Controlling radical-type reactivity with transition metals and supramolecular cages

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Chapter 6:

Mechanistic Investigation of the Cobalt Porphyrin Catalyzed Intramolecular Ring-Closing C–H Amination of Aliphatic Azides

Part of this chapter was submitted for publication as: P. F. Kuijpers, M. J. Tiekink, W. B. Breukelaar, D. L. J. Broere, N. P. van Leest, J. I. van der Vlugt, J. N. H. Reek, B. de Bruin, *Nitrene-radical approach to Saturated Heterocycles; Cobalt Porphyrin Catalyzed Intramolecular Ring-Closing C–H Amination of Aliphatic Azides.*
Abstract: Cobalt porphyrin catalyzed intramolecular ring-closing C–H bond amination enables direct synthesis of various N-heterocycles from aliphatic azides. Information about the mechanism of this reaction was collected with the aim to improve the efficiency of the catalytic reaction, and to explore possibilities for enantioselective C–H amination. 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. Subsequent low barrier intramolecular hydrogen atom transfer (HAT) from a benzylic 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 the rate limiting azide activation step (intermolecular KIE = 1). 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 between 100-80 °C) could be achieved in the ring closure of (4-azidobutyl)benzene using a new chiral cobalt porphyrin catalyst equipped with four (1S)-(−)-camphanic-ester groups. This demonstrates for the first time the feasibility of enantioselective radical-type ring closure reactions from aliphatic azides using metallo-radical catalysis, showing unambiguously 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.

6.1 Introduction

Saturated heterocycles are important substructures in many natural products and pharmaceuticals.¹² In Chapter 5, a new C–H amination protocol is described which enables the synthesis of a variety of N-heterocycles in a single reaction step in good to excellent yields with a cobalt(II) porphyrin catalyst (Co(TMP), 3, Figure 1). For application of this reaction in the synthesis of pharmaceuticals and other bio-active compounds it will, however, be important to understand the mechanistic features of this reaction and work towards the development of enantioselective protocols. Thus far, asymmetric versions of intramolecular ring-closing C–H bond amination of aliphatic azides are unknown.
Figure 1: Direct intramolecular C–H amination of aliphatic azides described in Chapter 5.

Additionally, the exact role of di-tert-butyl dicarboxylate (Boc₂O, 2) in the described protocol is poorly understood. Furthermore, to eventually apply the described procedure it is required to further improve the turnover number (TON) of the catalysts to reduce catalyst cost (currently a TON of 35 was obtained under optimized conditions with (4-azidobutyl)benzene 1 as substrate). Mechanistic information about this type of reactions could guide scientists in finding solutions for these remaining challenges. Additionally, detailed kinetic analysis of the reaction enables the optimization of reaction conditions in terms of concentration, temperature and stoichiometry.³,⁴

Several mechanisms have been reported for the activation of azides involving metal nitrene radical intermediates (Figure 2). Previous reports for the activation of aliphatic azides by iron⁵,⁶ and palladium⁷,⁸ catalysts suggest initial formation of the nitrene radical by loss of dinitrogen. For the iron system described by Betley and co-workers two pathways are postulated from the intermediate nitrene radical species (Figure 2, top left).⁵ Either a two-step H-atom abstraction and radical rebound mechanism is operative, or alternatively the observed product-bound iron complex is formed by direct nitrene insertion into the C–H bond. Van der Vlugt and co-workers favor a similar stepwise radical mechanism in which C–H abstraction is the rate-limiting step of the reaction (Figure 2, top right).⁷ In both reported mechanisms the nitrene (radical) moiety is proposed to remain coordinated to the metal center when involved in the C–H bond amination steps. Alternatively, Peters and co-workers reported iron⁹ and ruthenium¹⁰ complexes for which free triplet nitrenes are liberated from the metal of the catalyst, which are consequently involved in free nitrene reactivity (Figure 2, bottom left).
Figure 2: Proposed mechanisms for azide activation involving nitrene radicals.

Recent reviews also emphasized on the prospects of performing selective amination reactions via nitrogen-centered radical chemistry in general.\textsuperscript{11,12} In this perspective, it should be mentioned that metallo-radical cobalt(II) porphyrin catalysts have previously been shown to be active in radical-type aziridination (including enantioselective examples) and intramolecular and intermolecular C–H bond amination reactions (no enantioselective examples reported thus far). These reactions are also believed to proceed via cobalt(III) nitrene-radical intermediates (Co\textsuperscript{III}–N•–Y) (Figure 2, bottom right).\textsuperscript{13-15} However, in all previously reported examples, activated azides such as aryl azides (ArN\textsubscript{3}), phosphoryl azides ((RO)\textsubscript{2}(O)PO-N\textsubscript{3}), sulfonyl azides (RSO\textsubscript{2}N\textsubscript{3}) and carbonazidates (RO(CO)N\textsubscript{3}) were used as the nitrene-precursor.\textsuperscript{16-25} To the best of our knowledge, no examples involving activation of aliphatic azides by cobalt(II) porphyrin catalysts leading to formation of Co\textsuperscript{III}–N•–R intermediates have been reported to date.
By deducing the mechanism of the reaction it will be possible to determine whether enantioselective direct C-H amination reactions are accessible with cobalt porphyrin catalysts. As such, the development of an enantioselective ring closing reaction should be regarded in a much broader prospect, and represents a rare example of (enantio)selective catalytic conversions proceeding via one-electron substrate activation steps mediated by the metallo-radical cobalt(II) catalyst.

In this chapter we combined kinetic analysis, deuterium labeling studies and DFT calculations to determine the mechanism for the intramolecular ring-closing C–H bond amination reaction. Furthermore we used the obtained insights to improve the turnover number of the catalyst and to show, for the first time, the feasibility of enantioselective C-H amination of aliphatic azides with metallo-radical catalysis.

### 6.2 Results and Discussion

The mechanism of the intramolecular ring-closing C–H bond amination reaction was explored experimentally by kinetic analysis of the reaction progress. The conversion of (4-azidobutyl)benzene substrate 1 into tert-butyl 2-phenylpyrrolidine-1-carboxylate product 4 was monitored by 1H-NMR using [Co(TMP)] catalyst 3 (1.6 mol%) in the presence of 1.2 equivalents of Boc2O (Figure 3).

![Figure 3: Kinetic analysis of intramolecular C-H amination of (4-azidobutyl)benzene with [Co(TMP)] catalyst 3.](image-url)
Initially we evaluated the order of the substrate by plotting the logarithmic substrate concentration ($\ln[\text{substrate}]$) versus time (Figure 4). No substrate saturation effects were detected over a broad concentration range of azide 1. The reaction revealed clean first order kinetics in the substrate concentration. The reaction was monitored at different concentrations of the catalyst to reveal also a first order in catalyst concentration (Figure 5). The observed reaction rate was, however, independent of the concentration of Boc$_2$O (Figure 6).

![Figure 4: ln[A]$_t$-ln[A]$_0$ plots from kinetic experiments following the decrease of the substrate concentration ([A]$_t$) in time using different [Co(TMP)] catalyst 3 loadings.](image)

![Figure 5: Reaction rate $k_{\text{obs}}$ as a function of catalyst concentration (with $k_{\text{obs}} = k[3]$).](image)
This translates into the following empirical rate equation, with second order rate constant $k = 12 \text{ M}^{-1}\text{ h}^{-1}$:

$$\text{Rate} = -\frac{d[\text{substrate}]}{dt} = k[\text{substrate}] [\text{catalyst}]$$

These results are in agreement with a rate-limiting azide activation step of the substrate to form the intermediate nitrene radical complex. To exclude the alternative possibility of a rate limiting C–H bond activation step we performed an inter- and intramolecular kinetic isotope competition experiments using the bis-deuterated ($d_2$-1) and mono-deuterated ($d_1$-1) analogues of (4-azidobutyl)benzene substrate 1, respectively (see Scheme 1).

In the intermolecular competition experiment (Scheme 1, 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.$^{26}$ The intramolecular kinetic isotope competition experiment (Scheme 1, 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 2). The rather large intramolecular KIE suggests that some tunneling contribution to the C–H activation step (see computational mechanistic studies in Section 6.3), as can be expected for a radical-type hydrogen atom transfer (HAT) process.$^{27,28,29}$ Hence, the kinetic data point to a pre-equilibrium involving weak and reversible binding of azide 1 to [Co(TMP)] catalyst 3, followed by rate limiting substrate activation involving dinitrogen loss from the coordinated azide.
Scheme 1: Intermolecular kinetic isotope competition experiment between non-deuterated (4-azidobutyl)benzene substrate 1 and its bis-deuterated analogue $d_2$-1 (top) and intramolecular kinetic isotope competition experiment using mono-deuterated substrate $d_1$-1 (bottom).

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 2). The reaction rate was further evaluated at various temperatures (80-115 °C) to obtain the activation parameters from the Arrhenius and Eyring equations.

**Arrhenius plot**

In order to determine the experimental activation energy ($E_a$) the reaction was monitored at 353K, 363K, 373K, 383K and 388K. The obtained data from the various experiments are depicted in Table 1 and graphically represented in Figure 7.
Table 1: Experimental rate constants (k) at varying temperatures.

<table>
<thead>
<tr>
<th>Temperature (K)</th>
<th>k_{obs} (h^{-1})</th>
<th>[substrate] (M)</th>
<th>[catalyst] (M)</th>
<th>k (M^{-1} h^{-1})</th>
<th>1/T (K^{-1})</th>
<th>Ln(k/T)</th>
<th>Ln(k)</th>
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<td>353</td>
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<td>0.00238</td>
<td>3.611</td>
<td>0.002833</td>
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<td>1.2842</td>
</tr>
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<td>0.00214</td>
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<tr>
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<td>0.00214</td>
<td>13.766</td>
<td>0.002681</td>
<td>-3.299</td>
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</tr>
<tr>
<td>383</td>
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<td>0.1449</td>
<td>0.00214</td>
<td>27.205</td>
<td>0.002611</td>
<td>-2.644</td>
<td>3.3034</td>
</tr>
<tr>
<td>388</td>
<td>0.0678</td>
<td>0.1266</td>
<td>0.00214</td>
<td>31.638</td>
<td>0.002577</td>
<td>-2.506</td>
<td>3.4543</td>
</tr>
</tbody>
</table>

Using the equation:

\[ \ln(k) = \frac{-E_{a}^{\ddagger}}{RT} + \ln(A) \]

With \( k \) as the rate constant, \( E_{a}^{\ddagger} \) as the activation energy (J), \( R \) the universal gas constant (8.314 J K^{-1} mol^{-1}), \( T \) the temperature (K) and \( A \) the pre-exponential factor. The pre-
exponential term corrects for the amount of collisions with the appropriate energy to lead to a reaction. \( ^{30} \)

From Figure 7, \( -E_{a}^{\ddagger}/R \) can be obtained as the slope and \( \ln(A) \) as the intercept with the y-
axis resulting in an activation energy of \( E_{a}^{\ddagger} = +78.3 \pm 9.7 \text{ kJ mol}^{-1} = +18.7 \pm 2.3 \text{ kcal mol}^{-1}. \)
Eyring plot

The Eyring equation strictly only holds for single step reactions, and multistep reactions are most reliably analyzed with the Arrhenius equation. However, substrate binding and subsequent azide activation can be approached as a one-step rate limiting process in evaluation of the activation parameters, as such the $\Delta H^\ddagger$, $\Delta S^\ddagger$ and $\Delta G^\ddagger$ values determined from an Eyring plot (using the rates shown in Table 1) still provide useful information about the transition state relative to the resting state.

![Figure 8: Eyring plot of rate constants versus temperature.](image)

Using the equation:

$$\ln(k/T) = -\Delta H^\ddagger/RT + \ln(k'/h) + \Delta S^\ddagger/R$$

With $k$ as the rate constant, $T$ the temperature (K), $\Delta H^\ddagger$ the enthalpy of activation (J mol$^{-1}$), $R$ as the universal gas constant (8.314 J K$^{-1}$ mol$^{-1}$), $k'$ the Boltzmann constant (1.380 x 10$^{-23}$ J K$^{-1}$), $h$ is the Planck constant (6.63 x 10$^{-34}$ J s) and $\Delta S^\ddagger$ the entropy of activation (J mol$^{-1}$ K$^{-1}$).

From Figure 8, $-\Delta H^\ddagger/R$ can be obtained as the slope and $\ln(k'/h) + \Delta S^\ddagger/R$ as the intercept with the y-axis to yield $\Delta H^\ddagger = 75.2 \pm 9.7$ kJ mol$^{-1} = +18.0 \pm 2.3$ kcal mol$^{-1}$ and $\Delta S^\ddagger = -92.1 \pm 26.1$ J mol$^{-1}$ K$^{-1} = -22.0 \pm 6.2$ cal mol$^{-1}$ K$^{-1}$. At the applied reaction temperature of 373K these data lead to the Gibbs energy of activation of $\Delta G^{\ddagger,373K} = \Delta H^\ddagger - T\Delta S^\ddagger = +109.6 \pm 26.1$ kJ mol$^{-1} = +26.2 \pm 4.6$ kcal mol$^{-1}$. 
The rather large negative activation entropy (−22.0 ± 6.2 cal mol⁻¹ K⁻¹) points to an ordered, associative transition state, suggestive of an uphill substrate binding event preceding rate limiting azide activation (see the proposed mechanism in Scheme 2).

Because product inhibition was observed in the reaction without Boc₂O (see Chapter 5) we determined the association constant for 2-phenylpyrrolidine (5) binding to the [Co(TMP)] catalyst 3 with UV-Vis spectroscopy (Figure 9). By fitting the data of both wavelengths simultaneously, the equilibrium constant for the formation of five-coordinate complex [Co(TMP)(5)] from [Co(TMP)] and 5 at room temperature, was found to be $K_1 = 1.3 \times 10^3$ M⁻¹, while binding of a second molecule 5 to [Co(TMP)(5)] to form six-coordinate complex [Co(TMP)(5)₂] has a very low equilibrium constant of $K_2 = 8.1 \times 10^1$ M⁻¹ (Figure 10 and Figure 11). The fitting of both wavelengths was achieved with a low $R^2$ value (0.998 and 0.996 for 528 nm and 590 nm respectively).

![Figure 9: UV-vis titration for 2-phenylpyrrolidine (6a) to [Co(TMP)] catalyst 3.](image-url)
Chapter 6

Figure 10: Experimental and calculated absorption decrease at 528 nm with $K_1=1303 \ M^{-1}$, $K_2=81 \ M^{-1}$.

Figure 11: Experimental and calculated absorption increase at 590 nm with $K_1=1303 \ M^{-1}$, $K_2=81 \ M^{-1}$.

We were unable to determine the binding constant for (4-azidobutyl)benzene 1 coordination to 3 because the equilibrium is shifted towards the starting materials. This has previously also been observed for aromatic azide substrates.\textsuperscript{28}
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)(6a)] 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 Boc$_2$O (see Scheme 2).

Scheme 2: Proposed mechanism for [Co(por)] catalyzed intramolecular C–H bond amination ring-closing reaction of 1 to 4 and the corresponding DFT computed energies (BP86, def2-TZVP, disp3).$^a$

6.3 Computational mechanistic studies

The mechanism was further explored computationally (DFT, BP86, def2-TZVP, disp3), using a simplified model of the catalyst without substituents at the porphyrin ring (Scheme 2). Based on the kinetic studies described above, we anticipated that the initial steps of the mechanism involve coordination of the aliphatic azide 1 to cobalt(II), followed by dinitrogen loss to produce a nitrene-radical intermediate.
Similar rate limiting azide activation has also been proposed in the mechanisms for [Co(por)]-catalyzed aziridination and C–H bond amination reactions using *activated azides* (carbonazidates [ROC(O)N$_3$] or sulfonyl azides [RSO$_2$N$_3$]).$^{16-25}$ This indeed is a plausible pathway according to the DFT calculations (Scheme 2). 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, in good agreement with the experimental kinetic studies (vide supra). The energy profile as calculated by DFT (373K) for the rate limiting step is depicted in Figure 12.

![Figure 12: DFT calculated energy profile for the rate limiting azide activation step.](image)

A spin density plot of five-coordinate species C (Figure 13) 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 2).$^{13-15}$ 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 2) than along the six-coordinate pathway with an additional molecule of product 5 bound to cobalt as an axial ligand ($\Delta G^\ddagger = +28.5$ kcal mol$^{-1}$; L = 5 in Scheme 2). This is in agreement with the experimentally observed inhibiting effect of the unprotected amine product 5 on the reaction rates of catalytic reactions performed in absence of Boc$_2$O (see Chapter 5).
Figure 13: Spin density plot of intermediate C present in Scheme 2.

The computed activation parameters for TS1 ($\Delta G^\ddagger = +24.5$ kcal mol$^{-1}$, $\Delta H^\ddagger = +16.3$ kcal mol$^{-1}$, $\Delta S^\ddagger = -21.9$ cal mol$^{-1}$ K$^{-1}$) 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 $\Delta S^\ddagger = -22.0 \pm 6.2$ cal mol$^{-1}$ K$^{-1}$).

Hydrogen atom transfer (HAT) from the benzylic 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 (+8.5 and +1.9 kcal mol$^{-1}$ respectively). From the relative barriers of hydrogen and deuterium abstraction in the HAT step a KIE = 3.4 was calculated. Such calculations neglect any tunneling effects, as they take only differences in zero point energy (ZPE) into account, resulting from isotope exchange in the vibrational analysis. While 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 tunneling contribution to the C–H bond splitting process, as can be expected for a radical-type HAT process.\textsuperscript{27,28} In good agreement with the experimental data, dissociation of amine product 5 from cobalt(II) species E is endergonic, resulting in product inhibition (i.e. slower reactions) in absence of Boc$_2$O. 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, due to the extremely low computed barrier for the radical rebound step (<2 kcal mol$^{-1}$) this pathway is unlikely.
6.4 Additional experiments based on the mechanistic insights.

The mechanistic information gathered above called for some additional experimental studies. First of all, binding of unprotected product 5 to the catalyst is substantial, but the magnitude of the experimentally determined binding constant ($K_f = 1303 \text{ M}^{-1}$) at room temperature suggests that the activation barrier of the rate limiting azide activation step in absence of Boc$_2$O is raised to a limited extend. As such, we argued that it should be possible to obtain the unprotected cyclic amine 5 by conversion of substrate 1 in the absence of Boc$_2$O at elevated temperature. Indeed, full conversion of substrate 1 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 5 was indeed formed, albeit in a low yield (19%, TON = 5). Several undesired and unidentified side products could be observed in $^1$H-NMR under these non-optimized reaction conditions (see Figure 14).

![Figure 14: Mixture of products obtained in absence of Boc$_2$O, signals marked with * correspond to the desired product.](image)

The catalytic reactions (and kinetic studies) performed in the presence of Boc$_2$O allowed clean conversion of azide 1 to the Boc-protected cyclic amine 5 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 under these low temperature conditions. 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 2).
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 4 in 58% yield (TON = 59) after 16 h. The yield further increased to 73% (TON = 76) after a prolonged reaction time of 72 h. These are the highest TONs for the cyclization of substrate 1 reported to date.

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

In the proposed reaction mechanism shown in Scheme 2 the substrate remains coordinated to the cobalt center throughout the catalytic cycle. This should allow for enantioselective reactions when using a chiral cobalt porphyrin catalyst. We therefore performed the ring-closing C–H bond amination reaction of substrate 1 with a new chiral cobalt porphyrin catalyst equipped with four (1S)-(−)-camphanic-ester substituents (6, Figure 15).

![Figure 15: Structure of (1S)-(−)-camphanic acid based chiral catalyst 6 (4 mol%) used in the enantioselective ring-closing C–H bond amination reaction of substrate 1.](image)

The chiral catalyst 6 produces product 4 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 increased to 46% (enantiomeric ratio 27:73) by lowering the reaction temperature to 80 °C, although at the expense of the 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 15).\textsuperscript{31,34} Perhaps most importantly, the result clearly shows that the reaction does not proceed via formation of free nitrenes in a metal-free C–H bond activation pathway. This is an important observation, as in some Fe and Ru catalyzed nitrene transfer reactions, formation of free nitrenes (reacting outside the coordination sphere of the metal in an uncontrolled manner) has been observed.\textsuperscript{9,10} 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.

### 6.5 Conclusions

A cobalt catalyzed ring-closing C–H amination protocol was developed for the synthesis of a variety of saturated N-heterocycles in synthetically useful yields. 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 this type of reactions. The use of di-tert-butyl dicarbonate (Boc\textsubscript{2}O) 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 benzylic 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 (intermolecular KIE = 1). Enantioselective ring-closing amination proved possible when using a new chiral cobalt porphyrin catalyst equipped with four (1S)(−)−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.\textsuperscript{23} The observed chirality transfer holds important additional mechanistic information, showing unambiguously 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. Therefore, the hypothetical involvement of free nitrenes in these reactions can be excluded.
6.6 Experimental section

6.6.1 General information

All reactions involving air- or moisture sensitive compounds were carried out under nitrogen using standard Schlenk and vacuum line techniques. Toluene was distilled over sodium prior to use. All chemicals not listed below were purchased from Alfa Aesar, Acros, Fluka Strem and Aldrich without purification prior to use. $^1$H-NMR and $^{13}$C-NMR spectra were measured on a Bruker Avance-II 300 MHz, Bruker Avance-I 400 MHz, Bruker DRX 300 or a Bruker 500 MHz spectrometer. $^1$H-NMR chemical shifts are given in ppm, and were calibrated by using the residual non-deuterated solvent as internal reference (CHCl$_3$ (7.26 ppm)). $^{13}$C-NMR chemical shifts were recorded in ppm from the solvent peak employed as internal reference (CDCl$_3$ (77.0 ppm)). IR spectra were measured on a Bruker Alpha-P instrument as neat film. UV-Vis spectra were measured on a Hewlett Packard 8453. High resolution mass spectra were recorded on a HRMS JEOL AccuTOF GCv4g JMS-T 100 GCV and HRMS AccuTOF LCplus JMS-T 100 LP. Chiral GC analysis was performed on a Finigan Focus GC with CP-Chirasil-dex CB column.

CAUTION: Azides are potentially explosive and should be handled with care! Although under the conditions and scale described here we did not encounter any problems, appropriate precautions should be taken when handling these compounds in general. All reactions were performed open to the nitrogen Schlenk line with an overpressure valve to avoid pressure build up or were performed behind a blast shield (high temperature reactions).

Tetrakis(2,4,6-trimethylphenyl)porphyrin,$^{35}$ (4-azidobutyl)benzene (I)$^5$ and (4-azido-1-deuterobutyl)benzene ($d_1$-I)$^7$ were prepared according to published procedures.

6.6.2 General intramolecular C–H bond amination procedure

To a dry Schlenk flask was added catalyst (12 µmol), substrate (0.30 mmol) and di-tert-butyldicarbonate (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 (SiO$_2$, DCM/hexanes/TEA 50:50:1).
6.6.3 Synthesis of catalysts described in this study

Synthesis of Cobalt(II) tetra(2,4,6-trimethylphenyl)porphyrin ([Co(TMP)], 3)

Tetra(2,4,6-trimethylphenyl)porphyrin (180 mg; 0.23 mmol) and anhydrous cobalt(II) chloride (0.20 g; 1.54 mmol) were dissolved in acetic acid (25 mL). After addition of sodium acetate (0.30 g; 3.64 mmol) the mixture was heated to reflux temperature. After 3 h of reaction the mixture was cooled to room temperature and solvent was removed under reduced pressure. The purple solid was washed with a saturated aqueous solution of sodium bicarbonate (50 mL) and water (2 x 50 mL). The product was collected with DCM (50 mL) and dried over magnesium sulfate. After filtration and removal of the solvent the product was obtained as a purple powder (71.6 mg, 85 µmol, 38%). Analysis was in agreement with previously reported data.36

Synthesis of 5,15-bis(2,6-dimethoxyphenyl)-10,20-dimesitylporphyrin (7)

5-Mesityldipyrromethane (0.54 g; 1.89 mmol) and 2,6-dimethoxybenzaldehyde (0.31 g, 1.89 mmol) were dissolved in CHCl₃ (500 mL) and degassed with N₂ for 20 minutes. BF₃OEt₂ (0.12 mL, 0.14 g, 0.97 mmol) was added dropwise and the black mixture was stirred for 30 minutes. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (0.65 g, 2.86 mmol) was added and the mixture was stirred for one hour. Triethylamine (2.0 mL) was added, the mixture was filtered over silica and concentrated. The crude product was purified by column chromatography (SiO₂, CHCl₃) to yield the desired product 7 as a purple solid (0.25g, 0.30 mmol, 32%). ¹H NMR: (400 MHz, CDCl₃): 8.68 (d, J = 4.7 Hz, 4H), 8.58 (d, J = 4.7 Hz, 4H), 7.71 (t, J = 8.4 Hz, 2H), 7.24 (s, 4H), 7.00 (d, J=8.5 Hz, 4H), 3.51 (s, 12H), 2.61 (s, 6H), 1.86 (s, 12H), -2.48 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): 160.8, 139.7, 138.9, 137.5, 130.2, 127.7, 120.2, 117.0, 111.4, 104.5, 56.3, 21.9, 21.6 (not all quaternary carbons were fully resolved). UV-Vis (λ_max, nm) 419 (Soret), 514, 547, 591, 644 (Q-bands). CSI-ESI-MS; calculated (C₅₄H₅₁N₄O₄): 819.3910, experimental mass (m/z): 819.3949 [M+H]⁺.
Synthesis of 5,15-bis(2,6-dihydroxyphenyl)-10,20-dimesitylporphyrin (8)

To a stirred solution of 5,15-bis(2,6-dimethoxyphenyl)-10,20-
dimesitylporphyrin 7 (0.12 g, 0.15 mmol) in dry DCM (10 mL) under nitrogen was added dropwise boron tribromide (0.10 mL, 0.9 mmol). After 19 hours, the mixture was quenched with MeOH (5.0 mL) and transferred into a separatory funnel with EtOAc (50 mL). The mixture was washed with saturated aqueous sodium bicarbonate solution (2x 50 mL) and brine (50 mL). The organic layer was dried over MgSO₄, filtered and the solvents were removed under reduced pressure (40 °C) to yield the product 8 as a purple solid (0.11g, 0.15 mmol, quantitative). ^1H NMR (300 MHz, CDCl₃): 8.91 (d, J = 4.8 Hz, 4H), 8.78 (d, J = 4.8 Hz, 4H), 7.64 (t, J = 8.2 Hz, 2H), 7.29 (s, 4H), 6.99 (d, J = 8.3 Hz, 4H), 4.68 (s, 4H), 2.63 (s, 6H), 1.82 (s, 12H), -2.62 (bs, 2H). ^13C NMR (300 MHz, CDCl₃): 136.3, 139.4, 138.4, 137.5, 131.4, 128.1, 119.9, 115.4, 108.1, 105.0, 21.9, 21.6. (not all quaternary carbons were fully resolved).

UV-Vis (λ_max, nm) 418 (Soret), 513, 546, 588, 642 (Q-band). CSI-ESI-MS; calculated (C₅₀H₄₃N₄O₄): 763.3284, experimental mass: 763.3306 [M+H]^+.

Synthesis of (1S)-(-)-camphanic-ester substituted porphyrin (9)

A mixture of 5,15-bis(2,6-dihydroxyphenyl)-10,20-
dimesitylporphyrin 8 (50 mg; 66 µmol) and
(1S)-(-)-camphanic chloride (83 mg; 396 mmol; 6 eq) was was placed under nitrogen and dissolved in dry THF (3.0 mL). Triethylamine (0.1 mL) was added and the mixture was stirred for 68 hours at room temperature. The mixture was transferred into a separatory funnel with DCM (20 mL) and washed with saturated aqueous sodium bicarbonate solution (3x 20 mL). The organic layer was dried over MgSO₄, filtered and solvents were removed under reduced pressure. The crude product was washed with MeOH until a colorless filtrate was obtained and dried under vacuum to yield the product 9 as a purple solid (50 mg, 34 µmol, 51 %). ^1H NMR (300 MHz, CDCl₃): 8.77 (d, J = 4.6 Hz, 4H), 8.66 (d, J = 4.8Hz, 4H), 7.95 (t, J = 8.3 Hz, 2H), 7.53 (d, J = 8.3 Hz, 4H), 7.26 (s, 4H), 2.62 (s, 6H), 1.73 (s, 12H), 1.30-1.16 (m, 4H), 1.08-0.94 (m, 4H), 0.94-0.77 (m, 8H), 0.12 (s, 12H), -1.03 (s, 12H), -1.61 (bs, 12H), -2.84 (bs, 2H). ^13C NMR (75 MHz, CDCl₃): 176.6, 165.5,151.6, 138.8, 138.3, 137.7, 130.7, 128.8, 128.1, 121.0, 119.1, 107.3, 89.9, 53.9, 52.8, 29.9, 28.0, 21.6, 21.5, 14.6, 13.9, 9.1, 1.2 UV-Vis (λ_max, nm): 415 (Soret band), 510, 541, 586, 640 (Q-bands). CSI-ESI-MS; calculated (C₉₀H₉₁N₄O₁₆): 1483.6430, found (m/z) 1483.6428 [M+H]^+. 
Synthesis of cobalt(II)-5,15-bis(2,6-dihydroxyphenyl)-10,20-dimesitylporphyrin (10)

To a pressure tube was added under nitrogen 5,15-bis(2,6-dihydroxyphenyl)-10,20-dimesitylporphyrin 8 (30.0 mg, 39.3 µmol), anhydrous CoCl$_2$ (52 mg, 0.40 mmol, 10 equivalents) and 2,6-lutidine (10 µL, 9.3 mg, 86 µmol). The mixture was dissolved in dry THF (2.0 mL) and the solution was heated to 70 °C behind a blast shield. After 16 hours of reaction the mixture was cooled to room temperature, transferred into a separatory funnel with EtOAc (20 mL) and washed with water (3x 20 mL). The organic layer was dried over MgSO$_4$, filtered and solvents removed under reduced pressure (40 °C) to yield the product 10 as a dark red solid (40 mg, 49 µmol, 92%). UV-Vis ($\lambda_{\text{max}}$, nm): 410 (Soret), 526, 554 (Q-band). CSI-ESI-MS; calculated: 819.2382 (C$_{50}$H$_{40}$CoN$_4$O$_4$), found (m/z) 819.2364 [M$^+$].

Synthesis of (1S)-(−)-camphanic-ester substituted cobalt(II)-porphyrin (6)

To a dried Schlenk flask was added (subsequently, under dinitrogen) cobalt(II)-5,15-bis(2,6-dihydroxyphenyl)-10,20-dimesitylporphyrin 10 (40 mg, 48.8 µmol), (1S)-(−)-camphanic chloride (65 mg, 0.30 mmol) and triethylamine (0.1 mL, 71.6 µmol). The mixture was dissolved in dry THF (3.0 mL) and stirred for 64 hours at room temperature. The mixture was transferred in a separatory funnel with DCM (20 mL) and washed with a saturated aqueous sodium bicarbonate solution (3 x 20 mL). The organic layer was dried over MgSO$_4$, filtered and solvents removed under reduced pressure to yield the product 6 as a dark red solid (46 mg, 30 µmol, 61%). UV-Vis ($\lambda_{\text{max}}$, nm): 406 (Soret) 523, 553 (Q-band). CSI-ESI-MS; calculated (C$_{90}$H$_{88}$CoN$_4$O$_{16}$): 1539.5527, found 1539.5483 [M$^+$], calculated (C$_{90}$H$_{88}$CoN$_4$NaO$_{16}$): 1563.544, experimental mass (m/z): 1563.546 [M+Na$^+$].

Synthesis of 4-azido-1,1-bisdeutero-1-phenylbutane ($D_2$-1)

The regioselective benzylic deuteration was performed based on a modified literature procedure. A mixture of (4-bromobutyl)benzene (0.53 g, 2.5 mmol) and Pd/C (10 wt%, 0.33 g, 60 mol%) in CD$_3$OD (5 mL) was placed under nitrogen and equipped with a deuterium balloon. After 20h of reaction the mixture was filtered over celite and the product diluted with diethyl ether (20 mL).
Mechanistic Investigation of the Intramolecular Ring-Closing C–H Amination

The solution was washed with water (20 mL) and a saturated aqueous solution of sodium bicarbonate (2 x 20 mL). The organic fraction was dried over magnesium sulfate filtered and solvent removed to yield 4-bromo-1,1-bisdeutero-1-phenylbutane 11 as a colorless oil (0.40 g, 1.85 mmol, 74%) which was used in the next step without additional purification. $^1$H-NMR (300 MHz, CDCl$_3$): 7.34-7.13 (m, 5H), 3.42 (t, J= 6.6 Hz, 2H), 1.97-1.68 (m, 4H). $^2$H-NMR (300 MHz, CDCl$_3$): 2.61. $^{13}$C-NMR (75.5 MHz, CDCl$_3$): 141.9, 128.5, 126.0, 33.8, 32.3, 29.8. IR (neat, cm$^{-1}$): 3059, 3023, 2960, 2929, 2862, 2194, 1495, 1447, 1253, 733, 698. FD-MS; Experimental mass (m/z): 214.032, 216.031, calculated mass (C$_{10}$H$_{11}$BrD$_2$): 214.033, 216.031.

The obtained 4-bromo-1,1-bisdeutero-1-phenylbutane (11, 0.35 g, 1.6 mmol) was dissolved in DMF (10 mL) and sodium azide (0.30 g, 4.6 mmol) was added to the stirred solution. After heating at 80 °C for 16 hours the mixture was cooled to room temperature and water (20 mL) was added. The product was extracted with diethyl ether (20 mL) and the organic fraction was washed with water (5x30 mL), dried over MgSO$_4$, filtered and solvent removed to yield the desired product as a colorless oil (0.26 g, 1.46 mmol, 90%). $^1$H-NMR (300 MHz, CDCl$_3$): 7.40-7.21 (m, 5H), 3.35 (t, J=6.5 Hz, 2H), 1.83-1.62 (m, 4H). $^2$H-NMR (300 MHz, CDCl$_3$): 2.67 (s). $^{13}$C-NMR (75.5 MHz, CDCl$_3$): 141.9, 128.5, 128.5, 126.1, 51.5, 28.5, 28.4. IR (neat, cm$^{-1}$): 3025, 2931, 2863, 2088 (N$_3$), 1495, 1448, 1258, 734, 698. GC-EI; Experimental mass (m/z): 148.1078, calculated mass: 148.1080 [C$_{10}$H$_{13}$N, M-N$_2$+H]$^+$

6.6.4 Kinetic studies

To a dried NMR pressure tube was added (4-azidobutyl)benzene (11.5 mg, 65.6 µmol) and Boc$_2$O (18.2 mg, 83.4 µmol, 1.3 equivalents). The tube was placed under nitrogen and [Co(TMP)] catalyst 3 was added (1.8 mol% (0.9 mg, 1.1 µmol), 3.2 mol% (1.8 mg, 2.1 µmol), or 6.5 mol% (3.6 mg, 4.3 µmol). After addition of toluene-$d_8$ (0.5 mL) and triphenylmethane (4.7 mg, 19.2 µmol) as internal standard the NMR tube was closed and heated in the NMR spectrometer at 100 °C. A $^1$H-NMR spectrum was recorded every 10 minutes and the amount of substrate and product with respect to the standard was determined (Figure 3). Following the decrease of the substrate concentration ([A]$_t$) in time using different catalyst loadings and plotting the data as ln[A]$_t$-ln[A]$_0$ versus time plot reveal linear regression lines with R$^2$ values >0.99 showing first order kinetics in the [substrate] (Figure 4). The rate also increases linearly with the catalyst concentration (or loading), thus showing first order kinetics in [catalyst 3] (Figure 5). Following the decrease of the substrate concentration ([A]$_t$) in time using different amounts of Boc$_2$O and plotting the observed rate K$_{obs}$ (h$^{-1}$) versus the concentration of Boc$_2$O (Figure 6) shows zero order kinetics in [Boc$_2$O].
6.6.5 Isotopic labeling studies

Intermolecular kinetic isotope effect

\[
\begin{align*}
\text{H} & \text{H} & \text{N}_3 \\
\text{Ph} & \text{H} & \text{N}_3 \\
\text{D} & \text{D} & \text{N}_3 \\
\text{Ph} & \text{H} & \text{N}_3 \\
\text{Co(TMP)} & (1 \text{ mol\%}) & \text{tol, 100 °C} \\
\text{16h, N}_2 & \\
\end{align*}
\]

A mixture of (4-azidobutyl)benzene 1 (27.2 mg, 0.155 mmol) and 4-azido-1,1-bisdeutero-1-phenylbutane (31.7 mg, 0.179 mmol) was analyzed by \(^1\text{H-NMR (CDCl}_3, \text{Figure 16)}\) to show a \(\text{H}_2\) to \(\text{D}_2\) ratio of 1.00:1.00. The mixture was transferred quantitatively to a Schlenk flask and solvent was removed. The mixture was placed under nitrogen and Boc\(_2\)O (108.0 mg, 0.495 mmol, 1.5 equiv.) and [Co(TMP)] catalyst 3 (2.8 mg, 3.3µmol, 1.0 mol%) were added followed by dry toluene (3.0 mL). The mixture was heated to 100 °C for 16h and the crude product purified by column chromatography (SiO\(_2\), Hexanes/DCM/TEA; 50/50/1) to yield a light yellow oil (12.5 mg, 51µmol, 15%). The \(k_{\text{H}}/k_{\text{D}}\) ratio was determined from the ratio of the methylene and methine protons at the 2- and 4-position in the \(^1\text{H-NMR spectrum}.\) The reaction was performed in duplo resulting in a \(k_{\text{H}}/k_{\text{D}}\) ratio of 0.99, which corresponds to a KIE of 1 within the error-limits of NMR integrations. In Figure 17 a representative \(^1\text{H-NMR spectrum is shown.}\)

![Figure 16](image-url)

Figure 16: \(^1\text{H-NMR spectrum of the ratio of starting materials for the intermolecular kinetic isotope effect.}\)
Mechanistic Investigation of the Intramolecular Ring-Closing C–H Amination

Figure 17: Representative $^1$H-NMR spectrum of the product mixture after flash column chromatography.

**Intramolecular kinetic isotope effect**

(4-azido-1-deuterobutyl)benzene (8.2 mg, 47 µmol), Boc$_2$O (12.9 mg, 59 µmol, 1.26 equiv.), [Co(TMP)] catalyst 3 (0.9 mg, 1.1µmol, 2.3 mol%) and dry toluene (0.5 mL) were handled according to the general procedure. The $k_{HH}/k_{HD}$ ratio was determined from the ratio of the methylene and methine protons at the 2- and 4-position in the $^1$H-NMR spectrum. The reaction was performed in duplo resulting in a $k_{HH}/k_{HD}$ ratio of 7.0 which corresponds to a KIE of 7. In Figure 18 a representative $^1$H-NMR spectrum is shown.

Figure 18: Representative $^1$H-NMR spectrum of the product mixture after flash column chromatography.
6.6.6  Determination of the binding constant for 2-phenylpyrrolidine (5).

A stock solution [Co(TMP)] catalyst 3 (2.51 mg, 2.99 µmol) in dry toluene (25 mL) was prepared and diluted to obtain a concentration of 23.9 µM. 2-phenylpyrrolidine (5, 57.8 mg, 0.393 mmol) was dissolved in the catalyst stock solution (1.0 mL) to obtain the titration stock solution. Under nitrogen the stock solution of the guest (5) was titrated to the host solution (3) at 298K and the changes in absorption was monitored at 528 nm and 590 nm. The titration scheme is reported in Table 2 and the UV-vis spectra are shown in Figure 9.

Table 2: Titration data for binding of 2-phenylpyrrolidine (5) to [Co(TMP)] catalyst 3.

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<th>Absorption (590 nm)</th>
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6.6.7 Computational details

The mechanism of the [Co(por)] catalyzed intramolecular C–H amination ring-closing reaction of 1 to 4 was explored computationally, using DFT. A simplified model porphyrin without meso-substituents was used to reduce computation time. Geometry optimizations were carried out with the Turbomole program package\textsuperscript{38} coupled to the PQS Baker optimizer\textsuperscript{39} via the BOpt package.\textsuperscript{40} We used unrestricted ri-DFT-D3 calculations at the BP86 level,\textsuperscript{41,42} in combination with the def2-TZVP basis set,\textsuperscript{43,44} and a small (m4) grid size. Grimme’s dispersion corrections\textsuperscript{45} (version 3, disp3, ‘zero damping’) were used to include Van der Waals interactions. All minima (no imaginary frequencies) and transition states (one imaginary frequency) were characterized by calculating the Hessian matrix. ZPE and gas-phase thermal corrections (entropy and enthalpy, 298 K, 1 bar) from these analyses were calculated. The nature of the transition states was confirmed by following the intrinsic reaction coordinate. The relative free energies ($\Delta G^\circ_{298K}$ in kcal mol$^{-1}$) obtained from these calculations are reported in Scheme 2.

DFT calculations without dispersion corrections strongly underestimate the metal-ligand interactions, as was clear from a series of test calculations. We therefore employed Grimme’s version 3 (disp3) dispersion corrections. Used as such, the computed dispersion corrected metal-ligand association/dissociation energies to/from the non-solvated [Co(por)] catalyst A are overestimated. This is due to neglected dispersion interactions between the metal binding site of the catalyst and a solvent molecule in solution. We therefore used the Van der Waals $\pi$-complex between [Co(por)] catalyst A and a discrete toluene solvent molecule (interacting with the catalyst at the metal binding site) as the energetic reference point in our calculations to prevent overestimation of the metal-ligand interactions as a result of such uncompensated dispersion forces. However, this approach also leads to an erroneous cancelation of all translational entropy contributions to the computed free energies. This is because the translational entropy contributions to substrate/product association/dissociation are fully counterbalanced by the translational entropy contributions resulting from dissociation/association of the involved solvent molecule in the DFT calculated thermodynamics ($\text{A-solv} + \text{L} \rightleftharpoons \text{A-L} + \text{solv}$). This is not realistic in comparison to actual solution phase chemistry, for which the translational entropy contributions associated with substrate/product association/dissociation steps can of course not be neglected. In solution the catalyst is completely surrounded by solvent molecules, leading to small translational entropy contributions to the toluene molecule association/dissociation steps. These are of little influence on the translational entropy contributions associated with substrate/product association/dissociation. Hence, the latter are not canceled by the former in toluene solution. Therefore we applied a translational entropy contribution of 20 cal mol$^{-1}$ K$^{-1}$ to the computed free energies of all substrate/product binding/dissociation steps in the catalytic cycle. This leads to realistic metal-ligand binding entropies comparable to those reported for related systems in toluene.\textsuperscript{46}
6.6.8 Enantioselective intramolecular ring-closing C–H amination

(4-azidobutyl)benzene 1 (30.0 mg, 0.171 mmol), di-tert-butyldicarbonate (45.0 mg, 0.206 mmol, 1.2 equivalents), chiral porphyrin cobalt catalyst 6 (10.5 mg, 6.8 µmol, 4.0 mol%) and dry toluene (3.0 mL) were handled according to the general procedure (see main text) at 80 °C to yield the desired product 4 as a light yellow oil (9.4 mg, 38.0 µmol, 22%, TON = 6). The enantiomeric ratio was analyzed by chiral GC to yield the two enantiomers in a ratio of 73:27 (enantiomeric excess = 46%). The chromatogram is shown in Figure 15. The signals were compared with a racemic sample of the product to verify the retention time of the two enantiomers.

6.7 Acknowledgements

Ed Zuidinga is acknowledged for mass analysis of the obtained compounds. Financial support from NWO-CW (VICI project 016.122.613), the ERC (Starting Grants 202886 & 279097) and the University of Amsterdam (RPA Sustainable Chemistry) is gratefully acknowledged. Willem Breukelaar is acknowledged for the synthesis and catalytic investigation of catalyst 6.
6.8 References

\[38\] TURBOMOLE Version 6.5 (TURBOMOLE GmbH, Karlsruhe, Germany, 2013).