Controlling radical-type reactivity with transition metals and supramolecular cages

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Chapter 5:

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. Pyrrolidines, oxazolidines imidazolidines, isoindolines and tetrahydroisoquinoline can be obtained in good to excellent yields in a single reaction step with commercially available catalysts. The use of di-tert-butyl dicarbonate (Boc₂O) significantly enhances the reaction rate by preventing competitive binding of the formed amine product through trapping of the heterocycles as their Boc-protected analogues. The highest turnover numbers reported to date for the intramolecular C-H amination of (4-azidobutyl)benzene could be obtained with cobalt(II) tetrakis(mesityl)porphyrin [Co(TMP)] as catalyst. Furthermore the catalyst is bench stable and tolerates significant amounts of water during the reaction.

5.1 Introduction

Saturated heterocycles are important substructures in many natural products and pharmaceuticals.¹ ² For the synthesis of this important class of compounds the ring structure is usually introduced already at the start of the synthetic procedure. Subsequent functionalization of the core structure typically requires harsh conditions or exchange of functional groups, which is often accompanied by multistep synthesis routes and the generation of large amounts of waste. Currently, only a limited number of direct cyclization reactions to form complex aliphatic amine ring structures from relatively simple linear precursors are available.³ In most cases activating and/or directing groups are required to obtain good selectivity and activity.⁴ The use of a sacrificial oxidant is also often employed to obtain the corresponding N-heterocycles.⁵⁻⁹ A synthetically more attractive approach is to use aryl azides (ArN₃) in C–H amination ring closing protocols to produce unsaturated heterocycles.¹⁰⁻¹⁴ More recently, and most relevant to the investigations described in this chapter, some interesting examples of direct amination of C–H bonds using saturated aliphatic organic azides (RN₃) were reported,¹⁵,¹⁶ leading to formation of saturated heterocycles (see Figure 1).¹⁷⁻²³ A comparable approach was used to prepare cyclic oxazolidinone structures via ring-closing C–H bond amination of the corresponding carbonazidates by the use of enzymes.²⁴ Furthermore a palladium catalyzed reaction has been reported utilizing diazocarbonyl compounds to obtain pyrrolidines.²⁵
While these examples provide interesting lead-reactivity (in particular the system reported by Betley and coworkers\textsuperscript{17}), there are still a number of hurdles to overcome before catalytic intramolecular ring-closing C–H bond amination of aliphatic azides will become a practically useful synthetic method for the preparation of N-heterocyclic compounds (Figure 1): (1) All of the currently reported catalysts for this reaction are highly sensitive to air and water and require quite high catalysts loadings, thus resulting in quite low catalytic turn over numbers (TONs) with associated purification issues and costs. (2) Several of the reported catalysts produce significant amounts of (Boc-protected) linear amines as undesired side products, which also limits practical application of these reactions. (3) Last, but not least, the reported catalysts are not commercially available, which limits the general application of these catalysts.

Figure 1: Comparison of previously reported catalysts and those used in the present study for intramolecular ring-closing C–H bond amination of aliphatic azides.
Recent reviews also emphasized on the prospects of performing selective amination reactions from azide precursors in general.\textsuperscript{26,27} In this perspective, it should be mentioned that 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}) have previously been shown to be precursors for aziridination, intramolecular and intermolecular C–H bond amination reactions.\textsuperscript{28-37} However, to the best of our knowledge, no examples involving activation of \emph{aliphatic azides} by cobalt(II) porphyrin catalysts have been reported to date. Here we report on the cobalt(II) porphyrin catalyzed ring-closing C–H bond amination of aliphatic azides producing a variety of N-heterocyclic products. The catalysts are air and water stable, and cleanly produce cyclic (Boc-protected) amines in good yields and with higher TONs than reported for other catalysts.

\section{5.2 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 5 into tetrt-butyl 2-phenylpyrrolidine-1-carboxylate 6\textsubscript{a} (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). In the presence of high catalyst loadings (20 mol\%), however, stoichiometric amounts
of the product could be observed when Boc₂O was added at room temperature after the reaction. In the presence of di-tert-butyl dicarbonate (Boc₂O) during the reaction, we observed the desired Boc-protected cyclic amine product 6a (tert-butyl 2-phenylpyrrolidine-1-carboxylate) by ¹H-NMR spectroscopy (Figure 3, top). The product was isolated in 17% yield (Table 1, entry 2, turnover number (TON) = 17) after 16 hours of reaction (Figure 3, bottom). The product was obtained as a single product, but appaeared in solution as a mixture of rotamers which interconvert slowly on the NMR timescale. Under these conditions the TONs obtained with [Co(TPP)] catalyst 1 in the conversion of substrate 5 to product 6a are already higher than those for any of the previously reported homogeneous catalysts for this reaction (TONs up to 6).¹⁷-²⁰

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Loading (mol%)</th>
<th>Solvent</th>
<th>Conversion (NMR)</th>
<th>Yield (isolated)</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>1ᵇ</td>
<td>[Co(TPP)]</td>
<td>1</td>
<td>Toluene</td>
<td>&lt;c</td>
<td>&lt;c</td>
<td>n.d. d</td>
</tr>
<tr>
<td>2</td>
<td>[Co(TPP)]</td>
<td>1</td>
<td>Toluene</td>
<td>24%</td>
<td>17%</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>[Co(TPF₂₅P)]</td>
<td>1</td>
<td>Toluene</td>
<td>&lt;5%</td>
<td>n.d. d</td>
<td>n.d. d</td>
</tr>
<tr>
<td>4</td>
<td>[Co(TMPC)]</td>
<td>1</td>
<td>Toluene</td>
<td>38%</td>
<td>36%</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>[Co(TMPC)]</td>
<td>1</td>
<td>Benzene</td>
<td>39%</td>
<td>32%</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>[Co(TMPC)]</td>
<td>1</td>
<td>Toluene e</td>
<td>30%</td>
<td>n.d. d</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>[Co(Salophen)] f</td>
<td>1</td>
<td>Toluene</td>
<td>&lt;c</td>
<td>&lt;c</td>
<td>n.d. d</td>
</tr>
<tr>
<td>8</td>
<td>AIBN</td>
<td>4</td>
<td>Toluene</td>
<td>&lt;c</td>
<td>&lt;c</td>
<td>n.d. d</td>
</tr>
<tr>
<td>9</td>
<td>[Co(TMPC)]</td>
<td>2</td>
<td>Toluene</td>
<td>&gt;95%</td>
<td>89%</td>
<td>21</td>
</tr>
<tr>
<td>10</td>
<td>[Co(TMPC)]</td>
<td>4</td>
<td>Toluene</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 (1.2 equivalents) 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. b) no Boc₂O was used in the reaction. c) No product was detected by ¹H-NMR. d) Not determined. e) 3 vol% water present. f) Salophen = N,N'-bis-(3,5-di-tert-butylsalicylidene)-1,2-phenylenediamine.)
We continued our optimization by changing the catalyst; With cobalt(II) tetrakis(pentafluorophenyl)-porphyrin ([Co(TPF$_{20}$P)] complex 2, Figure 2) as the catalyst only trace amounts of the desired product 6a (<5%) were obtained (Table 1, entry 3). [Co(salophen)] complex 4 (Figure 2) proved to be completely inactive (entry 7). In contrast, marked improvements both in yield and TON were observed using the electron-donating porphyrin tetrakis(2,4,6-trimethylphenyl)-porphyrin complex 3 ([Co(TMP)], Figure 2) as the catalyst. The desired product 6a was obtained in 36% isolated yield using 1 mol% of catalyst (TON = 35; 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 volume percent 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.

Figure 3: Crude $^1$H-NMR spectra of (4-azidobutyl)benzene (5) cyclization with Co(TPP) (1 mol%) and Boc$_2$O (top) and after purification (bottom) to yield tert-butyl 2-phenylpyrrolidine-1-carboxylate (6a).
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 azobisisobutyributrylitrile (AIBN, entry 8). However, using 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 5 is observed after 16 hours, which 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 6a 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.17,19,20

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 bond (Table 2, entry 1, 7a), the oxazolidine product was obtained in high isolated yield (7b, 93%; TON = 23). Introduction of two methyl groups on the aliphatic chain was expected to further improve the efficiency of the cyclization reaction (by virtue of the Thorpe-Ingold effect).39 However, this modification led to a significant decrease in both the yield and TONs for formation of oxazolidine product 8b (Table 2, entry 2). Steric hindrance introduced by the two methyl groups apparently has a larger effect on the reactivity than pre-organization for cyclization when using substrate 8a.

The reaction did however proceed cleanly, as only product 8b and starting material 8a were observed upon analysis of the crude reaction mixture. In this reaction [Co(TPP)] complex 1 produced imidazolidine product 9b 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 equivalents of Boc₂O 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 catalysts 1 and 3 is small for this substrate. When substrate 9a was treated with Boc₂O to yield substrate 10a prior to the cyclization reaction no change in the product yield was observed as compared to the one pot procedure (Table 2, entry 4).
Table 2: Catalytic formation of oxazolidines and imidazolidines.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Isolated Yield</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{R = Me, } 11\text{a} )</td>
<td>(\text{R = Me, } 11\text{b} )</td>
<td>96%</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>(\text{R = Ph, } 12\text{a} )</td>
<td>(\text{R = Ph, } 12\text{b} )</td>
<td>91%</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>(\text{R = F, } 13\text{a} )</td>
<td>(\text{R = F, } 13\text{b} )</td>
<td>84%</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>(\text{R = Cl, } 14\text{a} )</td>
<td>(\text{R = Cl, } 14\text{b} )</td>
<td>87%</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>(\text{R = Br, } 15\text{a} )</td>
<td>(\text{R = Br, } 15\text{b} )</td>
<td>95%</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>(\text{R = OMe, } 16\text{a} )</td>
<td>(\text{R = OMe, } 16\text{b} )</td>
<td>82%</td>
<td>20</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Conditions: Substrate (0.3 mmol), Boc\textsubscript{2}O (1.2 equivalent), [Co(TMP)] (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 equivalents of Boc\textsubscript{2}O were added. In entries 3 and 5-10, full conversion of the starting material was always observed. The only observed side product was the corresponding azide with a Boc-protected secondary nitrogen (compound 10a and compounds 11c to 16c, see Figure 4). c) [Co(TPP)] catalyst 1 was used.
We further decided to investigate 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 9a, the commercially available [Co(TPP)] catalyst 1 was used for substrates 11a-16a. In these cases we also used 2.4 equivalents of Boc2O in the reaction (Table 2, entry 5-10) to prevent product inhibition. Using a 4 mol% catalyst loading, high yields (up to 96%) were obtained for all substrates containing a substituent on the para position of the phenyl ring. The effect of electron-donating and electron-withdrawing substituents is only marginal. At the end of the reaction we always observed full conversion of the starting material for substrates 9a and 11a-16a (even upon reducing the catalyst loading to 2 mol%). The only observed side products in these reactions were the corresponding Boc-protected azides (compound 10a and compounds 11c to 16c, Figure 4), again without formation of any significant amounts of undesired linear (Boc-protected) amines.17,19,20 The corresponding Boc-protected azides 10a and compounds 11c to 16c could also be obtained in good to excellent yield in absence of the catalyst (Figure 4).

![Figure 4: Synthesis of Boc-protected azide side products 11c-16c.](image)

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 arenes 17a-19a to obtain bicyclic isoindoline and tetrahydroisoquinoline derivatives (Scheme 1).
Scheme 1: Application of the [Co(por)]-mediated intramolecular C–H bond amination ring-closing protocol for the synthesis of alternative heterocycles 17b-20b.

The presence of the phenyl ring resulted in a decrease in the selectivity, as isoindoline product 17b was obtained in only 27% yield. However, full conversion of the substrate was obtained to form additionally the protected amine product 17c (35%) and some ill-defined oligomeric/polymeric side products. When the reaction was repeated in absence of Boc₂O the reaction showed full conversion to a mixture of products (Scheme 2).

Scheme 2: C–H bond amination of substrate 17a in absence of Boc₂O to yield a mixture of products.
The characteristic peak at 6.32 ppm of $2H$-isoindole (21) was observed in the $^1$H-NMR spectrum (Figure 5, bottom) and this compound has been reported to readily polymerize. The other two products are likely the corresponding $1H$-isoindole (22) tautomer and 2-methylbenzylamine (23).

![Figure 5: $^1$H-NMR spectra of 1-(azidomethyl)-2-methylbenzene 17a (top) and after reaction with [Co(TMP)] (bottom).](image)

It seems that if the desired ring-closing step requires breaking of a stronger C–H bond (higher 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. Upon replacing the methyl group with an ethyl group (substrate 18a), full conversion was observed after 16 h using 2 mol% of catalyst loading to yield the desired product 18b in 93% isolated yield (TON = 45). Apparently the increased stabilization of the benzylic radical is sufficient to avoid the competitive oligomerization/polymerization reactions observed for substrate 17a. Like for substrate 17a, also for this substrate the peaks at 3.9, 4.9 and 6.3 ppm could be observed upon repeating the reaction of 18a in absence of Boc$_2$O.

A six-membered heterocycle 19b was found to be accessible using substrate 19a, albeit in only 28% yield (TON = 7). As observed for substrate 17a, but in contrast to all other reactions described above, 37% of the corresponding linear Boc-protected amine product 19c and some ill-defined oligomers/polymers were obtained as side products in
this case. Finally, an allylic C–H bond can be activated from substrate \(20a\) to obtain a mixture of the six-membered heterocycle product \(20b\) (38%, TON = 10), starting material (37%), linear product \(20c\) and small amounts of unidentified products. Additional substrates used in the C–H amination protocol, varying in the BDE of the reacting C–H bond, are described in the experimental section (Table 3). The results obtained with these substrates indicate that intermolecular HAT starts to compete with intramolecular HAT if 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 five-membered N-heterocyclic rings without any indication for competing intermolecular HAT reactions (see Table 1 and Table 2).

### 5.3 Conclusions

In summary, 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 than other reported homogeneous catalyst systems based on Fe and Pd for this type of reactions. Di-tert-butyl dicarbonate (Boc\(_2\)O) is used to significantly enhance the reaction rate by preventing competitive binding of the formed amine product. A wide variety of N-heterocycles such as pyrrolidines, oxazolidines imidazolidines, isoindolines and tetrahydroisoquinoline could be obtained in good to excellent yields.

### 5.4 Experimental section

#### 5.4.1 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 before 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 at room temperature unless stated otherwise. \(^1\)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.

CAUTION: Azides are potentially explosive and should be handled with care! Although under the conditions and scale described in this chapter 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, cobalt(II)tetrakis(2,3,4,5,6-tentafluorophenyl)-porphyrin, Cobalt(II) (Salophen) (4), (4-azidobutyl)benzene, (2-azidoethoxy)methyl)-benzene, 2-azido-N-benzylenethanine, 2-azido-N-(4-methoxybenzyl)ethanamine, 2-azidoethyl 4-methylbenzenesulfonylate, 1-(azidomethyl)-2-methylbenzene, 1-(azidomethyl)-2-ethylbenzene, 1-(azidomethyl)-2-ethylbenzene, 1-(2-azidoethyl)-2-methylbenzene, ethyl 5-azidopentanoate, 1-azidohexane, 7-azidohept-1-ene, (6-azidoethyl)benzene, (4-azidobutoxy)-methyl)benzenes, were prepared according to published procedures.

5.4.2 Synthesis of described compounds

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

Tetrakis(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.
Synthesis of 2-(benzyloxy)-2-methylpropyl azide (8a)

To a solution of 2-benzyloxy-2-methylpropanol (23, 250 mg, 1.39 mmol) in DCM (3.0 mL) and pyridine (0.25 mL) at 0 °C was added p-toluenesulfonyl chloride (0.54 g, 2.8 mmol, 2.0 equiv.). After 24 hours of reaction demi-water (10 mL) was added and the products were extracted with DCM (3x20 mL). The combined organic fractions were washed with a saturated aqueous solution of sodium bicarbonate (30 mL) and brine (30 mL). The solution was dried over magnesium sulfate, filtered and solvent removed under reduced pressure. The crude product was purified by column chromatography (SiO₂, cyclohexane/ethyl acetate 10:1, Rf = 0.2) to yield the desired product 24 as a colorless oil (418 mg, 1.25 mmol, 90%). ¹H-NMR (300 MHz, CDCl₃): 7.78 (d, J = 8.3 Hz, 2H), 7.39 – 7.17 (m, 7H), 4.39 (s, 2H), 3.93 (s, 2H), 2.43 (s, 3H), 1.27 (s, 6H). ¹³C-NMR (75.5 MHz, CDCl₃, 60 °C): 144.8, 138.9, 132.8, 129.9, 128.3, 128.0, 127.4, 127.3, 75.0, 74.0, 64.4, 22.7, 21.7. IR (neat, cm⁻¹): 2980, 1357, 1174, 969, 794, 729, 665, 554. FD-MS; Experimental mass (m/z): 334.1197, calculated mass (C₁₈H₂₂O₄S): 334.1239 ([M]+).

A mixture of 2-(benzyloxy)-2-methylpropyl tosylate 24 (411 mg, 1.23 mmol) and sodium azide (160 mg, 2.46 mmol) in DMF (3 mL) was heated to 100 °C for three days. After cooling to room temperature the mixture was poured in water (20 mL) and extracted with diethyl ether (3x25 mL). The combined organic fractions were dried over magnesium sulfate, filtered and solvent removed under reduced pressure. The crude product was purified using column chromatography (SiO₂, cyclohexane/ethyl acetate 10/1) to yield the recovered starting material 21 (Rf = 0.2, 117 mg, 0.34 mmol, 28%) and the product 8a as a light yellow oil (Rf = 0.4, 105 mg, 0.51 mmol, 42%). ¹H-NMR (300 MHz, CDCl₃): 7.49-7.19 (m, 5H), 4.49 (s, 2H), 3.26 (s, 2H), 1.31 (s, 6H); ¹³C-NMR (300 MHz, CDCl₃): 139.0, 128.3, 127.3, 127.3, 75.9, 64.3, 60.0, 23.2. IR (neat, cm⁻¹): 2976, 2926, 2865, 2095 (N₃), 1298, 1160, 1060, 733, 695. FD-MS; Experimental mass (m/z): 204.1133, calculated mass (C₁₁H₁₄N₃O): 204.1137 ([M–H]+).
Synthesis of 2-azido-N-(4-methylbenzyl)ethanamine (11a)

A solution of 4-methylbenzyl amine (0.248 g, 2.05 mmol) and 2-azidoethyl 4-methylbenzenesulfonate (0.202 g, 0.84 mmol) in acetonitrile was stirred at reflux temperature for 20 hours. The crude product was purified by column chromatography (SiO₂, PE 40-60 °C/EtOAc 2:1) to yield the desired product 11a as a colorless oil (0.217 g, 1.14 mmol, 56%).

1H-NMR (400 MHz, CDCl₃): 7.23 (d, J = 8.0 Hz, 2H), 7.13 (d, 7.9 Hz, 2H), 3.81 (s, 2H), 3.45 (t, J = 5.6 Hz, 2H), 2.84 (t, J = 5.7 Hz, 2H), 2.36 (s, 3H), 13C-NMR (100.6 MHz, CDCl₃): 136.7, 136.6, 129.0, 127.9, 53.2, 51.4, 47.8, 21.0. IR (neat, cm⁻¹): 2922, 2828, 2093 (N₃), 1514, 1448, 1287, 1119, 802. FD-MS; Experimental mass (m/z): 190.1221, calculated mass (C₁₀H₁₄N₄): 190.1218 ([M⁺]).

Synthesis of 2-azido-N-(4-phenylbenzyl)ethanamine (12a)

To a solution of 2-azidoethyl 4-methylbenzenesulfonate (0.205 g, 0.850 mmol) in acetonitrile (5.0 mL) was added 4-phenylbenzylamine (0.365 g, 1.99 mmol). The stirred mixture was heated at reflux temperature for 16 hours. After cooling to room temperature solvent was removed at reduced pressure and the crude product was purified by column chromatography (SiO₂, hexane/EtOAc, 2:1, Rf = 0.15) to yield a very dense oil which solidified upon standing to a white solid (116 mg, 0.458 mmol, 54%).

1H-NMR (300 MHz, CDCl₃): 7.64-7.53 (m, 4H), 7.50-7.29 (m, 5H), 3.87 (s, 2H), 3.46 (t, J = 5.6 Hz, 2H), 2.86 (t, J = 5.6 Hz, 2H). 13C-NMR (75.5 MHz, CDCl₃): 141.1, 140.2, 139.1, 128.9, 128.7, 127.4, 127.2, 53.4, 51.6, 48.1. IR (neat, cm⁻¹): 3027, 2924, 2829, 2093 (N₃), 1514, 1448, 1287, 1119, 802. FD-MS; Experimental mass (m/z): 252.1383, calculated mass (C₁₅H₁₆N₄): 252.1375 ([M⁺]).

Synthesis of 2-azido-N-(4-fluorobenzyl)ethanamine (13a)

To a round-bottom flask was added 4-fluorobenzyl amine (0.250 mg, 2.0 mmol) and 2-azidoethyl 4-methylbenzenesulfonate (0.196 mg, 0.81 mmol) and acetonitrile (5.0 mL). The mixture was stirred for 16 hours at reflux temperature. After removal of the solvent the crude product was purified by column chromatography (SiO₂, hexanes/EtOAc 2:1) to yield the desired product 13a as a colorless oil (0.132 mg, 0.68 mmol, 84%).

1H-NMR (300 MHz, CDCl₃): 7.35-7.25 (m, 2H), 7.02 (t, J = 7.0 Hz, 2H), 3.79 (s, 2H), 3.43 (t, J = 5.5 Hz, 2H), 2.81 (t, J = 5.5 Hz, 2H). 13C-NMR (75.5 MHz, CDCl₃): 162.0 (d, J=245 Hz), 135.6, 129.6 (d, J=8 Hz), 115.3 (d, J=21 Hz), 52.9, 51.5, 47.9. 19F-NMR (282.4 MHz, CDCl₃): 115.8. IR (neat, cm⁻¹): 2928, 2835, 2093 (N₃), 1603, 1508, 1218, 823. FD-MS; Experimental mass (m/z): 194.0959, calculated mass (C₉H₁₁FN₄): 194.0968 ([M⁺]).
Synthesis of 2-azido-N-(4-chlorobenzyl)ethanamine (14a)

To a solution of 2-azidoethyl 4-methylbenzenesulfonate (0.194 g, 0.83 mmol) in acetonitrile (5 mL) was added 4-chlorobenzylamine (2.6 mL, 2.0 mmol, 2.4 equivalents) and the mixture was heated to reflux temperature. After 16 h of reaction a white precipitate had formed and the mixture was cooled to room temperature. After removal of the solvent under reduced pressure the product was purified by column chromatography (SiO$_2$, hexanes/ethyl acetate 2/1, Rf = 0.3) to yield the desired product 14a as a light yellow oil (0.149 g, 0.71 mmol, 85%). $^1$H-NMR (300 MHz, CDCl$_3$): 7.35-7.22 (m, 4H), 3.79 (s, 2H), 3.43 (t, $J$ = 5.8 Hz, 2H), 2.80 (t, $J$ = 5.8 Hz, 2H). $^{13}$C-NMR (75.5 MHz, CDCl$_3$): 138.4, 132.8, 129.4, 128.6, 52.9, 51.4, 47.9. IR (neat, cm$^{-1}$): 2925, 2832, 2091 (N$_3$), 1490, 1284, 1088, 1014, 802. FD-MS; Experimental mass (m/z): 210.0630, calculated mass (C$_9$H$_{11}$ClN$_4$): 210.0672 ([M]+).

Synthesis of 2-azido-N-(4-bromobenzyl)ethanamine (15a)

To a solution of 4-bromobenzyl amine (400 mg, 2.15 mmol) in acetonitrile (5.0 mL) was added 2-azidoethyl 4-methylbenzenesulfonate (206 mg, 0.85 mmol) and the mixture was stirred at reflux temperature for 16 hours. After removal of the solvent the mixture was redissolved in ethyl acetate (20 mL) and washed with aqueous sodium hydroxide (2M, 3x20 mL). The crude product was purified by column chromatography (SiO$_2$, hexane/EtOAc 4:1 $\rightarrow$ EtOAc gradient) to yield the desired product 15a as a colorless oil (156 mg, 0.61 mmol, 72%). $^1$H-NMR (300 MHz, CDCl$_3$): 7.45 (d, $J$=8.4 Hz, 2H), 7.21 (d, $J$ = 8.3 Hz, 2H), 3.77 (s, 2H), 3.43 (t, $J$ = 5.8 Hz, 2H), 2.80 (t, $J$ = 5 Hz, 2H). $^{13}$C-NMR (75.5 MHz, CDCl$_3$): 138.9, 131.6, 129.8, 120.9, 52.9, 51.4, 47.9. IR (neat, cm$^{-1}$): 2923, 2830, 2092 (N$_3$), 1486, 1285,1262, 1070, 1010, 798. FD-MS; Experimental mass (m/z): 254.0166, calculated mass (C$_9$H$_{11}$BrN$_4$): 254.0167 ([M]+).

General intramolecular C–H bond amination procedure

To a dry Schlenk flask was added catalyst (12 µmol), substrate (0.30 mmol) and di-tert-butyl dicarbonate (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).
Cobalt Porphyrin Catalyzed Intramolecular C–H Amination of Aliphatic Azides

Synthesis of tert-butyl 2-phenylpyrrolidine-1-carboxylate (6a)

(4-azidobutyl)benzene 5 (50.5 mg, 0.288 mmol), di-tert-butyl dicarbonate (65.1 mg, 0.298 mmol, 1.04 equivalents), [Co(TMP)] catalyst 3 (10.2 mg, 12.1 µmol, 4.2 mol%) and toluene (3.0 mL) were handled according to the general procedure to yield the desired product 6a as a light yellow oil (63.6 mg, 0.257 mmol, 89%, TON=21). Analysis data were in agreement to previously published data.17

Stoichiometric synthesis of 2-phenylpyrrolidine (6a)

(4-azidobutyl)benzene 5 (15.2 mg, 0.087 mmol), [Co(TMP)] catalyst 3 (14.6 mg, 17 µmol, 20 mol%) and toluene (3.0 mL) were heated to 100 °C under N₂ for 16 h. The reaction mixture was cooled to room temperature and Boc₂O (20.2 mg, 93 µmol) was added. After 1 h the mixture was analyzed by ¹H-NMR spectroscopy with mesitylene (4.3 mg, 36 µmol) as standard to yield 2-phenylpyrrolidine 6b (15 µmol, 17%).

Synthesis of tert-butyl 2-phenyloxazolidine-3-carboxylate (7b)

2-(benzylxy)ethyl azide (58.2 mg, 0.329 mmol), di-tert-butyl dicarbonate (89.5 mg, 0.410 mmol, 1.25 equivalents), [Co(TMP)] catalyst 3 (11.2 mg, 13.3 µmol, 4.1 mol%) and toluene (3.0 mL) were handled according to the general procedure to yield the desired product 7b as a light yellow oil (76.1 mg, 0.305 mmol, 93%). ¹H-NMR (300 MHz, CDCl₃, 60 °C): 7.50–7.25 (m, 5H), 6.03 (bs, 1H), 4.15–3.95 (m, 2H), 3.90–3.75 (m, 1H), 3.63–3.47 (m, 1H), 1.37 (bs, 9H). ¹³C-NMR (75.5 MHz, CDCl₃, 60 °C): 153.2, 139.9, 128.4, 128.1, 126.6, 89.3, 80.3, 65.6, 45.0, 28.2. IR (neat, cm⁻¹): 2975, 2887, 1697, 1391, 1364, 1161, 1129, 1060, 902, 754, 697. FD-MS; Experimental mass (m/z): 249.1361, calculated mass (C₁₄H₁₉NO₃): 249.1365 ([M⁺]).

Synthesis of tert-Butyl 2-phenyloxazolidine-3-carboxylate (8b)

To a flame dried Schlenk flask 2-benzyloxy-2-methyl-1-propyl azide (49.2 mg, 0.24 mmol), Boc₂O (66.8 mg, 0.31 mmol, 1.3 equivalents) and dry toluene (2.0 mL) were added under a nitrogen atmosphere. After addition of [Co(TMP)] catalyst 3 (8.2 mg, 9.8 µmol, 4.1 mol%) The stirred reaction mixture was heated at 100 °C for 16 h under a nitrogen atmosphere. The solvent was removed under reduced pressure and the crude product was purified using column chromatography (SiO₂, hexane:DCM:Et₃N; 50:50:1) to yield the product 8b as a yellow oil (21.4 mg, 77 µmol, 32%, TON=8). ¹H-NMR (CDCl₃, 300MHz, RT) 7.50–7.26 (m, 5H), 6.06 (bs, 0.28H rotamer) 5.88 (bs, 0.72 rotamer), 3.74 (bs, 1H), 3.31 (bs, 1H), 1.43 (s, 3H), 1.33 (s, 3H), 1.23 (bs, 9H); ¹H-NMR (CDCl₃, 300MHz, 60 °C) 7.45–7.25 (m, 5H), 5.97 (s, 1H), 3.75 (d, J=10.1 Hz, 1H), 3.28 (d, J=10.2 Hz, 1H), 1.43 (s, 3H), 1.34 (s, 3H), 1.33 (bs, 9H);
$^{13}$C-NMR (CDCl$_3$, 75MHz) 153.5, 140.8, 128.6, 128.3, 127.1, 88.9, 80.5, 79.9, 56.5, 28.5, 26.1, 25.0; IR (neat, cm$^{-1}$): 2975, 2932, 2882, 1697, 1364, 1149, 1027, 902, 753, 696; FD-MS; Experimental mass (m/z): 277.1662, calculated mass (C$_{16}$H$_{23}$NO$_3$): 277.1678 ([M]$^+$).

**Synthesis of di-tert-butyl 2-phenylimidazolidine-1,3-dicarboxylate (9b)**

2-azido-N-benzylethanamine (27.0 mg, 0.15 mmol), di-tert-butyldicarbonate (87.5 mg, 0.40 mmol, 2.6 equivalents), [Co(TMP)] catalyst 3 (5.0 mg, 6.0 µmol, 3.9 mol%) and toluene (1.0 mL) were handled according to the general procedure to yield the desired product as a light red oil (36.6 mg, 0.105 mmol, 69%). $^1$H-NMR (300 MHz, CDCl$_3$, 60 ºC): 7.43-7.24 (m, 5H), 6.15 (bs, 1H), 3.95-3.77 (m, 2H), 3.77-3.61 (m, 2H), 1.38 bs (18H). $^{13}$C-NMR (75.5 MHz, CDCl$_3$, 60 ºC): 152.9, 141.4, 128.0, 127.8, 126.6, 80.5, 72.6, 43.7, 28.2. IR (neat, cm$^{-1}$): 2975, 2931, 2894, 1692, 1365, 1160, 1106, 860, 697. FD-MS; Experimental mass (m/z): 348.2050, calculated mass (C$_{19}$H$_{28}$N$_2$O$_4$): 348.2049 ([M]$^+$).

**Synthesis of di-tert-butyl 2-phenylimidazolidine-1,3-dicarboxylate (10b)**

A solution of tert-butyl (2-azidoethyl)(benzyl)carbamate 10a (27.8 mg, 0.101 mmol) in toluene (1.0 mL) was degassed for 15 minutes by bubbling nitrogen through the solution. Boc$_2$O (29.7 mg, 0.136 mmol, 1.3 equivalents) and [Co(TMP)] catalyst 3 (3.5 mg, 4.2 µmol, 4.1 mol%) were added and the mixture was heated to 100 ºC under nitrogen. After 16 hours of reaction the mixture was cooled to room temperature and purified by flash chromatography to yield the product 10b (23.6 mg, 67.8 µmol, 67%, TON = 16). Analysis data was in agreement with 9b.

**Synthesis of di-tert-butyl 2-(p-tolyl)imidazolidine-1,3-dicarboxylate (11b)**

2-azido-N-(4-methylbenzyl)ethanamine 11a (51.3 mg, 0.27 mmol), Boc$_2$O (137.7 mg, 0.63 mmol, 2.4 equivalents), [Co(TPP)] catalyst 1 (7.2 mg, 10.5 µmol, 4.0 mol%) and toluene (3.0 mL) were handled according to the general procedure described to yield the desired product 11b as a dark orange oil (96.9 mg, 0.26 mmol, 96%, TON =24). $^1$H-NMR (300 MHz, CDCl$_3$): 7.23 (bs, 2H), 7.12 (d, J=7.8 Hz, 2H), 6.17 (rotamer bs, 0.65H), 5.92 (rotamer, bs 0.35H), 3.50-3.95 (m, 4H), 2.33 (s, 3H), 1.33 (bs, 9H). $^{13}$C-NMR (75.5 MHz, CDCl$_3$, 60 ºC): 152.9, 138.4, 137.5, 128.7, 126.5, 80.4, 72.3, 43.6, 28.3, 21.0. IR (neat, cm$^{-1}$): 2976, 2930, 1692, 1365, 1160, 1105, 731. FD-MS; Experimental mass (m/z): 362.2188, calculated mass (C$_{20}$H$_{30}$N$_2$O$_4$): 362.2206 ([M]$^+$).
Synthesis of di-tert-butyl 2-[(1,1′-biphenyl)-4-yl]imidazolidine-1,3-dicarboxylate (12b)

2-azido-N-(4-phenylbenzyl)ethanamine 12a (44.1 mg, 0.175 mmol), Boc₂O (91.5 mg, 2.4 equivalents), [Co(TMP)] catalyst 3 (6.0 mg, 7.1 µmol, 4.1 mol%) and dry toluene (1.7 mL) were handled according to the general procedure to yield the desired product 12b as an off-white solid (67.6 mg, 0.159 mmol, 91%, TON = 22). ¹H-NMR (500 MHz, CDCl₃, 60 °C): 7.59 (d, \( J = 7.5 \mathrm{Hz} \), 2H), 7.56 (d, \( J = 8.1 \mathrm{Hz} \), 2H), 7.46-7.39 (m, 4H), 7.33 (t, \( J = 7.4 \mathrm{Hz} \), 1H), 6.19 (bs, 1H), 3.92-3.81 (m, 2H), 3.74-3.65 (m, 2H), 1.39 (bs, 18H).

¹³C-NMR (125.7 MHz, CDCl₃, 60 °C): 152.9, 140.9, 140.9, 140.4, 128.7, 127.2, 127.1, 127.0, 126.8, 80.6, 72.4, 43.7, 28.3. IR (neat, cm⁻¹): 2975, 2931, 2894, 1691, 1365, 1160, 1107, 763, 733. FD-MS; Experimental mass (m/z): 424.2342, calculated mass (C₂₅H₃₂N₂O₄): 424.2362 ([M⁺]).

Synthesis of di-tert-butyl 2-(4-fluorophenyl)imidazolidine-1,3-dicarboxylate (13b)

2-azido-N-(4-fluorobenzyl)ethanamine 13a (53.4 mg, 0.27 mmol), di-tert-butyl dicarbonate (146.3 mg, 0.66 mmol, 2.4 equivalents), [Co(TPP)] catalyst 1 (7.5 mg, 10.9 µmol, 4.0 mol%) and dry toluene (3.0 mL) were handled according to the general procedure to yield the desired product 13b as a dark yellow oil (82.8 mg, 0.23 mmol, 84%, TON =21). ¹H-NMR (300 MHz, CDCl₃): 7.42-7.23 (bs, 2H), 7.00 (t, \( J = 8.7 \mathrm{Hz} \), 2H), 6.12 (bs, 0.67H, rotamer), 5.90 (bs, 0.33H, rotamer), 3.90-3.75 (m, 2H), 3.75-3.56 (m, 2H), 1.32 (bs, 18H). ¹³C-NMR (75.5 MHz, CDCl₃, 60 °C): 162.7 (d, \( J = 246 \mathrm{Hz} \)), 153.0, 137.6, 128.6 (d, \( J =8.2\mathrm{Hz} \)), 115.1 (d, \( J = 21.5 \mathrm{Hz} \)), 80.9, 72.2, 43.9, 28.5. ¹⁹F-NMR (282.4 MHz, CDCl₃): 114.2, 114.4. IR (neat, cm⁻¹): 2977, 2932, 2893, 1691, 1365, 1160, 1107, 766, 733. FD-MS; Experimental mass (m/z): 366.1949, calculated mass (C₁₉H₂₇FN₂O₄): 366.1955 ([M⁺]).

Synthesis of di-tert-butyl 2-(4-chlorophenyl)imidazolidine-1,3-dicarboxylate (14b)

2-azido-N-(4-chlorobenzyl)ethanamine 14a (65.3 mg, 0.310 mmol), di-tert-butyl dicarbonate (158.7 mg, 0.744 mmol, 2.4 equivalents), [Co(TPP)] catalyst 1 (8.3 mg, 12.4 µmol, 4.0 mol%) and toluene (3.0 mL) were handled according to the general procedure to yield the desired product as a light yellow oil (103.1 mg, 0.269 mmol, 87%, TON = 22). ¹H-NMR (300 MHz, CDCl₃): 7.49-7.10 (m, 4H), 6.12 (bs, 0.63H rotamer), 5.90 (bs, 0.37H rotamer), 3.83 (bs, 2H), 3.67 (bs, 2H), 1.32 (bs, 18H). ¹³C-NMR (75.5 MHz, CDCl₃): 152.8, 139.9, 133.8, 128.3, 128.1, 80.9, 71.9, 43.7, 28.3. IR (neat, cm⁻¹): 2977, 2932, 2893, 1691, 1365, 1159, 1107, 912, 730. FD-MS; Experimental mass (m/z): 382.1642, calculated mass (C₁₉H₂₇ClN₂O₄): 382.1659 ([M⁺]).
Synthesis of di-tert-buty1 2-(4-bromophenyl)imidazolidine-1,3-dicarboxylate (15b)

2-azido-N-(4-bromobenzyl)ethanamine 15a (73.8 mg, 0.29 mmol), [Co(TPP)] catalyst 1 (7.8 mg, 11.6 mmol, 4.0 mol%), di-tert-butyldicarbonate (171.3 mg, 0.79 mmol, 2.7 equivalents) and degassed toluene (3.0 mL) were handled according to the general procedure to yield the desired product 15b as a yellowish oil (118 mg, 0.276 mmol, 95%, TON=24). 1H-NMR (300 MHz, CDCl₃, 60 °C): 7.45 (d, J=8.0 Hz, 2H), 7.25 (d, J=8.0 Hz, 2H), 6.06 (s, 1H), 3.90-3.75 (m, 2H), 3.73-3.56 (m, 2H), 1.37 (s, 18H). 13C-NMR (75.5 MHz, CDCl₃, 60 °C): 153.0, 140.7, 131.4, 131.4, 128.6, 122.1, 81.0, 72.2, 43.9, 28.5. IR (neat, cm⁻¹): 2977, 2932, 2894, 1691, 1366, 1159, 1108, 729. FD-MS; Experimental mass (m/z): 426.1175, calculated mass (C₁₉H₂₇BrN₂O₄): 426.1154 ([M]+).

Synthesis of di-tert-buty1 2-(4-methoxyphenyl)imidazolidine-1,3-dicarboxylate (16b)

2-azido-N-(4-methoxybenzyl)ethanamine 16a (26.9 mg, 0.130 mmol), di-tert-butyldicarbonate (72.0 mg, 0.330 mmol, 2.5 equivalents) [Co(TPP)] catalyst 1 (3.6 mg, 5.4 µmol, 4.1 mol%) and dry toluene (2.5 mL) were handled according to the general procedure to yield the desired product 16b as a dark yellow oil (40.1 mg, 0.106 mmol, 82%, TON=20). The product still contained minor amounts of the Boc-protected starting material 16c. 1H-NMR (300 MHz, CDCl₃): 7.35-7.10 (m, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.14 (s, 0.62H, rotamer), 5.89 (s, 0.38H, rotamer), 3.88-3.54 (m, 4H), 3.79 (s, 3H), 1.33 (bs, 18H). 13C-NMR (75.5 MHz, CDCl₃, 60 °C): 159.6, 153.1, 128.0, 114.3, 113.7, 80.6, 72.4, 55.4, 43.8, 28.5. IR (neat, cm⁻¹): 2975, 2932, 2894, 1691, 1365, 1243, 1162, 1031, 761, 731. FD-MS; Experimental mass (m/z): 378.2157, calculated mass (C₂₀H₃₀N₂O₅): 378.2155 ([M]+).

Synthesis of tert-buty1 (2-azidoethyl)(benzyl)carbamate (10a)

To a solution of 2-azido-N-benzylethanamine (92.1 mg; 0.5 mmol) in toluene (2 mL) was added di-tert-butyl dicarbonate (222 mg, 1.0 mmol). Upon addition gas evolution was observed and the progress of the reaction was monitored by TLC (SiO₂; EtOAc). After 30 minutes the crude product was placed on a small silica column and washed extensively with hexane to remove all excess di-tert-butyl dicarbonate. The product 10a was collected with EtOAc to yield a light yellow oil (76.8 mg, 0.28 mmol, 56%). 1H-NMR (300 MHz, CDCl₃): 7.38-7.24 (m, 5H), 4.52 (s, 2H), 3.50-3.26 (m, 4H), 1.48 (s, 9H). 13C-NMR (75.5 MHz, CDCl₃, 60 °C): 155.5, 138.1, 128.5, 127.4, 127.3, 80.3, 51.4, 49.8, 46.1, 28.4. IR (neat, cm⁻¹): 2976, 2930, 2096 (N₃), 1689, 1408, 1365, 1243, 1162, 1126, 699. FD-MS; Experimental mass (m/z): 276.15855, calculated mass (C₁₄H₂₀N₄O₂): 276.1586 ([M]+).
Synthesis of tert-butyl (2-azidoethyl)(4-methylbenzyl)carbamate (11c)

To a solution of 2-azido-N-(4-methylbenzyl)ethanamine 11a (34.5 mg, 0.181 mmol) in toluene (1.0 mL) was added Boc₂O (89.2 mg, 0.409 mmol) and the mixture was stirred for 16 hours. The crude product was purified by column chromatography (SiO₂; PE40-60/MeOH 19:1 → DCM/MeOH 19:1 gradient) to yield the desired product 11c as light yellow oil (19.8 mg, 68.2 µmol, 38% yield).

1H-NMR (300 MHz, CDCl₃): 7.13 (bs, 4H), 4.46 (s, 2H), 3.45-3.20 (m, 4H), 2.34 (s, 3H), 1.48 (bs, 9H). 13C-NMR (75.5 MHz, CDCl₃, 60 °C): 155.5, 137.0, 135.0, 129.2, 127.5, 80.3, 49.7, 45.9, 28.4, 20.94. One of the carbons resulted in a very broad signal around δ = 52 which was not clearly resolved. IR (neat, cm⁻¹): 2976, 2929, 2097 (N₃), 1690 (C=O), 1405, 1366, 1245, 1162, 1126, 773. FD-MS; Experimental mass (m/z): 290.1740, calculated mass (C₁₅H₂₂N₄O₂): 290.1743 ([M]+).

Synthesis of tert-butyl (2-azidoethyl)(4-methoxybenzyl)carbamate (12c)

To a vial were added 2-azido-N-(4-phenylbenzyl)ethanamine 12a (7.3 mg, 28.9 µmol) toluene (1.0 mL) and Boc₂O (10.4 mg, 47.7 µmol). The mixture was stirred at room temperature for 1h after which full conversion was observed by TLC. The product was purified by gradient column chromatography (SiO₂, hexanes → hexanes/MeOH 19:1 → DCM/MeOH 19:1) to yield the desired product 12c as a white solid (8.4 mg, 23.8 µmol, 82%).

1H-NMR (500 MHz, CDCl₃, 60 °C): 7.58 (t, J= 8.0 Hz, 4H), 7.43 (dd, J=8.4, 7.0 Hz, 2H), 7.34 (t, J=7.4 Hz, 1H), 7.31 (d, J=8.0 Hz, 2H), 4.55 (s, 2H), 3.41 (s, 4H), 1.51 (s, 9H). 13C-NMR (126 MHz, CDCl₃, 60 °C): 155.8, 141.1, 140.7, 137.4, 128.9, 128.1, 127.6, 127.5, 127.2, 80.7, 51.5, 50.1, 46.4, 28.6. IR (neat, cm⁻¹): 2975, 2930, 2097 (N₃), 1688 (C=O), 1404, 1365, 1163, 1129, 759, 698. FD-MS; Experimental mass (m/z): 352.1898, calculated mass (C₂₀H₂₄N₄O₂): 352.1899 ([M]+).

Synthesis of tert-butyl (2-azidoethyl)(4-fluorobenzyl)carbamate (13c)

To a solution of Boc₂O (11.6 mg, 53.1 µmol) in toluene (1.0 mL) was added 2-azido-N-(4-fluorobenzyl)ethanamine 13a (9.6 mg, 49.4 µmol) and the mixture was stirred for 1h. Additional Boc₂O (8.0 mg, 36.6 mg) was added and after 3h the mixture was purified by column chromatography (SiO₂, toluene/MeOH 20:0 → 19:1) to obtain the product 13c as a colorless oil (6.6 mg, 22.4 µmol, 45%).

1H-NMR (500 MHz, CDCl₃, 60 °C): 7.21 (dd, J=8.5, 5.5 Hz, 2H), 7.02 (t, J = 8.7 Hz, 2H), 4.47 (s, 2H), 3.36 (bs, 4H), 1.49 (s, 9H). 13C-NMR (126 MHz, CDCl₃, 60 °C): 162.51 (d, J = 246 Hz), 155.7, 134.2, 129.3, 115.7 (d, 21.4 Hz), 80.8, 51.1, 50.1, 46.4, 28.6. IR (neat, cm⁻¹): 2977, 2931, 2097 (N₃), 1688 (C=O), 1458, 1406, 1220, 1155, 1095, 815. FD-MS; Experimental mass (m/z): 294.1496, calculated mass (C₁₄H₁₉FN₂O₂): 294.1492 ([M]+).
Synthesis of tert-butyl (2-azidoethyl)(4-chlorobenzyl)carbamate (14c)

To a solution of 2-azido-N-(4-chlorobenzyl)ethanamine 14a (23.7 mg, 0.113 mmol) in toluene was added di-tert-butyl dicarbonate (25.8 mg, 0.118 mmol, 1.05 equivalents). After 1 h of reaction solvent was removed under reduced pressure to obtain the desired product 14c as light yellow oil (containing still 5% of Boc₂O which can be removed by the work-up described for 10a). ¹H-NMR (300 MHz, CDCl₃, 60 °C): 7.30 (d, J = 7.9 Hz, 2H), 7.17 (d, J = 7.9 Hz, 2H), 4.47 (s, 2H), 3.36 (bs, 4H), 1.48 (s, 9H). ¹³C-NMR (75.5 MHz, CDCl₃, 60 °C): 155.6, 136.9, 133.5, 129.0, 129.0, 80.8, 51.1, 50.1, 46.5, 28.6. IR (neat, cm⁻¹): 2977, 2932, 2098 (N₃), 1692 (C=O), 1403, 1164, 1129, 798. FD-MS; Experimental mass (m/z): 310.1224, calculated mass (C₁₄H₁₉ClN₄O₂): 310.1197 ([M]+).

Synthesis of tert-butyl (2-azidoethyl)(4-bromobenzyl)carbamate (15c)

To a vial was added 2-azido-N-(4-bromobenzyl)ethanamine 15a (13.3 mg, 52.1 µmol), Boc₂O (22.7 mg, 0.104 mmol) and toluene (1.0 mL). After 16 h of reaction the crude product was purified by column chromatography (SiO₂, PE40-60 → PE40-60/MeOH 19:1 → DCM/MeOH 19:1) to yield the desired product 15c as a colorless oil (17.1 mg, 48.1 µmol, 92%). ¹H-NMR (300 MHz, CDCl₃): 7.46 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 4.45 (s, 2H), 3.36 (bs, 4H), 1.48 (s, 9H). ¹³C-NMR (75.5 MHz, CDCl₃, 60 °C): 155.4, 137.2, 131.7, 129.1, 121.2, 80.6, 51.1, 49.9, 46.3, 28.3. IR (neat, cm⁻¹): 2976, 2930, 2096 (N₃), 1688 (C=O), 1400, 1366, 1161, 1128, 1011, 824. FD-MS; Experimental mass (m/z): 354.0694, calculated mass (C₁₄H₁₉BrN₄O₂): 354.0691 ([M]+).

Synthesis of tert-butyl (2-azidoethyl)(4-methoxybenzyl)carbamate (16c)

To a solution of 2-azido-N-(4-methoxybenzyl)ethanamine 16a (13.1 mg, 63.5 µmol) in toluene (1.0 mL) was added di-tert-butyl dicarbonate (25.0 mg, 0.115 mmol) and the mixture was stirred at room temperature for 16 hours. The crude product was purified by column chromatography (SiO₂, hexanes → hexanes/MeOH 19:1 → DCM/MeOH 19:1) to yield the product 16c as a colorless oil (14.0 mg, 45.7 µmol, 72%). ¹H-NMR (500 MHz, CDCl₃, 60 °C): 7.16 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.44 (s, 2H), 3.80 (s, 3H), 3.34 (bs, 4H), 1.50 (s, 9H). ¹³C-NMR (126 MHz, CDCl₃, 60 °C): 159.4, 155.7, 130.5, 129.1, 114.4, 80.5, 55.5, 51.1, 50.0, 46.1, 28.6. IR (neat, cm⁻¹): 2975, 2933, 2097 (N₃), 1688 (C=O), 1512, 1407, 1243, 1161, 1126, 1034. FD-MS; Experimental mass (m/z): 306.1704, calculated mass (C₁₅H₂₂N₄O₃): 306.1692 ([M]+).
Synthesis of tert-butyl isoindoline-2-carboxylate (17c)

1-(azidomethyl)-2-methylbenzene 17a (45.4 mg, 0.308 mmol), Boc₂O (80.3 mg, 0.368 mmol, 1.2 equivalents), dry toluene (3.0 mL) and [Co(TMP)] catalyst 3 (10.1 mg, 12.0 µmol, 3.9 mol%) were handled according to the general procedure to yield a mixture of tert-butyl isoindoline-2-carboxylate 17b (27%, TON= 7) and tert-butyl 2-methylbenzylcarbamate 17c (35%). The mass balance is incomplete due to the formation of oligomeric/polymeric material under the applied reaction conditions. In the absence of Boc₂O the reaction still leads to full conversion however the expected isoindolene product was not observed. The characteristic peak at 6.32 ppm of 2H-isoinilene was however observed (Figure 5) which is known to readily polymerize.⁴⁰

Synthesis of 2-tert-Butoxycarbonyl-1,3-dihydro-1-methylisoindole (18b)

To a dry Schlenk flask was added under nitrogen 1-(azidomethyl)-2-ethylbenzene (32.0 mg, 0.199 mmol), di-tert-butyldicarbonate (51.6 mg, 0.236 mmol, 1.19 equivalents) and [Co(TMP)] catalyst 3 (3.2 mg, 3.8 µmol, 1.9 mol%). After addition of dry toluene (1.0 mL) the mixture was heated to 100 °C under nitrogen. After 16 h of reaction the mixture was poured over a silica plug and eluted with DCM containing 1 vol% triethylamine. The mixture was purified by flash column chromatography (SiO₂, DCM:TEA 99:1) to yield the product as a light yellow oil (43.6 mg, 0.187 mmol, 94%, TON=49). Analysis data was in agreement to previously reported spectra.⁵²

Synthesis of tert-butyl 3,4-dihydroisoquinoline-2-carboxylate (19b)

1-(2-azidoethyl)-2-methylbenzene 19a (53.4 mg, 0.331 mmol), di-tert-butyldicarbonate (92.0 mg, 0.422 mmol, 1.3 equivalents), [Co(TMP)] catalyst 3 (11.4 mg, 13.6 µmol, 4.1 mol%) and dry toluene (3.0 mL) were handled according to the general procedure to yield a mixture of tert-butyl 3,4-dihydroisoquinoline-2-carboxylate (19b, 28%, TON = 7)⁵³ and tert-butyl 2-methylphenethylcarbamate (19c, 37%).⁵⁴ As previously described for substrate 17a when the reaction was performed in absence of Boc₂O full conversion was observed however no products could be identified suggesting oligomer/polymer formation is a competing reaction for this cyclization.
Synthesis of tert-butyl 2-phenylpiperidine-1-carboxylate (20b)

7-azidohept-1-ene (43.9 mg, 0.315 mmol), di-tert-butyldicarbonate (73.7 mg, 0.338 mmol, 1.1 equivalents), [Co(TMP)] catalyst 3 (9.7 mg, 11.5 µmol, 3.7 mol%) and dry tolene (3.0 mL) were handled according to the general procedure to yield a mixture of tert-butyl 2-phenylpiperidine-1-carboxylate (20b, 38%, TON = 10) tert-butyl hept-6-ene-1-ylcarbamate (20c, 12%), starting material (20a, 37%) and some unidentified decomposition products. The product 20b could be isolated by column chromatography (38%). Analysis was in agreement to previously reported data.55

Additional substrates used in the intramolecular C–H amination protocol.

In order to guide scientists for the application of the described C–H amination reaction we examined several additional substrates containing less activated (or unactivated) C–H bonds (Table 3). Upon replacement of the phenyl ring with an ester the C–H bond dissociation energy (BDE) increases significantly (85 and 96 kcal mol-1, respectively). Using the substrate listed in entry 1 leads to formation of several unidentified side products in addition to the desired ring closing reaction. In a stoichiometric reaction it is possible to convert hexylazide. However, with this substrate a 1:1 mixture of tert-butyl hexylcarbamate and hexane-nitrile was obtained.

The high BDE of the unactivated C–H bonds at the delta postion apparently prevents ring-closure and the more reactive alpha C–H bond of the azide substrate reacts instead (entry 2). This likely involves an intermolecular HAT between the nitrene radical intermediate and an additional azide substrate molecule. Such pathways would also explain the formation of oligomers/polymers, as observed for some of the reactions shown in Scheme 1. The allylic C–H bond of 7-azidohept-1-ene (83 kcal mol-1) can be activated to form the pyrrolidinone product (entry 3). The formation of six-membered heterocycles is however more challenging and the increased ring-strain in formation of a six-membered ring leads to a higher barrier for HAT. This leads to incomplete conversion (63%) and a moderate yield of the ring product (entry 3).55 In addition, formation of the linear Boc-protected amine product was observed in the crude 1H-NMR spectrum when using this substrate. The benzylic hydrogen atom of the substrate shown in entry 4 has a slightly higher BDE (85 kcal mol-1). This, in combination with the challenging formation of a six-membered ring product, again leads to low conversion of the substrate (<10%). Apparently, competing intermolecular reactions also lead to enhanced catalyst deactivation. Finally, activation of the benzylic C–H bond of the substrate shown in entry 5, which is further activated by the neighboring oxygen atom (BDE = 82 kcal mol-1), leads to the desired six-membered product, albeit in low yield (10%).
Table 3: Additional substrates studied in intramolecular C-H amination by [Co(TMP)] catalyst 3.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>BDE(^b)</th>
<th>Conversion(^c)</th>
<th>Products</th>
<th>Yield(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtO</td>
<td>96</td>
<td>74%</td>
<td></td>
<td>26%</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>98</td>
<td>72%(^d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>83</td>
<td>63%</td>
<td></td>
<td>38%</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>85</td>
<td>&lt;10%</td>
<td></td>
<td>Traces</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>82</td>
<td>40%</td>
<td></td>
<td>10% cyclic product</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: Substrate (0.3 mmol), Boc\(_2\)O (1.2 equivalent), [Co(TMP)] (4 mol%), and toluene (3.0 mL) were added and reacted for 16 h at 100 °C. \(^b\) Bond dissociation energy (kcal mol\(^{-1}\)) of the C-H bond for cyclization. \(^c\) isolated unless stated otherwise. \(^d\) stoichiometric reaction. \(^e\) not isolated

The results shown in Table 3 indicate that if the ring-closing step requires breaking of a stronger C–H bond (higher BDE), the reaction is partially driven to intermolecular HAT reactions, most likely involving the alpha position of another azide substrate. This is consistent with the formation of oligomeric/polymeric products (see main text), linear Boc protected amines as well as nitriles from substrates containing even stronger C–H bonds. Substrates with weaker benzylic C–H bonds at the delta position lead to selective formation of five-membered rings without indications for intermolecular HAT (see Table 1 and Table 2).
5.5 Acknowledgements

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5.6 References

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