Manipulating radicals

*Using cobalt to steer radical reactions*

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Carbene Radicals in Cobalt(II) Porphyrin-Catalysed Carbene Carbonylation Reactions; A Catalytic Approach to Ketenes

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Abstract

Cobalt(III)-carbene radicals generated by metallo-radical activation of diazo compounds and $N$-tosylhydrazones sodium salts at cobalt(II) complexes of porphyrins readily undergo radical addition to carbon monoxide, allowing catalytic production of ketenes. These ketenes subsequently react with various amines, alcohols and imines in one-pot tandem transformations to produce substituted amides, esters and $\beta$-lactams in good isolated yields. The mechanism of the carbene carbonylation reactions was further investigated by IR spectroscopy and computationally.
1. Introduction

Ketenes have intrigued chemists with their unusual physical properties and their unique spectrum of chemical reactivity.[1] Ketenes are usually prepared by thermolysis, pyrolysis or in a stoichiometric manner from acyl chlorides using base promoted elimination reactions.[2] Synthesis of ketenes from α-diazoketones via Wolff rearrangement[2d] is also noteworthy. However, all these synthetic methods have severe limitations and involve specialized equipment and/or highly unstable starting materials.

Carbonylation of metal-carbene species[3-6] is an interesting alternative method to produce such highly reactive ketenes, which find synthetic applications in various organic transformations.[1,4,5] The synthesis of medicinally important β-lactams via [2+2] ketene-imine cycloaddition reactions is of special synthetic interest.[5] Carbonylation reactions of Fischer-type carbene complexes have indeed been applied successfully to synthesize β-lactams.[5a,b] However, these are stoichiometric transformations, which leads to substantial waste generation. Following the discovery of stoichiometric carbonylation reactions of Fischer-type carbene complexes, thus far only a few transition metal-catalysed processes have been developed.[5,6] While interesting results have recently been obtained with a noble (palladium) metal catalyst,[5c] carbene carbonylation reactions mediated by base-metal catalysts as reported thus far have typically been associated with low efficiencies and require quite harsh reaction conditions (elevated temperatures and high CO pressures).[6] Therefore, we focused on the development of new catalytic carbene carbonylation processes that uses catalysts based on abundant first-row transition metals that operate under comparably mild reaction conditions.

As stable metalloradicals with well-defined open-shell doublet d7-electronic configuration, cobalt(II) complexes of porphyrins [CoII(Por)] have emerged as a new class of catalysts capable of carbene transfer reactions[7] proceeding via radical mechanisms involving discrete CoIII-carbene radical intermediates C (Scheme 1).[8] In comparison with classic electrophilic Fischer-type carbenes, the increased nucleophilicity of the carbene radical intermediate C slows-down unwanted carbene dimerization while allowing for catalytic cyclopropanation through radical addition to olefinic substrates, including electron-deficient olefins.[7,8] In this perspective, we envisioned that similar intermediates might well be effective in carbene carbonylation reactions, which can be considered as an attack of a nucleophilic cobalt-carbene radical (C) at the π-accepting CO substrate. At the same time, both the [Co(Por)] catalyst and the carbenoid intermediates are expected to interact only
weakly with amines, alcohols, imines and the ketene reaction products. Hence we expected smooth catalytic ketene formation under comparatively mild conditions, allowing convenient subsequent \textit{in situ} reactions with nucleophiles in one-pot tandem procedures (see Scheme 1).

![Scheme 1](image_url)

\textbf{Scheme 1. (por)Co\textsuperscript{II}-catalyzed carbene carbonylation leading to ketene formation in one-pot tandem transformations producing amides, esters and \(\beta\)-lactams. DFT calculated relative free energies (\(\Delta G^0\)) in kcal mol\(^{-1}\) between brackets (TurboMole, BP86, def2-TZVP, employing Grimme’s disp3 dispersion corrections).}

In this chapter we report an efficient one-pot tandem protocol involving Co\textsuperscript{II}-porphyrin metalloradical catalysed carbonylation of \(\alpha\)-diazocarbonyl compounds and a variety of \(N\)-tosylhydrazones leading to formation of ketenes, which subsequently react with a variety of nucleophiles and imines to form esters, amides and \(\beta\)-lactams. This system has a broad substrate scope and can be applied to various combinations of carbene precursors, nucleophiles and imines. The use of \(N\)-tosylhydrazones as precursors of diazo compounds in cobalt-porphyrin-based
carbene transfer reactions is unprecedented, and represents an efficient and convenient way to prepare the key carbenoid intermediates (C in Scheme 1) responsive for ketene formation. The key ketene formation steps were further investigated computationally (DFT).

2. Results and discussion

Since ketenes are highly reactive[5,6] and can generally only be trapped in the presence of a strong nucleophile, we first evaluated the activity of [CoII(TPP)] in the catalytic carbonylation of ethyl diazoacetate (EDA) (1) in presence of aniline (2a) under 10 bar CO at 50 °C. Under these conditions, (ethoxycarbonyl)ketene was formed and trapped by aniline to produce ethyl 2-(phenyl-carbamoyl)acetate (3a) in 57% isolated yield (Table 1, entry 1).

Further, initial experiments focused on the evaluation of ligand and solvent effects on the carbonylation of EDA in the presence of aniline. Four different CoII-porphyrin complexes were used in this study.

Figure 1. Structures of Cobalt(II) porphyrin complexes used in this study.
catalysts including two chiral ones were employed in an attempt to improve the catalytic process and to investigate potential asymmetric induction of the reaction (Figure 1). The catalysts [Co\textsuperscript{II}(P1)], [Co\textsuperscript{II}(P2)], and [Co\textsuperscript{II}(P3)] (see supporting information for experimental details) showed more or less similar activity, while the catalyst [Co(P4)] was found to be ineffective for this reaction (Table 1). No enantioselectivity was obtained using the chiral catalysts [Co\textsuperscript{II}(P3)] and [Co\textsuperscript{II}(P4)] under the various reaction conditions applied. This suggests that the ketene intermediate is liberated from the catalyst to react subsequently with the amine, freely in solution.

Table 1. Conditions of [Co\textsuperscript{II}(Por)]-catalysed β-ketoester synthesis using CO, EDA and aniline.\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>PhMe</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>THF</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>Dioxane</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>DCE</td>
<td>10-15</td>
</tr>
<tr>
<td>5</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>MeCN</td>
<td>&lt;5</td>
</tr>
<tr>
<td>6</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>DMF</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>PhCl</td>
<td>55</td>
</tr>
<tr>
<td>8</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>PhMe/K\textsubscript{3}PO\textsubscript{4}</td>
<td>69</td>
</tr>
<tr>
<td>9</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>PhMe/K\textsubscript{2}CO\textsubscript{3}</td>
<td>65</td>
</tr>
<tr>
<td>10</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>PhMe/KHCO\textsubscript{3}</td>
<td>58</td>
</tr>
<tr>
<td>11</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>PhMe/NEt\textsubscript{3}</td>
<td>63</td>
</tr>
<tr>
<td>12</td>
<td>[Co\textsuperscript{II}(P2)]</td>
<td>PhMe/K\textsubscript{3}PO\textsubscript{4}</td>
<td>70</td>
</tr>
<tr>
<td>13</td>
<td>[Co\textsuperscript{II}(P3)]</td>
<td>PhMe/K\textsubscript{3}PO\textsubscript{4}</td>
<td>72</td>
</tr>
<tr>
<td>14</td>
<td>[Co\textsuperscript{II}(P4)]</td>
<td>PhMe/K\textsubscript{3}PO\textsubscript{4}</td>
<td>35</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Stoichiometry EDA:aniline = 1:2. \textsuperscript{b}Isolated yields after column chromatography.

Optimization of the reaction conditions revealed that the reaction proceeded most efficiently in nonpolar solvents such as toluene and chlorobenzene, whereas reactions in solvents of higher polarities such as THF, dioxane, MeCN, and DMF
afforded poor yields (Table 1, entries 2-6). The use of inorganic bases K$_2$CO$_3$ or K$_3$PO$_4$ further improved the yields (Table 1, entries 8-11).

Table 2. [Co$^{II}$(Por)]-catalyzed β-ketoester synthesis using CO, α-diazocarbonyl compounds and different nucleophiles.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>NuH</th>
<th>Yield(%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>PhNH$_2$</td>
<td>69 (3a)</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>p-MeOC$_6$H$_4$NH$_2$</td>
<td>64 (3b)</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>p-NO$_2$C$_6$H$_4$NH$_2$</td>
<td>61 (3c)</td>
</tr>
<tr>
<td>4</td>
<td>Et</td>
<td>3,4-Cl$_2$C$_6$H$_3$NH$_2$</td>
<td>64 (3d)</td>
</tr>
<tr>
<td>5</td>
<td>Et</td>
<td>Ph$_2$NH</td>
<td>63 (3e)</td>
</tr>
<tr>
<td>6</td>
<td>Et</td>
<td>PhCH$_2$NH$_2$</td>
<td>67 (3f)</td>
</tr>
<tr>
<td>7</td>
<td>Et</td>
<td>n-BuNH$_2$</td>
<td>57 (3g)</td>
</tr>
<tr>
<td>8</td>
<td>Et</td>
<td>Morpholine</td>
<td>53 (3h)</td>
</tr>
<tr>
<td>9</td>
<td>Et</td>
<td>Ph(CH$_2$)$_3$OH</td>
<td>63 (3i)</td>
</tr>
<tr>
<td>10</td>
<td>Et</td>
<td>EtOH</td>
<td>62 (3j)</td>
</tr>
<tr>
<td>11</td>
<td>t-Bu</td>
<td>PhNH$_2$</td>
<td>75 (3k)</td>
</tr>
<tr>
<td>12</td>
<td>CH$_2$Ph</td>
<td>PhNH$_2$</td>
<td>72 (3l)</td>
</tr>
</tbody>
</table>

$^a$Stoichiometry EDA:NuH = 1:2. $^b$Isolated yields after column chromatography.

Reactions with other nucleophiles were evaluated to investigate the versatility of the reaction. The experiments indeed showed that the ketenes generated by the Co$^{II}$-Porphyrin-catalysed carbene carbonylation could be trapped by a wide range of nucleophiles (Table 2). The reaction occurred smoothly with substituted aromatic amines (Table 2, entries 1-5), primary and secondary aliphatic amines (Table 2, entries 6-8) and alcohols (Table 2, entries 9 and 10).
To further investigate the scope of the reaction, imines were introduced into the reaction medium in an attempt to produce β-lactams in a one-pot tandem procedure involving [2+2] cycloaddition of the intermediate ketene with the imine. Indeed, a 1:2 mixture of ethyl diazoacetate (EDA) (1) and N-methylbenzaldimine (4a) in dichloroethane (DCE) under a carbon monoxide atmosphere (20 bar) at 50 °C in the presence of a catalytic amount of [Co\textsuperscript{II}(TPP)] (2 mol%) led to formation of trans-N-methyl-α-ethoxycarbonyl-β-phenyl-β-lactam 5a in 60% isolated yield (Table 3). Similar reactions using other imines PhCH=NR (R = CH\textsubscript{2}Ph (4b) and 'Bu (4c)) also produced the desired β-lactams (Table 3). Notably, the (ethoxycarbonyl)ketene generated by [Co\textsuperscript{II}(TPP)]-catalysed carbene carbonylation participates selectively in [2+2] cycloaddition reactions with imines to produce the desired β-lactams (Table 3).

Table 3. [Co\textsuperscript{II}(Por)]-catalysed trans-selective β-lactam synthesis from α-diazocarbonyl compounds.\textsuperscript{a}

| Entry | Catalyst | Diazo | Imine | Yield(%)
\textsuperscript{b} (trans:cis) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>R = Et</td>
<td>R' = Me</td>
<td>65 (5a) (&gt;95:5)</td>
</tr>
<tr>
<td>2</td>
<td>[Co\textsuperscript{II}(P2)]</td>
<td>R = Et</td>
<td>R' = Me</td>
<td>65 (5a) (&gt;95:5)</td>
</tr>
<tr>
<td>3</td>
<td>[Co\textsuperscript{II}(P3)]</td>
<td>R = Et</td>
<td>R' = Me</td>
<td>67 (5a) (&gt;95:5)</td>
</tr>
<tr>
<td>4</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>R = Et</td>
<td>R' = CH\textsubscript{2}Ph</td>
<td>50 (5b) (&gt;90:5)</td>
</tr>
<tr>
<td>5</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>R = Et</td>
<td>R' = 'Bu</td>
<td>55 (5c) (&gt;95:5)</td>
</tr>
<tr>
<td>6</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>R = 'Bu</td>
<td>R' = Me</td>
<td>66 (5d) (&gt;95:5)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Stoichiometry EDA:imine = 1:2. \textsuperscript{b}Isolated yields after column chromatography.

Scheme 2. Markedly different behaviour of [(por)Co\textsuperscript{II}] compared to [Pd\textsubscript{2}(dba)\textsubscript{3}] in reactions with α-diazocarbonyl compounds and imines.
Reactions of other diazoacetates with imines also produced the desired β-lactams (Table 3). This behaviour is markedly different from the [4+2] cycloaddition reactions producing 1,3-dioxin-4-ones reported by Wang and coworkers in related palladium-catalysed reactions (see Scheme 2).[5c]

Again, the use of chiral catalyst [Co II(P3)] and [Co II(P4)] did not lead to any enantioselectivity, pointing to liberation of free ketene in solution reacting subsequently with the imine. Introduction of Cinchona alkaloid, quinidine and its derivatives into the reaction mixture in an attempt to trap the liberated ketene with a chiral organocatalysts[9] for chirality transfer in a one-pot cascade manner produced the beta-lactams with a low ee of only 5% at 30 °C. This temperature is probably much too high for efficient chirality transfer with these organocatalysts (typically operating at -78 °C), but this is the lowest possible temperature at which still some conversion can be achieved with these cobalt(II)-based catalysts. Nonetheless, this result reveals the potential of combining metallo- and organocatalysts in cascade processes, which may become a useful concept to achieve enantioselective ketene reactivity when combined with more active cobalt catalysts working at lower temperatures in the future.

To expand the scope of the catalytic ketene synthesis methodology, carbonylation reactions were carried out with N-tosylhydrazones. N-tosylhydrazones[10] are widely used as precursors for in-situ generation of non-stabilized diazo compounds. The use of N-tosylhydrazones as precursors of diazo compounds in cobalt-porphyrin-based carbene transfer reactions was thus far unprecedented. The easy synthesis of these N-tosylhydrazones from ketones and aldehydes combined with the above described [Co(Por)]-catalysed carbene carbonylation methodology offers a convenient method to convert an organic carbonyl moiety into a ketene functionality, applicable in one-pot three-component tandem transformations.

Reaction of the benzaldehyde tosylhydrazone sodium salt (6a) and aniline (2a) was catalysed by [Co II(TPP)] under similar reaction conditions as mentioned above (50 °C, 10 bar CO). The benzyl ketene, thus generated in-situ, reacted with aniline to produce N,N2-diphenylacetamide (7a) in 70% isolated yield (Table 4, entry 1). Further optimization of the reaction conditions revealed that the yield could be improved by adding a phase transfer agent (Aliquat 336, trioctylmethylammonium chloride) (Table 6, Experimental Section). Both polar and nonpolar solvents were suitable for this reaction, and again toluene was the best solvent. The use of inorganic bases K2CO3 or K3PO4 further improved the yields (Table 6).
Reactions with nucleophiles other than aniline were also investigated. The experiments showed that the ketenes generated from the tosylhydrazone sodium salts via the \([\text{Co}^{II}(\text{TPP})]\)-catalysed carbene carbonylation method could also be trapped by different nucleophiles. Expected products were obtained with several amines and alcohols (Table 4, entries 1-8).

Table 4. [\text{Co}^{II}(\text{Por})]-catalysed amide/ester synthesis using \(N\)-tosylhydrazone Sodium Salt and different nucleophiles.\(^a\)

\[
\begin{array}{cccc}
\text{Entry} & \text{R} & \text{R'} & \text{NuH} & \text{Yield} \, (\%)^b \\
1 & \text{Ph} & \text{H} & \text{PhNH}_2 & 75 (7a) \\
2 & \text{Ph} & \text{H} & p-\text{MeOC}_6\text{H}_4\text{NH}_2 & 79 (7b) \\
3 & \text{Ph} & \text{H} & p-\text{NO}_2\text{C}_6\text{H}_4\text{NH}_2 & 72 (7c) \\
4 & \text{Ph} & \text{H} & \text{PhCH}_2\text{NH}_2 & 75 (7d) \\
5 & \text{Ph} & \text{H} & \text{Ph}_2\text{NH} & 79 (7e) \\
6 & \text{Ph} & \text{H} & \text{n-BuNH}_2 & 75 (7f) \\
7 & \text{Ph} & \text{H} & \text{Morpholine} & 77 (7g) \\
8 & \text{Ph} & \text{H} & \text{Ph(CH}_2)_3\text{OH} & 65 (7h) \\
9 & p-\text{MeC}_6\text{H}_4 & \text{H} & \text{PhNH}_2 & 82 (7i) \\
10 & o-\text{MeC}_6\text{H}_4 & \text{H} & \text{PhNH}_2 & 75 (7j) \\
11 & p-\text{ClC}_6\text{H}_4 & \text{H} & \text{PhNH}_2 & 72 (7k) \\
12 & p-\text{MeOC}_6\text{H}_4 & \text{H} & \text{PhNH}_2 & 80 (7l) \\
13 & 2-\text{naph} & \text{H} & \text{PhNH}_2 & 77 (7m) \\
14 & \text{Ph} & \text{CH}_3 & \text{PhNH}_2 & 56 (7n) \\
15 & \text{PhCH}=\text{CH} & \text{H} & \text{PhNH}_2 & 65 (7o) \\
\end{array}
\]

\(^a\)Stoichiometry \(N\)-Tosylhydrazone:NuH = 1:3, PTA used. \(^b\)Isolated yields after column chromatography.

These results prompted us to explore the scope of the catalytic carbene carbonylation reactions using a series of \(N\)-tosylhydrazone sodium salts under the above optimized
reaction conditions. The reactions produced the expected acetamide derivatives in good to high yields (Table 4, entries 9–13). The reaction also worked well with disubstituted N-tosylhydrazones, although requiring longer reaction times (Table 4, entry 14). Also α,β-unsaturated N-tosylhydrazones could be converted to amides, albeit in modest yields (Table 4, entry 15).

Table 5. [Co\textsuperscript{II}(Por)]-catalysed trans-selective β-lactam synthesis using different N-tosylhydrazone Sodium Salts and imines.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>R</th>
<th>R'</th>
<th>R''</th>
<th>Yield (%)\textsuperscript{b} (trans:cis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>Ph</td>
<td>Ph</td>
<td>Me</td>
<td>64 (8a) (&gt;95:5)</td>
</tr>
<tr>
<td>2</td>
<td>[Co\textsuperscript{II}(P2)]</td>
<td>Ph</td>
<td>Ph</td>
<td>Me</td>
<td>65 (8a) (&gt;95:5)</td>
</tr>
<tr>
<td>3</td>
<td>[Co\textsuperscript{II}(P3)]</td>
<td>Ph</td>
<td>Ph</td>
<td>Me</td>
<td>65 (8a) (&gt;95:5)</td>
</tr>
<tr>
<td>4</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>Ph</td>
<td>Ph</td>
<td>PhCH\textsubscript{2}</td>
<td>62 (8b) (&gt;90:10)</td>
</tr>
<tr>
<td>5</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>Ph</td>
<td>pClC\textsubscript{6}H\textsubscript{4}</td>
<td>Me</td>
<td>63 (8c) (&gt;95:5)</td>
</tr>
<tr>
<td>6</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>Ph</td>
<td>pOMeC\textsubscript{6}H\textsubscript{4}</td>
<td>Me</td>
<td>73 (8d) (&gt;90:10)</td>
</tr>
<tr>
<td>7</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>pMeC\textsubscript{6}H\textsubscript{4}</td>
<td>Ph</td>
<td>Me</td>
<td>77 (8e) (&gt;95:5)</td>
</tr>
<tr>
<td>8</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>pClC\textsubscript{6}H\textsubscript{4}</td>
<td>Ph</td>
<td>Me</td>
<td>62 (8f) (&gt;95:5)</td>
</tr>
<tr>
<td>9</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>pMeOC\textsubscript{6}H\textsubscript{4}</td>
<td>Ph</td>
<td>Me</td>
<td>73 (8g) (&gt;85:15)</td>
</tr>
<tr>
<td>10</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>2-naphthyl</td>
<td>Ph</td>
<td>Me</td>
<td>67 (8h) (&gt;95:5)</td>
</tr>
<tr>
<td>11</td>
<td>[Co\textsuperscript{II}(P1)]</td>
<td>PhCH=CH</td>
<td>Ph</td>
<td>Me</td>
<td>52 (8i) (&gt;95:5)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Stoichiometry: N-tosylhydrazone:imine = 1:2. \textsuperscript{b}Isolated yields after column chromatography.

Upon introduction of imines to the reaction medium, the ketenes generated from these N-tosylhydrazone salts also reacted smoothly to produce the desired β-lactams. The use of a phase transfer agent in this case did not have any influence on the outcome of the reaction. A series of N-tosylhydrazone salts were subjected to the reaction conditions with different benzaldimines (Table 5). In all cases, the
corresponding β-lactams were obtained in good yields. Interestingly, for most of the substrates, the reactions afforded *trans* products with excellent diastereoselectivity. However, again no enantioselectivity was obtained using either chiral catalysts or by adding quinidine based chiral organocatalysts into the reaction mixture.

To obtain more insight into the mechanistic aspects of Co(por) catalyzed ketene formation, several controlled infrared studies of the reaction mixtures were carried out. Since, diphenylketene is known to be more stable than the corresponding mono-substituted ketenes, diphenyl tosylhydrazone sodium salt was intentionally chosen as the carbene source for IR analysis of the carbene-carbonylation reaction mixtures (See Experimental Section). Indeed, carbonylation of the diphenyl tosylhydrazone sodium salt with 20 bar CO produces free diphenyl ketene, as indicated by observation of a characteristic IR stretch frequency at 2102 cm\(^{-1}\) directly after the reaction.\(^{[11]}\) Formation of the diphenyl diazo compound\(^{[12]}\) from the diphenyl tosylhydrazone sodium salt was also detected by IR spectroscopy, as revealed by observation of a characteristic stretch frequency at 2042 cm\(^{-1}\). These data are in agreement with the proposed reaction mechanism shown in Scheme 1.

Repeated attempts to detect the more reactive benzyl ketene directly after reaction of the corresponding tosylhydrazone sodium salt with 20 bar CO were unsuccessful. This is likely due to too rapid dimerization/oligomerisation and/or other side-reactions of the ketene in absence of a nucleophile or imine. The reaction mixture obtained directly after reacting the benzaldehyde tosylhydrazone salt with 20 bar CO in the presence of N-methylbenzaldimine does show characteristic C=O stretch frequency of the β-lactam at 1752 cm\(^{-1}\).\(^{[5c]}\)

The mechanism of the above carbene carbonylation reactions was further investigated computationally using DFT methods (see Experimental Section for details). In these studies, in contrast to previous investigations reported by our group, we decided to include dispersion (VdW) corrections in the geometry optimizations. Remarkably, this modification had a profound influence on the affinity of the cobalt centre for the diazo compound methyl diazoacetate (MDA) (coordinated via the carbon atom), shifting the association equilibrium from A to B and resulting in a somewhat lower transition state barrier TS1 (from B) for formation of the key Co(III)-carbene radical intermediate C (Scheme 1) than reported previously. Noteworthy is also that with dispersion forces the carbon bound MDA adduct B was calculated to be more stable than the nitrogen bound MDA adduct B', while this was reversed in previous calculations without dispersion corrections.\(^{[8]}\) Apart from this interesting effect of inclusion of dispersion forces in the calculations, this part of the catalytic mechanism is in fact identical to carbenoid
formation in the calculated mechanism for olefin cyclopropanation.\[^{[8]}\] Carbone radicals C are in equilibrium with ‘bridging carbenes’ C’ according to these calculations (nearly thermo-neutral), and both C- and C’-type species were previously detected by EPR spectroscopy after reacting [Co\(^{II}\)(P\(_3\))] with ethyl diazoacetate.\[^{[8a]}\]

Subsequent carbonylation of terminal carbenoid C proceeds via concerted one-step CO addition to the carbene moiety with simultaneous homolysis of the Co–C bond to produce the free ketene, according to DFT. The ketene has little to no affinity for cobalt, and spontaneously dissociates from the cobalt centre directly after its formation. These calculations are in good agreement with the detection of free ketene in the above-mentioned IR experiments. The computed carbene-carbonylation step has a somewhat lower energy barrier (\(\Delta G^\ddagger(\text{TS2})\) = 8.6 kcal mol\(^{-1}\) from C; \(\Delta G^\ddagger(\text{TS2})\) = 9.2 kcal mol\(^{-1}\) from C’) than the barrier for formation of C through dinitrogen loss from diazo adduct B (\(\text{TS1} = 13.6\) kcal mol\(^{-1}\)).\[^{[8a]}\] The rate limiting step in the catalytic cycle should therefore be the formation of carbene radical C, according to these DFT calculations under standard conditions in the gas phase. However, the energy differences between \(\text{TS1}\) and \(\text{TS2}\) are not large and at relative low CO concentrations and relative high EDA concentrations (i.e. non-standard conditions as in the catalytic experiments) the entropy contributions could lower the relative barrier of \(\text{TS1}\) compared to \(\text{TS2}\), possibly allowing side reactions of C (e.g. carbene dimerization, reaction with the solvent). This, in combination with the relatively low solubility of CO in common organic solvents,\[^{[13]}\] most likely explains why CO pressures > 10 bar are required in the experimental catalytic runs.

The ketene, thus generated \textit{in-situ}, has no affinity for the [Co(Por)] catalyst according to these DFT calculations, and hence most likely reacts subsequently in a non-catalysed manner with nucleophiles or imines present in solution, leading to the final ester, amide or β-lactam products.\[^{[5c,6]}\] Given that carbon monoxide has a weak affinity for the cobalt(II) centre,\[^{[14]}\] it is unlikely for carbon monoxide to bind to the catalyst and thus influence the carbonylation of diazo compounds under the applied catalytic reaction conditions. The more nucleophilic character of C compared to Fischer-type carbenes further reduces its reactivity towards nucleophiles, which is likely an important feature in preventing unwanted side-reactions.
3. Summary and Conclusions

In summary, we have demonstrated [CoII(Por)] complexes are effective metalloradical catalysts for carbene carboxylation, producing ketenes from CO and diazo compounds or tosylhydrazones under mild conditions. The [CoII(Por)]-catalysed reaction, which involves a low-barrier carbene carboxylation step, provides a valuable synthetic alternative for the production of ketenes, which can be in-situ trapped with amines, alcohols or imines to produce esters, amides or β-lactams in a one-pot cascade manner. This straightforward methodology has a broad substrate scope and can be applied for various combinations of diazo compounds and nucleophiles or imines. In addition to diazo compounds, [CoII(Por)]-catalysed carboxylation process can also employ tosylhydrazones derived from aldehydes and ketones as carbene sources. Consequently, this procedure offers an efficient way for the homologation of ketones and aldehydes, and also provides a diastereoselective method for the transformation of aldehydes to β-lactam derivatives.

4. Experimental Section

General Procedures. All manipulations, except the carboxylation reactions, were performed under a nitrogen atmosphere using standard Schlenk techniques. All solvents used for catalysis were dried over and distilled from sodium (toluene) or CaH₂ (dichloromethane, hexane, ethyl acetate, methanol). All the Cobalt-porphyrin catalysts [CoII(P1)], [CoII(P2)] [CoII(P3)], [CoII(P4)] and N-tosylhydrazone sodium salts were synthesized according to published procedures.[15,16] Ethyl diazoacetate (EDA) was used as purchased from Aldrich (up to 15% dichloromethane, actual content determined by NMR). tert-Butyl diazoacetate, Benzyl diazoacetate were also used as purchased from Aldrich. Quinidine was purchased from Aldrich and its ester derivative with benzoyl chloride was prepared according to the reported procedure. All other chemicals were purchased from commercial suppliers and used without further purification. NMR spectra (1H, and 13C{1H}) were measured on a Varian INOVA 500 MHz, a Bruker AV400 or a Varian MERCURY 300 MHz spectrometer. Infrared spectra were recorded on a Thermo Nicolet NEXUS 670 FT-IR.

Typical Carbene Carboxylation Procedures. In a typical carboxylation experiment a stainless steel autoclave (150 mL) equipped with inserts suitable for five glass vials (4 mL) was employed. The vials were charged with appropriate amounts of solvent, substrates (Diazo/N-tosylhydrazone sodium salts and nucleophiles), catalyst [CoII(porphyrin)] along with Teflon stirring bars. Before starting the catalytic reactions, the charged autoclave was purged three times with CO and then pressurised to the desired pressure. After catalysis, the autoclave was cooled to 0 °C, and any excess gas was removed after which the reaction mixture was analysed directly.

[CoII(Porphyrin)]-catalysed β-ketoester synthesis using CO, α-diazocarbonyl compounds and different nucleophiles. Under a nitrogen atmosphere, [CoII(Porphyrin)] (2
mol%) and K$_3$PO$_4$ (1.0 mmol) were added to a 4 ml flame-dried glass vial. Then the vial was sealed with a stopper, evacuated and cooled to $-78^\circ$C in a dry-ice/acetone bath. To this precooled vial a solution of diazoacetate (1a-c) (0.5 mmol) and nucleophile (2a-j) (1.0 mmol) in 3.0 ml of toluene was added via syringe. A small needle was inserted at the top of the vial. The vials are then quickly inserted into an autoclave (150 mL) equipped with inserts suitable for five such glass vials and pressurized with 10 bar of CO. The pressurized autoclave was then stirred at 50 $^\circ$C for 12h. The autoclave was subsequently cooled to 0 $^\circ$C, and any excess gas was removed. The resulting mixture was concentrated and the residue was purified by flash silica gel chromatography to give the products (3a-l).

**[Co$^{II}$(Porphyrin)]-catalysed β-lactam synthesis from different α-diazoacyarbonyl compounds.** Under a nitrogen atmosphere, [Co$^{II}$](Porphyrin)] (2 mol%) was added to a 4 ml flame-dried glass vial. Then the vial was sealed with a stopper and evacuated to vacuum and cooled to $-78^\circ$C in a dry-ice/acetone bath. To this precooled vial a solution of diazoacetate (1a-c) (0.5 mmol) and imine (4a-c) (1.0 mmol) in 3.0 ml of dichloroethane (DCE) was added via syringe. A small needle was inserted at the top of the vial. The vials are then inserted quickly into an autoclave (150 mL) equipped with inserts suitable for five such glass vials and pressurized with 20 bar of CO. The pressurized autoclave was then stirred at 50 $^\circ$C for 16h. The autoclave was subsequently cooled to 0 $^\circ$C, and any excess gas was removed. The resulting mixture was concentrated and the residue was purified by flash silica gel chromatography to give the products (5a-e).

**[Co$^{II}$(Porphyrin)]-catalysed amide/ester synthesis using N-tosyl hydrazone sodium salt and different nucleophiles.** Under a nitrogen atmosphere, [Co$^{II}$(Porphyrin)] (2 mol%), K$_3$PO$_4$ (0.6 mmol), and N-tosylhydrazone sodium salt (6a-h) (0.2 mmol) were added to a 4 ml flame-dried glass vial. Then the vial was sealed with a stopper and evacuated. Anhydrous toluene (3.0 mL), Aliquat 336® (20 μL, 0.5 M solution in toluene), and nucleophile (2a-j) (0.6 mmol) were added via syringe. A small needle was inserted at the top of the vial. The vials were then inserted into an autoclave (150 mL) equipped with inserts suitable for five such glass vials and pressurized with 10 bar of CO. The pressurized autoclave was then stirred at 50 $^\circ$C for 18h. The autoclave was subsequently cooled to 0 $^\circ$C, and any excess gas was removed. The resulting mixture was concentrated and the residue was purified by flash silica gel chromatography to give the products (7a-o).

**[Co$^{II}$(Porphyrin)]-catalysed β-lactam synthesis using different N-tosylhydrazone sodium salts and imines.** Under a nitrogen atmosphere, [Co$^{II}$(Porphyrin)] (2 mol%), and N-tosylhydrazone sodium salt (6a-h) (0.5 mmol) were added to a flame-dried 4 ml glass vial. Then the vial was sealed with a stopper and evacuated. Imine (4a-e) (1.0 mmol) in 3.0 ml of dichloroethane (DCE) were added via syringe. A small needle was inserted at the top of the vial. The vials were then inserted into an autoclave (150 mL) equipped with inserts suitable for five such glass vials and pressurized with 20 bar of CO. The pressurized autoclave was then stirred at 50 $^\circ$C for 24h. The autoclave was subsequently cooled to 0 $^\circ$C, and any excess gas was removed. The resulting mixture was concentrated and the residue was purified by flash silica gel chromatography to give the products (8a-i).
Figure 2. FT-IR spectrum of diphenyltosylhydrazone in acetonitrile.

Figure 3. FT-IR spectrum of the reaction mixture of the diphenyltosylhydrazone sodium salt and a catalytic amount of [Co^{II}(TPP)] in acetonitrile.
Figure 4. FT-IR spectrum of the reaction mixture of diphenyltosylhydrazone sodium salt and a catalytic amount of [Co^II(TPP)] in acetonitrile (reaction performed under 20 bar CO).

Figure 5. FT-IR spectrum of the reaction mixture of benzaldehyde tosylhydrazone salt, N-methylbenzaldimine and catalytic amount of [Co^II(TPP)] in dichloroethane (reaction performed under 20 bar CO).
Table 6. Conditions of [Co(por)]-Catalysed β-ketoamide synthesis using CO with N-Tosylhydrazone Sodium Salt and Aniline.

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<th>entry</th>
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<th>yield (%)</th>
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<td>57</td>
</tr>
<tr>
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<td>[Co(P1)]</td>
<td>Dioxane</td>
<td>57</td>
</tr>
<tr>
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<td>[Co(P1)]</td>
<td>DCE</td>
<td>55</td>
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<tr>
<td>5</td>
<td>[Co(P1)]</td>
<td>MeCN</td>
<td>51</td>
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<td>[Co(P1)]</td>
<td>DMF</td>
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<td>13</td>
<td>[Co(P2)]/K3PO4/PTC</td>
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<td>73</td>
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</table>

*a* Stoichiometry N-Tosylhydrazone:NuH = 1:3, PTA used. *b* Toluene solvent. *c* Isolated yield after column chromatography.

Product characterization:

**Ethyl 3-oxo-3-(phenylamino)propanoate (3a)**

1H NMR (500 MHz, CDCl3): δ 1.27 (t, J = 7.2 Hz, 3H), 3.43 (s, 2H), 4.21 (q, J = 7.2 Hz, 2H), 7.08 (t, J = 7.2 Hz, 2H), 7.28 (t, J = 8.0 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H), 9.19 (s, 1H).

13C NMR (500 MHz, CDCl3): δ 13.94, 41.37, 61.82, 119.97, 124.45, 128.88, 137.32, 162.77, 169.92.

**Ethyl 3-((4-methoxyphenyl)amino)-3-oxopropanoate (3b)**

1H NMR (500 MHz, CDCl3): δ 1.33 (t, J = 7.0 Hz, 3H), 3.47 (s, 2H), 3.81 (s, 3H), 4.26 (q, J = 7.3 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 9.13 (s, 1H).

13C NMR (500 MHz, CDCl3): δ 14.31, 41.79, 55.81, 62.19, 114.42, 128.88, 137.32, 162.77, 169.29.

**Ethyl 3-((4-nitrophenyl)amino)-3-oxopropanoate (3c)**

1H NMR (500 MHz, CDCl3): δ 1.35 (t, J = 7.2 Hz, 3H), 3.54 (s, 2H), 4.28 (q, J = 7.2 Hz, 2H), 7.76 (d, J = 9 Hz, 2H), 8.22 (d, J = 9 Hz, 9.85 (s, 1H).

13C NMR (500 MHz, CDCl3): δ 14.03, 41.31, 62.33, 119.49, 125.05, 143.26, 143.72, 163.54, 169.91.

**Ethyl 3-((3,4-dichlorophenyl)amino)-3-oxopropanoate (3d)**

1H NMR (500 MHz, CDCl3): δ 1.34 (t, J = 7.2 Hz, 3H), 3.47 (s, 2H), 4.26 (q, J = 7.2 Hz, 2H), 7.37 (s, 2H), 7.83 (s, 1H), 9.50 (s, 1H).

13C NMR (500 MHz, CDCl3): δ 14.02, 41.21, 62.08, 119.18, 121.65, 127.62, 130.41, 132.62, 136.87, 163.36, 169.91.
Cobalt(II) Porphyrin-Catalysed Carbene Carbonylation Reactions

Ethyl 3-(diphenylamino)-3-oxopropanoate (3e) \(^{17b}\)
\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 1.24\) (t, \(J = 7.2\) Hz, 3H), \(3.43\) (s, 2H), \(4.15\) (q, \(J = 7.2\) Hz, 2H), \(7.23-7.44\) (br, 10 H). \(^{13}\)C NMR (500 MHz, CDCl\(_3\)): \(\delta 14.12, 42.76, 61.40, 126.29, 128.71, 129.01, 129.94, 166.11, 167.52\).

Ethyl 3-(benzylamino)-3-oxopropanoate (3f) \(^{17b, 20}\)
\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 1.29\) (t, \(J = 7.2\) Hz, 3H), \(3.38\) (s, 2H), \(4.19\) (q, \(J = 7.2\) Hz, 2H), \(4.50\) (d, \(J = 6\) Hz, 2H), \(7.29-7.38\) (m, 5H), \(7.50\) (s, 1H). \(^{13}\)C NMR (500 MHz, CDCl\(_3\)): \(\delta 14.06, 41.09, 43.59, 61.65, 127.53, 127.72, 128.73, 137.88, 164.95, 169.58\).

Ethyl 3-(butylamino)-3-oxopropanoate (3g) \(^{17b, 21}\)
\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 0.92\) (t, \(J = 7.2\) Hz, 3H), \(1.26-1.43\) (m, 5H), \(1.58\) (m, 2H), \(3.27-3.35\) (m, 4H), \(4.23\) (q, \(J = 7\) Hz, 2H), \(7.23\) (s, 1H). \(^{13}\)C NMR (500 MHz, CDCl\(_3\)): \(\delta 13.09, 14.01, 20.03, 31.03, 39.27, 41.09, 61.49, 164.89, 169.73\).

Ethyl 3-morpholino-3-oxopropanoate (3h) \(^{17b, 22}\)
\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 1.29\) (t, \(J = 7.2\) Hz, 3H), \(3.45\) (t, \(J = 6\) Hz, 4H), \(3.65-3.72\) (m, 6H), \(4.20\) (q, \(J = 7\) Hz, 2H). \(^{13}\)C NMR (500 MHz, CDCl\(_3\)): \(\delta 14.93, 41.84, 43.04, 47.58, 62.34, 67.28, 67.46, 67.46, 165.36, 168.23\).

Ethyl (3-phenylpropyl) malonate (3i) \(^{17b}\)
\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 1.28\) (t, \(J = 7.2\) Hz, 3H), \(1.95\) (tt, \(J = 7.5, 7.5\)), \(2.69\) (t, \(J = 7.5\) Hz, 2H), \(3.39\) (s, 1H), \(4.13-4.27\) (m, 4H), \(7.18-7.33\) (m, 5H). \(^{13}\)C NMR (300 MHz, CDCl\(_3\)): \(\delta 14.10, 30.04, 31.98, 41.65, 61.55, 64.77, 126.05, 128.40, 128.45, 140.98, 166.58, 166.63\).

Diethyl malonate (3j) \(^{23}\)
\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 1.24\) (t, \(J = 7.2\) Hz, 6H), \(3.34\) (s, 2H), \(4.15\) (q, \(J = 7.2\) Hz, 4H). \(^{13}\)C NMR (500 MHz, CDCl\(_3\)): \(\delta 14.01, 41.63, 61.43, 166.56\).

tert-Butyl 2-(phenylcarbamoyl)acetate (3k) \(^{17b}\)
\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 1.49\) (s, 9H), \(3.36\) (s, 2H), \(7.12\) (t, \(J = 7.8\) Hz, 1H), \(7.32\) (t, \(J = 7.5\) Hz, 2H), \(7.54\) (d, \(J = 8\) Hz, 2H), \(9.30\) (s, 1H). \(^{13}\)C NMR (500 MHz, CDCl\(_3\)): \(\delta 28.06, 42.59, 83.15, 118.57, 124.50, 129.04, 137.66, 163.61, 169.25\).

Benzyl 2-(phenylcarbamoyl)acetate (3l) \(^{17b}\)
\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 3.48\) (s, 2H), \(5.20\) (s, 2H), \(7.12\) (t, \(J = 7.5\) Hz), \(7.29-7.37\) (m, 7H), \(7.50\) (d, \(J = 8.5\) Hz, 2H), \(9.11\) (s, 1H). \(^{13}\)C NMR (500 MHz, CDCl\(_3\)): \(\delta 28.06, 42.59, 83.15, 118.57, 124.50, 129.04, 137.66, 163.61, 169.25\).

N-Methyl-trans-α-ethoxycarbonyl-β-phenyl-β-lactam (5a) \(^{24, 25}\)
\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 1.15\) (t, \(J = 7.0, 3\) Hz), \(2.19\) (s, 1H), \(3.95\) (d, \(J = 10.5\) Hz, 1H), \(4.12\) (dq, \(J = 2.1, 7.2\) Hz, 2H), \(4.44\) (d, \(J = 10.5\) Hz, 2H), \(7.15-4.42\) (m, 5H). \(^{13}\)C NMR (500 MHz, CDCl\(_3\)): \(\delta 13.86, 36.38, 50.06, 58.31, 61.38, 127.86, 128.35, 128.46, 137.15, 164.93, 169.51\).
**N-Benzyl-trans-α-ethoxycarbonyl-β-phenyl-β-lactam (5b)**

1H NMR (500 MHz, CDCl₃): δ 1.28 (t, J = 7.1 Hz, 3H), 3.80 (d, J = 15.0 Hz, 1H), 3.89 (d, J = 2.5 Hz, 1H), 4.22 (dq, J = 2.2, 7.2 Hz, 2H), 4.68 (d, J = 2.0 Hz, 1H), 4.84 (d, J = 15.2 Hz), 7.1-7.4 (m, 10 H). 13C NMR (500 MHz, CDCl₃): δ 14.01, 44.7, 56.88, 61.38, 63.4, 126.58, 127.85, 128.45, 128.85, 129.0, 129.15, 134.63, 135.84, 162.14, 166.93.

**N-tert-Butyl-trans-α-ethoxycarbonyl-β-phenyl-β-lactam (5c)**

1H NMR (500 MHz, CDCl₃): δ 1.27 (s, 9H), 1.29 (t, J = 6 Hz, 3H), 3.69 (d, J = 2.5 Hz, 1H), 4.84 (d, J = 5 Hz, 1H), 7.33-7.42 (m, 5H). 13C NMR (500 MHz, CDCl₃): δ 14.02, 27.97, 55.09, 55.34, 61.59, 62.41, 126.54, 128.63, 128.85, 139.05, 162.06, 167.04.

**N-Methyl-trans-α-tert-butoxycarbonyl-β-phenyl-β-lactam (5d)**

1H NMR (500 MHz, CDCl₃): δ 1.29 (s, 9H), 2.87 (s, 3H), 3.81 (d, J = 10.5 Hz, 1H), 4.34 (d, J = 10.5 Hz, 1H), 7.11-7.23 (m, 5H). 13C NMR (500 MHz, CDCl₃): 27.83, 36.42, 51.02, 58.19, 127.90, 127.96, 128.13, 128.37, 137.32, 165.48, 168.61.

**N,2-diphenylacetamide (7a)**

1H NMR (500 MHz, CDCl₃): δ 3.73 (s, 2H), 7.05 (t, J = 7.2 Hz, 1H), 7.24-7.40 (m, 9H), 7.54 (s, 1H). 13C NMR (500 MHz, CDCl₃): δ 44.91, 119.81, 124.50, 127.74, 128.96, 129.30, 129.57, 134.40, 137.58, 169.05.

**N-(4-methoxyphenyl)-2-phenylacetamide (7b)**

1H NMR (500 MHz, CDCl₃): δ 3.66 (s, 2H), 3.70 (s, 3H), 6.74 (d, J = 8.5 Hz, 2H), 6.89 (s, 1H), 7.19-7.35 (m, 7H). 13C NMR (500 MHz, CDCl₃): δ 44.59, 55.36, 113.96, 121.67, 127.56, 129.14, 129.46, 130.52, 134.42, 156.44, 168.80.

**N-(4-nitrophenyl)-2-phenylacetamide (7c)**

1H NMR (500 MHz, CDCl₃): δ 3.75 (s, 2H), 7.28-7.39 (m, 5H), 7.54 (d, J = 11.5 Hz, 2H), 7.80-7.90 (m, 5H), 8.04 (br, 1H), 8.09 (d, J = 11 Hz). 13C NMR (500 MHz, CDCl₃): δ 44.76, 119.29, 125.06, 127.98, 129.35, 129.48, 133.73, 143.53, 143.77, 170.06.

**N-benzyl-2-phenylacetamide (7d)**

1H NMR (500 MHz, CDCl₃): δ 3.61 (s, 2H), 4.39 (s, 2H), 5.74 (s, 1H), 7.16-7.34 (m, 10H). 13C NMR (500 MHz, CDCl₃): δ 43.59, 43.86, 127.44, 127.50, 128.68, 129.10, 129.49, 134.78, 138.14, 170.93.

**N,N,2-triphenylacetamide (7e)**

1H NMR (500 MHz, CDCl₃): δ 3.70 (s, 2H), 7.09-7.50 (m, 15H). 13C NMR (500 MHz, CDCl₃): δ 42.27, 126.58, 128.48, 129.35, 135.10, 142.88, 171.15.

**N-butyl-2-phenylacetamide (7f)**

1H NMR (500 MHz, CDCl₃): δ 0.85 (t, J = 7.5 Hz, 3H), 1.2 (m, 2H), 1.36 (m, 2H), 3.17 (q, J = 6.7 Hz, 2H), 5.56 (s, 2H), 5.34 (s, 1H), 7.24-7.37 (m, 5H). 13C NMR (500 MHz, CDCl₃): δ 13.73, 19.99, 31.55, 39.42, 43.96, 127.35, 129.05, 129.49, 135.05, 170.88.
1-morpholino-2-phenylethanone (7g)\textsuperscript{rb,33}
$^1$H NMR (500 MHz, CDCl$_3$): δ 3.41-3.44 (m, 2H), 3.46-3.48 (m, 2H), 3.63 (s, 4H), 3.75 (s, 2H), 7.23-7.32 (m, 5H). $^{13}$C NMR (500 MHz, CDCl$_3$): δ 41.04, 42.04, 46.88, 66.32, 66.93, 126.68, 128.10, 128.96, 134.78, 169.58.

3-phenylpropyl 2-phenylacetate (7h)\textsuperscript{34}
$^1$H NMR (500 MHz, CDCl$_3$): δ 1.94 (m, 2H), 2.64 (t, $J = 7.5$ Hz, 2H), 3.65 (s, 2H), 4.12 (t, $J = 6.5$ Hz, 2H), 7.14-7.38 (m, 10 H). $^{13}$C NMR (500 MHz, CDCl$_3$): δ 41.04, 42.04, 46.88, 66.32, 66.93, 126.68, 128.10, 128.96, 134.78, 169.58.

2-(4-Methylphenyl)-N-phenylacetamide (7i)\textsuperscript{rb}
$^1$H NMR (500 MHz, CDCl$_3$): δ 2.39 (s, 3H), 3.72 (s, 2H), 7.08 (t, $J = 7.5$ Hz, 1H), 7.14 (br, 1H), 7.19-7.29 (m, 6H), 7.38-7.41 (m, 2H). $^{13}$C NMR (500 MHz, CDCl$_3$): δ 21.21, 44.49, 119.80, 124.37, 128.94, 129.56, 129.99, 131.29, 137.49, 137.64, 169.37.

2-(2-Methylphenyl)-N-phenylacetamide (7j)\textsuperscript{rb}
$^1$H NMR (500 MHz, CDCl$_3$): δ 3.70 (s, 2H), 7.10 (t, $J = 7.5$ Hz, 1H), 7.14 (br, 1H), 7.19-7.29 (m, 6H), 7.38-7.41 (m, 2H). $^{13}$C NMR (500 MHz, CDCl$_3$): δ 44.05, 104.63, 119.85, 124.64, 129.02, 129.32, 130.85, 137.74, 158.97, 169.73.

2-(4-Chlorophenyl)-N-phenylacetamide (7k)\textsuperscript{rb}
$^1$H NMR (500 MHz, CDCl$_3$): δ 3.70 (s, 2H), 7.10 (t, $J = 7.5$ Hz, 1H), 7.22-7.40 (m, 9H). $^{13}$C NMR (500 MHz, CDCl$_3$): δ 44.05, 104.63, 119.85, 124.64, 129.02, 129.32, 130.85, 137.74, 158.97, 168.50.

2-(4-Metoxyphenyl)-N-phenylacetamide (7l)\textsuperscript{rb}
$^1$H NMR (500 MHz, CDCl$_3$): δ 3.70 (s, 2H), 7.10 (t, $J = 7.5$ Hz, 1H), 7.22-7.40 (m, 9H). $^{13}$C NMR (500 MHz, CDCl$_3$): δ 44.05, 104.63, 119.85, 124.64, 129.02, 129.32, 130.85, 137.74, 158.97, 168.50.

N,2-diphenylpropanamide (7j)\textsuperscript{rb,35}
$^1$H NMR (500 MHz, CDCl$_3$): δ 1.59 (d, $J = 5$ Hz, 3H), 3.71 (q, $J = 6.6$ Hz, 1H), 7.05 (t, $J = 6.8$ Hz, 1H), 7.21-7.41 (m, 10H). $^{13}$C NMR (500 MHz, CDCl$_3$): δ 18.51, 48.04, 119.72, 124.19, 125.73, 128.78, 128.92, 129.02, 137.78, 140.95, 172.45.

(E)-N,4-diphenylbut-3-enamide (7k)\textsuperscript{rb}
$^1$H NMR (500 MHz, CDCl$_3$): δ 3.28 (d, $J = 7.5$ Hz, 2H), 6.36 (m, 1H), 6.56 (d, $J = 15$ Hz, 1H), 7.02 (t, $J = 7.2$ Hz, 1H), 7.28-7.43 (m, 7H), 7.49-7.51 (d, $J = 10$ Hz, 2H), 7.72 (br, 1H). $^{13}$C NMR (500 MHz, CDCl$_3$): δ 41.97, 119.87, 121.80, 124.51, 126.42, 128.06, 128.73, 129.03, 135.12, 136.39, 137.90, 169.10.
trans-1-Methyl-3,4-diphenylazetidin-2-one (8a-trans)\textsuperscript{7b, 36}
\[\text{H NMR (500 MHz, CDCl}_3\text{): }\delta 2.87 (s, 3H), 4.17 (s, 1H), 4.45 (d, J = 2.5 Hz, 1H), 7.26-7.45 (m, 10 H). \text{C NMR (500 MHz, CDCl}_3\text{): }\delta 26.95, 65.25, 65.61, 126.18, 127.26, 127.53, 128.58, 128.78, 129.08, 134.96, 137.27, 168.35.\]

trans-1-benzyl-3,4-diphenylazetidin-2-one (8b)\textsuperscript{37}
\[\text{H NMR (300 MHz, CDCl}_3\text{): }\delta 3.77 (d, J = 15 Hz, 1H), 4.17 (d, J = 1.2 Hz, 1H), 4.31 (d, J = 2.1 Hz, 1H), 4.92 (d, J = 15 Hz, 1H), 7.16-7.40 (m, 15 H). \text{C NMR (500 MHz, CDCl}_3\text{): }\delta 44.63, 63.13, 65.14, 126.55, 127.37, 127.80, 128.56, 128.82, 128.90, 129.13, 129.65, 134.98, 135.57, 137.19, 168.33.\]

trans-4-(4-Chlorophenyl)-1-methyl-3-phenylazetidin-2-one (8c-trans)
\[\text{H NMR (300 MHz, CDCl}_3\text{): }\delta 2.89 (s, 3H), 4.16 (s, 1H), 4.46 (d, J = 2 Hz, 1H), 7.29-7.45 (m, 9H). \text{C NMR (500 MHz, CDCl}_3\text{): }\delta 27.15, 64.79, 65.90, 127.35, 127.66, 127.67, 127.82, 128.97, 128.99, 128.43, 129.47, 129.68, 134.59, 134.72, 135.91, 168.30.\]

trans-4-(4-Methoxyphenyl)-1-methyl-3-phenylazetidin-2-one (8d-trans)\textsuperscript{7b}
\[\text{H NMR (300 MHz, CDCl}_3\text{): }\delta 2.84, (s, 3H), 3.85 (s, 3H), 4.14 (s, 1H), 4.41 (d, J = 2 Hz, 1H), 6.95 (d, J = 7.5 Hz), 7.22-7.36 (m, 7H). \text{C NMR (500 MHz, CDCl}_3\text{): }\delta 27.02, 55.34, 65.07, 65.73, 114.62, 127.16, 127.35, 127.65, 128.92, 129.12, 135.17, 159.99, 168.85.\]

trans-1-Methyl-4-phenyl-3-p-tolylazetidin-2-one (8e-trans)\textsuperscript{7b}
\[\text{H NMR (300 MHz, CDCl}_3\text{): }\delta 2.34 (s, 3H), 2.85 (s, 3H), 4.11 (s, 1H), 4.41 (d, J = 2 Hz, 1H), 7.10-7.19 (m, 4H), 7.29-7.46 (m, 7H). \text{C NMR (500 MHz, CDCl}_3\text{): }\delta 21.12, 27.07, 65.22, 65.77, 126.27, 127.16, 128.53, 129.18, 129.76, 131.85, 137.33, 137.47, 168.89.\]

trans-3-(4-Chlorophenyl)-1-methyl-4-phenylazetidin-2-one (8f-trans)\textsuperscript{7b}
\[\text{H NMR (300 MHz, CDCl}_3\text{): }\delta 2.86 (s, 2H), 4.14 (s, 1H), 4.41 (d, J = 2 Hz, 1H), 7.20-7.45 (m, 9H). \text{C NMR (500 MHz, CDCl}_3\text{): }\delta 27.14, 64.97, 65.32, 126.27, 128.75, 128.88, 129.08, 129.29, 133.48, 133.54, 137.04, 167.95.\]

trans-3-(4-Methoxyphenyl)-1-methyl-4-phenylazetidin-2-one (8g-trans)\textsuperscript{7b}
\[\text{H NMR (300 MHz, CDCl}_3\text{): }\delta 2.87 (s, 3H), 3.80 (s, 3H), 4.41 (s, 1H), 4.40 (d, J = 2 Hz, 1H), 6.89 (d, J = 9 Hz, 2H), 7.21-7.45 (m, 7H). \text{C NMR (500 MHz, CDCl}_3\text{): }\delta 27.07, 55.35, 65.22, 65.77, 114.31, 126.27, 127.26, 128.53, 128.65, 129.18, 137.47, 159.10, 168.89.\]

cis-3-(4-Methoxyphenyl)-1-methyl-4-phenylazetidin-2-one (8g-cis)\textsuperscript{7b}
\[\text{H NMR (300 MHz, CDCl}_3\text{): }\delta 2.92 (s, 3H), 3.67 (s, 3H), 4.81 (J = 5Hz, 1H), 4.92 (d, J = 5 Hz, 1H), 6.59 (d, J = 9 Hz, 2H), 7.93-7.17 (m, 7H). \text{C NMR (500 MHz, CDCl}_3\text{): }\delta 27.38, 55.08, 60.71, 62.36, 113.45, 124.91, 127.16, 127.87, 128.25, 129.76, 135.17, 158.35, 168.83.\]
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**trans-2-methyl-4-(naphthalen-2-yl)-3-phenylcyclobutanone (8h-trans)**

$^1$H NMR (500 MHz, CDCl$_3$): δ 2.82 (s, 3H), 4.25 (s, 1H), 4.44 (d, J = 2.0 Hz, 1H), 7.17-7.40 (m, 8H), 7.70-7.76 (m, 4H). $^13$C NMR (500 MHz, CDCl$_3$): δ 27.18, 65.46, 65.92, 125.09, 126.08, 126.38, 127.71, 127.87, 128.79, 129.28, 132.41, 132.81, 133.47, 137.33, 168.45.

$^1$H NMR (500 MHz, CDCl$_3$): δ 2.82 (s, 3H), 4.25 (s, 1H), 4.44 (d, J = 2.0 Hz, 1H), 7.17-7.40 (m, 8H), 7.70-7.76 (m, 4H). $^13$C NMR (500 MHz, CDCl$_3$): δ 27.18, 65.46, 65.92, 125.09, 126.08, 126.38, 127.71, 127.87, 128.79, 129.28, 132.41, 132.81, 133.47, 137.33, 168.45.

**trans-2-methyl-3-phenyl-4-styrylcyclobutanone (8i-trans)**

$^1$H NMR (500 MHz, CDCl$_3$): δ 2.83 (s, 3H), 3.76 (d, J = 8.5 Hz, 1H), 4.37 (d, J = 2.0 Hz, 1H), 6.36 (m, 1H), 6.62 (d, J = 15H, 1H), 7.21-7.44 (m, 10H).

$^13$C NMR (500 MHz, CDCl$_3$): δ 27.18, 63.11, 64.60, 122.32, 126.08, 126.35, 127.87, 128.58, 128.79, 129.28, 134.11, 136.23, 137.36, 168.49.

**Table S2. Energies of the DFT calculated species.**

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<th>Species</th>
<th>SCF au</th>
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<th>ZPE au</th>
<th>SCF+ZPE au</th>
<th>Negative Eigenvalues</th>
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<td>MDA</td>
<td>SV(P)</td>
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<td>[Co(por)]</td>
<td>SV(P)</td>
<td>-2370.65554</td>
<td>-2370.42942</td>
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<td>[Co(por)] MDA adduct (B) (C-bound)</td>
<td>SV(P)</td>
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<tr>
<td>[Co(por)] MDA adduct (B') (N2-bound)</td>
<td>SV(P)</td>
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<td>TS1_N2 elimination</td>
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<td>Co_Carbene (C)</td>
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<td>-2637.59352</td>
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<td>Co_Carbene (bridged) (C')</td>
<td>SV(P)</td>
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<td>CO</td>
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<td>TS2_CO addition</td>
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Computational details. Geometry optimizations were carried out with the Turbomole program package\[38\] coupled to the PQS Baker optimizer\[39\] via the BOpt package,\[40\] at the spin unrestricted ri-DFT level using the BP86\[41\] functional and the resolution-of-identity (ri) method.\[42\] We optimized the geometries of all stationary points both at the SV(P) and at the def2-TZVP basis set level.\[43\] In the latter case we also employed Grimme's dispersion corrections (disp 3 version).\[44\] 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 relative (free) energies obtained from these calculations are reported in Table S2 and in Scheme 1 in the main text of the paper.

5. Acknowledgements

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6. References


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