ring closure of (4-azidobutyl)benzene using a new chiral cobalt-porphyrin catalyst equipped with four (15S)-(−)-camphamic-ester groups.

Introduction

Organic azides are interesting nitrene precursors for direct C–H amination reactions, producing linear or cyclic amines and only N₂ as a harmless side product. For example, Warren and co-workers reported on the Cu-catalyzed activation of adamantyl azide, followed by intramolecular nitrene insertion into several different C–H bonds. In general, however, most reported C–H amination examples involve activation of electronically pre-activated and/or bulky, sterically protected tertiary azide substrates, such as fBuN₃, adamantyl azide, aryl azides (ArN₃), phosphoryl azides [(RO)₂P(=O)N₃], sulfonyl azides (RSO₂N₃) or carbonazidates (ROCON₃) as the nitrene-precursors. Intramolecular C–H amination reactions involving organic azides constitute an interesting protocol for the preparation of N-heterocyclic compounds, but to date, most of the reported protocols are limited to the use of electronically pre-activated azides. More recently, and most relevant to the investigations described in this paper, some interesting examples involving intramolecular amination of C–H bonds using primary aliphatic organic azides (RCH₂N₃) as the “nitrene” source were reported (see Figure 1). Although these examples provide interesting lead-reactivity for the synthesis of saturated heterocycles (in particular the system reported by Betley and co-workers), there are still a number of hurdles to overcome; (1) most of the previously reported catalysts for this reaction are highly sensitive to air and water and require relatively high catalyst loadings, thus resulting in low catalytic turnover numbers (TONs); (2) several of the reported catalysts produce significant amounts of (Boc-protected) linear amines as undesired side products; (3) asymmetric versions of intramolecular ring-closing C–H bond amination reactions of unactivated aliphatic azides are unknown; and (4) relatively limited mechanistic information for these types of reactions is available to guide scientists in finding solutions to the above challenges, thus hampering the design and development of more efficient catalysts. Cobalt porphyrin systems have been reported for related C–H functionalization protocols. The reported mechanistic proposals for these types of reactions are quite interesting. Based on spectroscopic studies and supporting DFT calculations, activation of...
electronically pre-activated organic azides [i.e., CH₃C₆H₄SO₂N₃ (TsN₃), NO₂C₆H₅SO₂N₃ (NsN₃), CCl₃CH₂O(C=O)N₃ (TroCN₃)] by cobalt(II)-porphyrin catalysts is believed to produce unique cobalt(III)-nitrene-radical intermediates (Co=NN-Y), which subsequently react with C–H bonds in a hydrogen-atom transfer (HAT) radical rebound process.¹¹ Moreover, related nitrene-radical intermediates (albeit with more complicated electronic structures) have been proposed as intermediates in the Fe- and Pd-catalysed formation of N-heterocycles from (4-azidobutyl)benzene.¹³,¹⁴ However, kinetic and/or spectroscopic evidence to unambiguously support these mechanistic proposals is thus far lacking. Furthermore, the mechanism of activation of primary aliphatic azides might differ from the catalytic pathways followed by more activated organic azides such as NsN₃ and TroCN₃ (also for cobalt-based catalysts).

Alternative resting states and rate-limiting steps may be operational, and the C–H activation steps could either involve an HAT-rebound mechanism, direct nitrene insertion into the C–H bond or even both at the same time.¹¹ Moreover, as the activation of aliphatic azides typically requires elevated reaction temperatures, even the involvement of free nitrene intermediates and with higherTONs than reported for other catalysts. Additionally, detailed mechanistic information was gathered from reaction progress kinetics, kinetic isotope competition experiments and supporting DFT studies, all of which strongly support the involvement of aliphatic Co=NN-R species as key intermediates in these reactions. Furthermore, as a proof of principle, we present the first example of an enantiomERICally pure C–H amination reaction of the type shown in Figure 1, strongly suggesting that the C–H bond activation and C–N bond formation steps of the overall catalytic ring-closing reaction occur in the coordination sphere of cobalt. No free nitrene intermediates seem to be involved in these reactions.

Results and Discussion

We started our evaluation of the catalytic activity of cobalt(II)-porphyrin complexes under various conditions by monitoring the conversion of azide 5a into pyrrolidine 5b (Table 1) with the commercially available cobalt(II)-tetraphenylporphyrin complex 1 [(Co(TPP)], Figure 2). In the absence of an amine trapping agent, complete recovery of the starting material was observed after 16 hours at 100 °C using 1 mol% of the catalyst (Table 1, entry 1). Some conversion could, however, be observed when high catalyst loadings were used (see the Supporting Information). In the presence of di-tert-butylcarboxylate (Boc₂O), we observed the desired Boc-protected cyclic amine product 5b (tert-butyl 2-phenylpyrrolidine-1-carboxylate) as a benchmark.

Table 1. Catalyst evaluation in intramolecular ring-closing C–H bond amination of azide 5a.¹⁵

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Loading [mol%]</th>
<th>Conversion [%]</th>
<th>Yield [%]</th>
<th>TON</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>[Co(TPP)]</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>n.d.¹⁶</td>
</tr>
<tr>
<td>2</td>
<td>[Co(TPP)]</td>
<td>1</td>
<td>24</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>[Co(TPP)]</td>
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<td>&lt; 5</td>
<td>n.d.</td>
<td>n.d.¹⁶</td>
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<tr>
<td>4</td>
<td>[Co(TPP)]</td>
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<td>35</td>
</tr>
<tr>
<td>5</td>
<td>[Co(TPP)]</td>
<td>1</td>
<td>39</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>[Co(TPP)]</td>
<td>1</td>
<td>30</td>
<td>n.d.</td>
<td>n.d.¹⁶</td>
</tr>
<tr>
<td>7</td>
<td>[Co(Salophen)]</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>n.d.¹⁶</td>
</tr>
<tr>
<td>8</td>
<td>[Co(Salophen)]</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>n.d.¹⁶</td>
</tr>
<tr>
<td>9</td>
<td>[Co(TPP)]</td>
<td>1</td>
<td>57</td>
<td>54</td>
<td>27</td>
</tr>
<tr>
<td>10</td>
<td>[Co(TPP)]</td>
<td>4</td>
<td>&gt; 95</td>
<td>89</td>
<td>21</td>
</tr>
</tbody>
</table>

[a] Conditions: Substrate 5 (0.3 mmol), catalyst [1–4 mol%], Boc₂O (0.36 mmol) and solvent (3.0 mL) were mixed and reacted for 16 h at 100 °C. After the reaction only starting material and expected products were observed. Conversions are based on ¹H NMR analysis of the ratio between starting materials and products. Yields are of isolated material.
[b] No product was detected by ¹H NMR.
[c] Not determined.
[d] No Boc₂O was used in the reaction.
[e] Benzene was used as the solvent.
[f] 3% v/v water was present in the solvent.
[g] Salophen = N,N'-bis-(3,5-di-tert-butyl-salicylidene)-1,2-phenylenediamine.

Figure 1. Comparison of previously reported catalysts and those used in the present study for intramolecular ring-closing C–H bond amination taking (4-azidobutyl)benzene as a benchmark.

ing in particular on the mechanism, scope and prospect of these reactions (see Figure 1).

The catalysts reported here are air and water stable, and cleanly produce cyclic (Boc-protected) amines in good yields and with higher TONs than reported for other catalysts. Additionally, detailed mechanistic information was gathered from reaction progress kinetics, kinetic isotope competition experiments and supporting DFT studies, all of which strongly support the involvement of aliphatic Co=NN-R species as key intermediates in these reactions. Furthermore, as a proof of principle, we present the first example of an enantiomERICally pure C–H amination reaction of the type shown in Figure 1, strongly suggesting that the C–H bond activation and C–N bond formation steps of the overall catalytic ring-closing reaction occur in the coordination sphere of cobalt. No free nitrene intermediates seem to be involved in these reactions.
ate) by $^1$H NMR spectroscopy. The product was isolated in 17% yield (Table 1, entry 2, TON = 17) after 16 hours of reaction. We were pleased to see that under these conditions the TONs obtained with [Co(TPP)] catalyst 1 in the conversion of substrate 5a to product 5b are already higher than those of most of the recently reported homogeneous catalysts for this reaction.\cite{13–15}

We continued our optimisation by changing the catalyst; with cobalt(II)-tetra(pentafluorophenyl)-porphyrin ([Co(TFP$_2$P)$_2$]) complex 2, Figure 2) as the catalyst, only trace amounts of the desired product 5b (<5%) were obtained (Table 1, entry 3). [Co(salophen)] complex 4 (Figure 2)\cite{16} proved to be completely inactive (entry 7). In contrast, marked improvements both in yield and TON were observed using the electron-rich tetra(2,4,6-trimethylphenyl)-porphyrin complex 3 ([Co(TMP)], Figure 2) as the catalyst. The desired product 5b was obtained in 36% isolated yield using 1 mol% of catalyst (TON = 36; Table 1, entry 4) at 38% conversion of the substrate. No significant change in the isolated product yield was observed upon changing the solvent to benzene (entry 5). To our surprise, the presence of up to 3% v/v of water in the solvent mixture did not result in a significant decrease in activity (entry 6), which is quite remarkable as previously reported catalysts are all very sensitive to the presence of even trace amounts of water.

To verify whether the cobalt-porphyrin complex is an active component in the catalysis or merely initiating a metal-free radical reaction, we replaced cobalt(II) by azobis(isobutyronitrile) (AIBN, entry 8). However, use of this well-known radical initiator did not lead to any product formation. At the low cobalt catalyst loadings used so far, incomplete conversion of the azide 5a was observed after 16 hours, which nicely allows for proper comparison of the TONs of the different catalysts (Table 1, entries 1–7). To obtain synthetically useful yields of the desired product 5b within the same reaction time, however, higher catalyst loadings were used. With 2 and 4 mol% of [Co(TMP)] catalyst 3, the product yield increased to 54% and 89%, respectively (Table 1, entries 9 and 10). Importantly, none of these reactions produced any significant amounts of undesired linear (Boc-protected) amine products previously observed for related systems.\cite{13,15} Next, we explored the substrate scope by examining the synthesis of oxazolidines and imidazolidines using the above [Co(por)]-catalyzed ring-closing C–H bond-amination protocol. By introducing an oxygen atom in the aliphatic chain at the alpha-position to the benzylic C–H (Table 2, entry 1, 6a), the oxazolidine product was obtained in high isolated yield (6b, 93%; TON = 23). Introduction of two methyl groups on the aliphatic chain was expected to further improve the efficiency of the cyclisation reaction (by virtue of the Thorpe–Ingold effect\cite{19}). However, this modification led to a significant decrease in both the yield and TON for formation of oxazolidine product 7b (Table 2, entry 2). Steric hindrance introduced by the two methyl groups apparently has a larger effect on the reactivity than pre-organisation for cyclisation when using substrate 7a. The reaction did however proceed cleanly, as only product 7b and starting material 7a were observed upon analysis of the crude reaction mixture. Substitution of oxygen for an NH-functionality in the aliphatic chain resulted in a small decrease in the product yield using [Co(TMP)] complex 3 as the catalyst (69% yield, TON = 17; entry 3). In this reaction, [Co(TPP)] complex 1 produced imidazolidine product 8b in a comparable yield (67%, TON = 17). In all reactions involving a secondary NH-group in the substrate (entries 3–10), we used 2.4 equiv of Boc$_2$O to protect both nitrogen atoms.

The decrease in yield could be due to the increased bulk of the substrate after Boc-protection of the secondary amine. This also explains why the difference in activity between the two

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield ( [%]</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6a</td>
<td>6b</td>
<td>93</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>7a</td>
<td>7b</td>
<td>32</td>
<td>8</td>
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<tr>
<td>3</td>
<td>8a</td>
<td>8b</td>
<td>69([a])</td>
<td>17([a])</td>
</tr>
<tr>
<td>4</td>
<td>8c</td>
<td>8b</td>
<td>69([a])</td>
<td>16([a])</td>
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<tr>
<td>5([a])</td>
<td>R = Me, 9a</td>
<td>R = Me, 9b</td>
<td>96</td>
<td>24</td>
</tr>
<tr>
<td>6([a])</td>
<td>R = Ph, 10a</td>
<td>R = Ph, 10b</td>
<td>91</td>
<td>22</td>
</tr>
<tr>
<td>7([a])</td>
<td>R = F, 11a</td>
<td>R = F, 11b</td>
<td>84</td>
<td>21</td>
</tr>
<tr>
<td>8([a])</td>
<td>R = Cl, 12a</td>
<td>R = Cl, 12b</td>
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<td>22</td>
</tr>
<tr>
<td>9([a])</td>
<td>R = Br, 13a</td>
<td>R = Br, 13b</td>
<td>95</td>
<td>24</td>
</tr>
</tbody>
</table>

\([a]\) Conditions: Substrate (0.3 mmol), Boc$_2$O (1.2 equivalent), [Co(TPP)] (4 mol%), and toluene (3.0 mL) were added and reacted for 16 h at 100 °C. At the end of the reaction only starting material and products were observed. (b) 2.4 equiv of Boc$_2$O were added. Yields are of isolated material. In entries 3 and 5–10, full conversion of starting material was always observed. The only observed side product was the corresponding azide with a Boc-protected secondary nitrogen (compound 8c and compounds S6–S11, see the Supporting Information). (c) Commercially available [Co(TPP)] 1 was used as the catalyst.

![Figure 2. Achiral cobalt(III) complexes used in this study: cobalt(II) tetraphenylporphyrin ([Co(TPP)], 1), cobalt(II) pentafluorophenylporphyrin ([Co(TFP$_2$P)$_2$]), cobalt(II) tetramesitylporphyrin ([Co(TMP)], 3) and cobalt(III) salophen ([Co(salophen)], 4).](Image)
catalysts 1 and 3 is small for this substrate. When substrate 8a was treated with Boc<sub>O</sub> to yield substrate 8c prior to the cyclisation reaction, no change in the product yield was observed as compared to the one-pot procedure (Table 2, entry 4). We further investigated to test the tolerance of the reaction for substitution on the phenyl ring of the amine-containing substrates (Table 2, entries 5–10). Because of the small difference in activity between [Co(TPP)] (1) and [Co(TMP)] (3) for substrate 8a, the commercially available [Co(TPP)] catalyst 1 was used for substrates 9a–14a. In these cases, we also used 2.4 equiv of Boc<sub>O</sub> in the reaction (Table 2, entries 5–10) to prevent product inhibition. Using 4 mol% catalyst loading, high yields (up to 96%) were obtained for all substrates containing a substituent in the para-position of the phenyl ring. The effect of electron-donating and electron-withdrawing substituents is marginal, which is in agreement with the kinetic and computational studies described below, showing that azide activation is rate-limiting. At the end of the reaction, we always observed full conversion of the starting material for substrates 8a–14a. The only observed side product in these reactions was the corresponding Boc-protected azide (compound 8c and compounds S6–S11, see the Supporting Information), again without formation of any significant amounts of undesired linear (Boc-protected) amines from the azide substrates.<sup>13,15</sup>

To further explore the scope of the cobalt-porphyrin catalyst for the preparation of N-saturated heterocycles from alkyl-azide fragments, we examined the azide-containing disubstituted amines 15a–17a to obtain bicyclic isoidoline and tetra-hydroisoquinoline derivatives (Scheme 1). The presence of the phenyl ring resulted in a decrease in the selectivity because isoidoline product 15b was obtained in only 27% yield. However, full conversion of the substrate was observed. The protected linear amine product 15c (35%) and some ill-defined oligomeric/polymeric side products were observed (see the Supporting Information). It seems that if the desired ring-closing step requires breaking of a stronger C–H bond [higher bond dissociation energy (BDE)], the reaction is partially driven to intermolecular HAT reactions (most likely from the alpha position of another azide substrate), producing undesired side products. This is consistent with the formation of oligomeric/polymeric products, linear Boc-protected amines as well as nitriles from substrates containing even stronger C–H bonds (see the Supporting Information).

It is worth mentioning that substrate 16a also reacts selectively to form the N-heterocyclic ring product 16b, which supports a correlation between the BDE of the reacting C–H bond and the ease and selectivity of the ring-closing step. Note that replacing the methyl group in 15a by an ethyl group (substrate 16a) lowers the BDE of the reacting C–H bond. Full conversion was observed after 16 h using 2 mol% catalyst loading to yield the desired product 16b in 93% isolated yield (TON = 45). Apparently, the increased stabilisation of the benzylic radical is sufficient to avoid the competitive oligomerisation/polymerisation reactions observed for substrate 15a. Finally, a six-membered heterocycle 17b was found to be accessible using substrate 17a, albeit in only 28% yield (TON = 7). As observed for substrate 15a, but in contrast to all other reactions described above, 37% of the corresponding linear Boc-protected amine product 17c and some ill-defined oligomers/polymer were obtained as side products in this case. In addition, activation of the allylic C–H bond of substrate 18a yields the six-membered heterocycle product 18b (38%, TON = 10). Other compounds detected in the reaction mixture were the starting material 18a (37%), linear product 18c (12%) and small amounts of unidentified products. Additional substrates used in the C–H amination protocol, varying the BDE of the reacting C–H bond, are described in the Supporting Information (Table S1). The results obtained with these substrates indicate that intermolecular HAT starts to compete with intramolecular HAT when the barrier for C–H bond activation at the targeted position for ring-closing amination becomes too strong (i.e., higher BDEs of the targeted C–H bond and/or formation of six-membered rings instead of five-membered rings). Substrates with weaker benzylic C–H bonds at the delta position react selectively to form five-membered N-heterocyclic rings without any indication for competing intermolecular HAT reactions (see Tables 1 and 2).

**Mechanistic investigations**

**Kinetic studies**

The mechanism of the intramolecular ring-closing C–H bond-amination reaction was explored experimentally by kinetic analysis of the reaction progress monitoring the conversion of (4-azidobutyl)benzene substrate 5a into tert-butyl 2-phenylpyrrolidine-1-carboxylate product 5b, using [Co(TMP)] catalyst 3 in the presence of Boc<sub>O</sub>. Following the reaction in time (see Supporting Information) revealed clean first-order kinetics in both the [substrate] and the [catalyst], but zero-order kinetics in [Boc<sub>O</sub>]. No substrate saturation effects were detected over a broad concentration range of azide 5a. This translates into
the following empirical rate equation, with second-order rate constant \( k = 12 \text{ M}^{-1} \text{h}^{-1} \) (Eq. (1)).

\[
\text{Rate} = -d[\text{substrate}] / dt = k[\text{substrate}\ 5a][\text{catalyst}\ 3]
\]  

To exclude the alternative possibility of a rate-limiting C–H bond-activation step, we performed an inter- and intramolecular kinetic isotope competition experiment using the bis-deuterated (\( d_2\) \( 5a \)) and mono-deuterated (\( d_1\) \( 5a \)) analogues of (4-azidobutyl)benzene substrate \( 5a \) (see Scheme 2). In the inter-

molecular competition experiment (Scheme 2, top), no kinetic isotope effect (KIE = 1) was observed, thus showing that the C–H bond-activation step occurs after the rate-limiting azide activation step.\(^ {20} \) The intramolecular kinetic isotope competition experiment (Scheme 2, bottom) does reveal a substantial kinetic isotope effect (KIE = 7), showing that the C–H activation step is in itself not barrierless (see also Scheme 3). The rather large intramolecular KIE is perhaps suggestive of some tunneling contribution to the C–H activation step (see computational mechanistic studies), as can be expected for a radical-type hydrogen-atom transfer (HAT) process.\(^ {21,22} \) Hence, the kinetic data point to a pre-equilibrium involving weak and reversible binding of azide \( 5a \) to [Co(TMP)] catalyst 3, followed by rate-limiting substrate activation involving dinitrogen loss from the coordinated azide. Subsequent C–H activation leading to C–N bond formation and ring closure is faster, but not barrierless (see also the proposed mechanism in Scheme 3).

The reaction rate was further evaluated at various temperatures (80–115 °C) to obtain the activation parameters from the Arrhenius and Eyring equations (see Supporting Information for details). This led to the following experimental values: \( E_A = +18.7 \pm 2.3 \text{ kcal mol}^{-1}, \Delta G^\ddagger = +26.2 \pm 4.6 \text{ kcal mol}^{-1}, \Delta H^\ddagger = +18.0 \pm 2.3 \text{ kcal mol}^{-1} \) and \( \Delta S^\ddagger = -22.0 \pm 6.2 \text{ cal mol}^{-1} \text{K}^{-1} \). The rather large negative activation entropy (\( -22.0 \pm 6.2 \text{ e.u.} \)) points to an ordered, associative transition state, suggestive of an uphill substrate binding event preceding rate-limiting azide activation (see proposed mechanism in Scheme 3). When the reaction was performed in presence of TEMPO as a radical trap, a large decrease in the turnover number of catalyst 2 was observed (with 5 equiv TEMPO, TON = 9; with 25 equiv TEMPO, TON = 3), in good agreement with the proposed radical mechanism (Scheme 3).

Because product inhibition was observed in the reaction without \( \text{Boc}_2\O \), we determined the association constant for 2-phenylpyrrolidine (\( 5c \)) binding to the [Co(TMP)] catalyst 3. The equilibrium constant for the formation of five-coordinate complex [Co(TMP)(\( 5c \))] from [Co(TMP)] and \( 5c \) at room temperature was found to be \( K_1 = 1300 \), whereas binding of a second molecule \( 5c \) to [Co(TMP)(\( 5c \))] to form six-coordinate complex [Co(TMP)(\( 5c \)\( 5c \))] has a very low equilibrium constant of \( K_2 = 80 \) (see Supporting Information). We were unable to determine the binding constant for (4-azidobutyl)benzene coordination to 3 because the equilibrium is shifted towards the starting materials. This has previously also been observed for aromatic azide substrates.\(^ {22} \) Assuming that substrate binding and activation requires the free four-coordinate [Co(TMP)] catalyst, and thus competes with product binding, the considerable binding constant \( K_1 \) associated with formation of the product adduct [Co(TMP)(\( 5c \)\( 5c \))] should indeed result in a significant additional energy penalty to the rate-limiting step (also at 373 K) when the reaction is performed in absence of \( \text{Boc}_2\O \) (see Scheme 3).

**Computational mechanistic studies**

The mechanism was further explored computationally (DFT, B986, def2-TZVP, disp3), using a simplified model of the catalyst without substituents at the porphyrin ring (Scheme 3). Based on the kinetic studies described above, we anticipated that the initial steps of the mechanism involve coordination of the aliphatic azide \( 5a \) to cobalt(II), followed by dinitrogen loss to produce a nitrene-radical intermediate. Rate-limiting azide activation has also been proposed in the mechanisms for \([\text{Co}(\text{por})]\)-catalysed C–H bond-amination reactions using activated azides (carbonazidates [ROC(O)N] or sulfonyl azides [RSO_2N\_3]).\(^ {5,11,16} \) This indeed is a plausible pathway according to the DFT calculations (Scheme 3; for more details see the Supporting Information). Azide coordination is slightly endergonic
(+3.2 kcal mol\(^{-1}\)) and subsequent loss of dinitrogen from intermediate B via TS1 to produce the key nitrene-radical species C is also the rate-limiting step in the computed mechanism, which is in good agreement with the experimental kinetic studies (vide supra).

The computations further show a lower barrier for the rate-limiting azide activation step along the five-coordinate pathway (\(\Delta G^\ddagger = +24.5\) kcal mol\(^{-1}\); \(L = []\) in Scheme 3) than along the six-coordinate pathway with an additional molecule of product 5c bound to cobalt as an axial ligand (\(\Delta G^\ddagger = +28.5\) kcal mol\(^{-1}\); \(L = 5c\) in Scheme 3). This is in agreement with the experimentally observed inhibiting effect of the unprotected amine product 5c on the reaction rates of catalytic reactions performed in absence of Boc\(_2\)O. The computed activation parameters for TS1 (\(\Delta G^\ddagger = +24.5\) kcal mol\(^{-1}\), \(\Delta H^\ddagger = +16.3\) kcal mol\(^{-1}\), \(\Delta S^\ddagger = -21.9\) e.u.) are in excellent agreement with the experimental values determined from the Arrhenius and Eyring equations (\(E_a = +18.7 \pm 2.3\) kcal mol\(^{-1}\), \(\Delta G^\ddagger = +26.2 \pm 4.6\) kcal mol\(^{-1}\), \(\Delta H^\ddagger = +18.0 \pm 2.3\) kcal mol\(^{-1}\) and \(\Delta S^\ddagger = -22.0 \pm 6.2\) e.u.). A spin density plot of five-coordinate species C (Figure 3) shows 88% spin population at the nitrene moiety and only 6% at Co, thus confirming the nitrene-radical nature of this key intermediate (see also Scheme 3).\(^{[19]}\) HAT from the benzyllic position of the activated substrate to the nitrene-radical moiety (TS2) to produce amido-benzyl radical intermediate D and the subsequent radical rebound step (TS3) both have remarkably low barriers. From the relative barriers of hydrogen and deuterium abstraction in the HAT step, a KIE = 3.4 was calculated. Such calculations neglect any tunnelling effects, as they take only differences in zero point energy (ZPE) into account, resulting from isotope exchange in the vibrational analysis.

Although the predicted KIE calculated as such is in good qualitative agreement with the experiments, the experimental value is larger (KIE = 7). This is suggestive of some tunnelling contribution to the C–H bond-splitting process, as can be expected for a radical-type HAT process.\(^{[20]}\) In good agreement with the experimental data, dissociation of amine product 5c from cobalt(II) species E is endergonic, thus resulting in product inhibition (i.e., slower reactions) in the absence of Boc\(_2\)O (see the Supporting Information for more DFT details). Attack of Boc\(_2\)O on radical intermediate D prior to radical rebound cannot be fully excluded on the basis of the available experimental data. However, in view of the very low computed barrier for the radical rebound step (\(<2\) kcal mol\(^{-1}\)), this pathway seems unlikely.

**Figure 3.** Spin-density plot of intermediate C present in Scheme 3.

**Additional catalytic experiments based on the mechanistic insights gathered**

The mechanistic information gathered above called for some additional experimental studies. First of all, binding of unprotected product 5c to the catalyst is substantial, but the magnitude of the experimentally determined binding constant (\(K_b = 1300\)) suggests that the activation barrier of the rate-limiting azide activation step in absence of Boc\(_2\)O is raised only to a limited amount, and thus it should be possible to overcome this increased barrier at higher temperatures. As such, we argued that it might be possible to obtain the unprotected cyclic amine 5c by conversion of substrate 5a without Boc\(_2\)O at elevated temperatures. Indeed, full conversion of substrate 5a was observed when performing the catalytic reaction with 4 mol% of [Co(TMP)] catalyst 3 at 140 °C in chlorobenzene. As expected, the desired 2-phenylpyrrolidine 5c was indeed formed, albeit in a low yield (19%, TON = 5). Several undesired and unidentified side products were formed under these non-optimised reaction conditions (see Supporting Information).

In marked contrast to the reaction performed at 140 °C in absence of Boc\(_2\)O, the catalytic reactions (and kinetic studies) performed in the presence of Boc\(_2\)O allowed for clean conversion of azide 5a to the Boc-protected cyclic amine 5b at lower reaction temperatures (80–115 °C). Combined with clean first-order kinetics in both the [catalyst] and the [azide substrate], the data suggest that catalyst deactivation processes are minor and slow. As such, we wondered if higher TONs would be attainable when performing the reaction at lower catalyst loading but, at the same time, at higher absolute concentration of both the substrate and the catalyst. Such conditions are expected to shift the pre-equilibrium for substrate binding somewhat further in the direction of the coordinated complex B (Scheme 3), and simultaneously, may reduce any detrimental effects of impurities in the solvent. This indeed leads to higher TONs. Performing the reaction at a high substrate concentration of 0.44 M, using 1 mol% of [Co(TMP)] catalyst 3, led to formation of product 5b in 58% yield (TON = 59) after 16 h, and the yield further increased to 73% (TON = 76) after 72 h of reaction. These are the highest TONs for the cyclisation of substrate 5a reported to date.

**Enantioselective intramolecular ring-closing C–H bond amination**

In the proposed reaction mechanism shown in Scheme 3, the substrate remains coordinated to the cobalt centre throughout the catalytic cycle. If correct, this should allow for enantioselect-
tive reactions when using a chiral cobalt porphyrin catalyst. We therefore performed the ring-closing C–H bond-amination reaction of substrate 5a with a new chiral cobalt porphyrin catalyst equipped with four (15S)-(--)-camphanic-ester substituents (19, Figure 4).

Figure 4. Structure of (15S)-(--)-camphanic acid based chiral catalyst 19 used in the enantioselective ring-closing C–H bond-amination reaction of substrate 5a with 4 mol% catalyst loading.

Synthesis and characterisation of the new catalyst 19 is described in the Supporting Information. The chiral catalyst 19 produces product 5b in lower yields (33% yield, TON = 8, at 4 mol% catalyst loading) compared to [Co(TMP)] catalyst 3, but indeed allowed enantioselective product formation in 29% enantiomeric excess (ee) at 100 °C (enantiomeric ratio 35:65). The ee value increased to 46% (enantiomeric ratio 27:73) by lowering the reaction temperature to 80 °C, although at a somewhat reduced product yield (22%, TON = 6). Chirality transfer at these rather high reaction temperatures is quite remarkable, and the results demonstrate for the first time the feasibility of enantioselective radical-type ring closure reactions from aliphatic azides using metallo-radical catalysis (Figure 4).[23]

This clearly calls for additional screening of chiral catalysts for these types of reactions in follow-up studies. Perhaps most importantly, the result strongly suggests that the reaction does not proceed through formation of free nitrenes in a metal-free C–H bond-activation pathway. This is an important observation, because in some Fe- and Ru-catalysed nitrene-transfer reactions, formation of free nitrenes (reacting outside the coordination sphere of the metal in an uncontrolled manner) has been observed.[25] The observed chirality transfer thus holds important additional mechanistic information, and shows unambiguously that the C–H bond-activation and C–N bond-formation steps in the overall catalytic ring-closing reaction occur within the coordination sphere of cobalt.

Conclusion

A cobalt-catalysed ring-closing C–H amination protocol was developed for the synthesis of a variety of saturated N-heterocycles. The applied air- and moisture-stable [Co(por)] catalysts give significantly higher turnover numbers (up to 76) than other reported homogeneous catalyst systems based on Fe and Pd for these type of reactions. The use of di-tert-butylidcarbonate (Boc₂O) prevents competitive binding of the formed amine product, thereby significantly enhancing the reaction rate. Detailed kinetic studies, kinetic isotope competition experiments and supporting DFT calculations reveal a metallo-radical-type mechanism involving rate-limiting azide activation to form the key cobalt(III)-nitrene-radical intermediate. Subsequent low barrier intramolecular HAT from a benzyl C–H bond to the nitrene-radical intermediate followed by a radical rebound step leads to formation of the desired N-heterocyclic ring products. Kinetic isotope competition experiments are in agreement with a radical-type C–H bond-activation step (intramolecular KIE = 7), which occurs after rate-limiting azide activation (intramolecular KIE = 1). Enantioselective ring-closing amination proved possible when using a new chiral cobalt-porphyrin catalyst equipped with four (15S)-(--)-camphanic-ester substituents in the second coordination sphere. Modest enantioselectivities (up to 46% ee) were achieved in the ring closure of (4-azidobutyl)benzene, despite the high reaction temperature used (80 °C). This demonstrates for the first time the feasibility of enantioselective radical-type ring closure of aliphatic azides using metallo-radical catalysis,[23] and strongly suggests that the C–H bond-activation and C–N bond-formation steps of the overall catalytic ring-closing reaction occur in the coordination sphere of cobalt. The involvement of free nitrenes in these reactions seems unlikely. The ring-closing amination reactions described in this paper are rare examples of selective catalytic transformations proceeding through one-electron substrate-activation steps producing discrete metal-bound nitrogen-centred radical intermediates.[26] We hope that the prospects and mechanistic information provided in this paper will guide others and stimulate further research in this field.

Experimental Section

General intramolecular C–H bond-amination procedure: To a dry Schlenk flask was added catalyst (12 µmol), substrate (0.30 mmol) and di-tert-butylidcarbonate (0.36 mmol) in dry toluene (3.0 mL). The stirred reaction mixture was heated to 100 °C for 16 h. After cooling to room temperature, the crude mixture was purified by flash chromatography (SiO₂, DCM/hexanes/TEA 50:50:1).

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Conflict of interest

The authors declare no conflict of interest.
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