Manipulating radicals

*Using cobalt to steer radical reactions*

Chirilă, A.

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Diastereoselective Radical-Type Cyclopropanation of Electron Deficient Alkenes mediated by the Highly Active [Co(MeTAA)] Catalyst

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Abstract

A new protocol for the catalytic synthesis of cyclopropanes using electron deficient alkenes is presented, using a series of affordable, easy to synthesize and highly active substituted cobalt(II) tetraaza[14]annulenes. These catalysts are compatible with the use of sodium tosylhydrazone salts as precursors to diazo compounds in one-pot catalytic transformations, affording the desired cyclopropanes in almost quantitative yields. The reaction takes advantage of the metalloradical character of the cobalt complexes to activate the diazo compounds. The reaction is practical and fast, and proceeds from readily available starting materials. It does not require slow addition of diazo reagents or tosylhydrazone salts nor heating, and tolerates many solvents including protic ones such as MeOH.

The cobalt(II) complexes derived from the tetramethyltetraaza-[14]annulene (MeTAA) ligand are easier to prepare than cobalt(II) porphyrins, present similar catalytic carbene radical reactivity, but are more active. The reaction proceeds at 20°C in a matter of minutes and even at −78°C in a few hours. The catalytic system is robust and can operate with either the alkene or the diazo reagent as limiting reagent, totally inhibiting the dimerization of diazo compounds. The protocol has been successfully applied to synthesize a variety of substituted cyclopropanes. High yields and selectivities were achieved for various substrates, with an intrinsic preference for trans-cyclopropanes.
1. Introduction

Although cyclopropanes are uncommon building blocks in natural products, they constitute to the backbone of many biologically active synthetic compounds, such as drugs and insecticides (Figure 1). Several methods are available for the synthesis of cyclopropanes, of which the transition metal catalysed cyclopropanation of olefins with diazo compounds is among the most robust and atom efficient methods. The first reports on asymmetric catalysed cyclopropanation were disclosed by Noyori and co-workers, and date back to 1966.\textsuperscript{[1]} The catalyst they introduced is a copper complex with a chiral chelating ligand. This discovery was followed by many others, with most catalysts developed based on copper,\textsuperscript{[2]} rhodium\textsuperscript{[3]} and ruthenium.\textsuperscript{[4]} These catalysts typically work well for the synthesis of chiral cyclopropanes derived from diazoacetates and electron-rich olefins, giving high yields and selectivities. However, these catalysts are typically poorly active for the cyclopropanation of electron-deficient olefins due to the electrophilic nature of the metal-carbene intermediates.\textsuperscript{[5]}

![Figure 1. Representative natural products and drug molecules containing the cyclopropane unit.](image)

A major drawback for obtaining cyclopropanes by reacting electron deficient alkenes and diazo compounds is the competing uncatalysed 1,3-dipolar cycloaddition reaction which forms pyrazolines (Scheme 1).\textsuperscript{[6]} When the dipolarophile is an α,β-unsaturated ester, such as an acrylate, the reaction rate and selectivity are determined by the HOMO-LUMO interactions, so that the diazo compound tends to attack the β-position of the unsaturated ester substrate. The higher the gap, and the smaller the substituents, the more favourable the 1,3-dipolar cycloaddition. In first
instance, the formed product is a 1-pyrazoline, but due to its instability, isomerization leads to formation of 2-pyrazolines.

Another competing pathway leading to undesired side products is carbene-carbene dimerization reaction. This process easily occurs by nucleophilic attack of the carbon atom of the diazo substrate at the prototypical electrophilic Fischer-type metal-carbene intermediates generated at the catalyst. To avoid the 1,3-dipolar cycloaddition, and form cyclopropanes instead, a catalyst must be used that has a high activity towards activation of diazo compounds, favouring carbene formation and subsequent coupling to the alkene over the undesired cycloaddition or carbene-carbene dimerization pathways. Such catalysts are still quite rare. Only few examples are reported in literature, mostly based on cobalt(II), as highlighted by Doyle.\(^7\)

A. 1,3-dipolar cycloaddition

![Diagram](image1)

B. Carbene dimerization

![Diagram](image2)

Scheme 1. Side reactions during cyclopropanation. A: 1,3-dipolar cycloaddition between a diazo compound and an electron deficient alkene. B: Diazoo compound dimerization towards alkenes via metal carbenoids\(^8\)

In 1978, Nakamura, Otsuka and co-workers introduced cobalt(II)-dioximato complexes as enantioselective catalysts for the cyclopropanation of diazo compounds and alkenes.\(^9\) These catalysts produce cyclopropanes in high yields and with high enantioselectivities for specific substrates, but for alkenes bearing electron withdrawing substituents the yields were very low. Further investigation of these catalysts was also discouraged due to difficulties with catalyst homogeneity when using chiral dioximato ligands. Chiral cobalt(II)-salen complexes were later explored by Katsuki and co-workers as cyclopropanation catalysts.\(^10\) The group of Yamada\(^11\) reported on the cyclopropanation of styrene derivatives with ethyl diazoacetate using similar complexes. However, again neither of these catalysts resulted in high yields, diastereoselectivities or enantioselectivities when using electron-deficient olefins. In
2003, Gallo, Cenini and co-workers and the group of Zhang independently reported on the use of cobalt(II) catalysts with chiral porphyrins as ligands, producing cyclopropanes in high yields and selectivities when using substituted styrenes and diazoacetates.\[^{12}\] In later reports, the Zhang group demonstrated that these catalysts also allow for cyclopropanation of electron deficient alkenes (such as acrylates) in high chemical yields, diastereomeric excess and enantiomeric excess (ee).\[^{13}\]\[^{13}\] Several enantioselective protocols for the cyclopropanation of styrenes with cobalt porphyrins were also developed.\[^{14}\]\[^{14}\] The cyclopropanation reactivity of group 9 transition metal (Co, Rh, Ir) porphyrin complexes in general was reviewed by Gallo and co-workers.\[^{15}\]\[^{15}\]

Figure 2. Mechanism of Co(II)-catalysed cyclopropanation (A), and the schematic representation of frontier orbitals involved in binding of carboxymethyl carbene to Co(II) (B).
This unique reactivity was explained by the groups of Zhang and de Bruin in 2010 through a detailed study of the mechanism of cyclopropanation reaction catalysed by low spin planar cobalt(II) systems using DFT calculations and experimental (EPR and MS) studies.\textsuperscript{[16]} During their investigations, they concluded that this reaction proceeds via a radical mechanism of (Figure 2A). Metalloradical activation of diazo compounds produces metal-carbenoids with radical carbon character, which can best be described as one-electron reduced Fischer-type carbenes (Figure 2B). Carbene generation at cobalt(II) leads to electron transfer from cobalt(II) to the carbene moiety, thus leading to the formation of a cobalt(III)-carbene radical intermediate. Occupation of the carbenoid p-orbital with an unpaired electron gives the cobalt-carbenoid intermediate its unique radical-type reactivity, and makes them less electrophilic than common Fischer-type carbenes. While in common Fischer-type carbenes the (LUMO) carbenoid p-orbital is completely empty, the respective carbon p-orbital of the cobalt-carbene radical intermediates shown in Figure 2 is half-filled (SOMO). This explains the enhanced reactivity of the cobalt(III)-carbene radical intermediates towards electron-deficient olefins, as well as their reduced tendency to undergo unwanted carbene-carbene dimerization reactions.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{cobalt_catalysts.png}
\caption{Cobalt(II) catalysts used in this study.}
\end{figure}

Due to the synthetic challenges of preparing highly substituted Co\textsuperscript{II}(por) catalysts that can efficiently activate diazo compounds via carbene radical intermediates, we decided to pursue the development of cheaper, easier to prepare and potentially more active low spin planar cobalt(II) catalysts. Based on current understanding of the catalytic system (Figure 2), more electron rich complexes should facilitate...
electron transfer to the carbene in the diazo activation, thus creating a more active catalyst. Therefore, we have chosen to investigate the catalytic properties of the class of cobalt(II) tetraaza-[14]annulenes (Figure 3, top row) in alkene cyclopropanation reactions. They are cheap, easy to prepare and their macrocycle is smaller than the porphyrin analogue, thus making the metal centre more electron rich. These complexes have been prepared and characterized in the late 1970s,[17] but their catalytic activity was never fully explored. The ligands are recently attracting renewed attention in view of their stronger electron donating properties and the higher reactivity of their coordination complexes as compared to porphyrins,[18] but catalytic application of the cobalt complexes was thus far not investigated.

In this chapter we tested the performance of similar cobalt complexes for the cyclopropanation of electron-deficient alkenes with (precursors of) diazo compounds using a metalloradical approach. In addition, we demonstrate an unprecedented one-pot methodology for cyclopropanation of electron deficient alkenes with tosylhydrazone salts as carbene precursors, thus showing that the catalyst is fully compatible with the in situ generation of diazo compounds from tosylhydrazone salts in cyclopropanation reactions.

2. Results and Discussion

The synthesis of cobalt(II) tetraaza[14]annulenes [Co(MeTAA)], [Co(MePhTAA)] and [Co(Bz-MeTAA)] is straightforward and is performed via a template condensation between 1,2-diaminobenzene and a 2,4-substituted diketone (Scheme 2).[19] The metal used for the template reaction can either be NiII or CoII. The nickel(II) complex has the advantage that is diamagnetic, that it is not sensitive to air and that it is easy to demetalate to obtain the free ligand. Substitution of the methine carbon of the 2,4-pentanediiminato ring is possible using aromatic acyl chlorides and is easier and higher yielding when using [Ni(MeTAA)] or [Ni(MePhTAA)] complexes rather than using the metal-free ligand. Heating the metal-free ligands in the presence of cobalt acetate in acetonitrile to reflux yields the desired cobalt(II) complexes in high yields.

The catalytic activity of the thus obtained cobalt(II) tetramethyltetraaza[14] annulene [Co(MeTAA)] was investigated, initially using ethyl diazoacetate (EDA) and methyl acrylate as the model substrates. This reaction was carried out at room temperature for 1 h in dichloromethane using 1.5 mol % catalyst, 1.0 equiv EDA and 3.0 equiv. methyl acrylate, yielding the desired cyclopropane product in 85% isolated yield. For comparison, cobalt(II) meso-tetraphenylporphyrin [Co(TPP)] was tested as a catalyst under identical conditions as well, yielding the cyclopropane in less than
30% isolated yield after 1 h. Therefore, the reaction was continued for 20 h, yielding 67% of the cyclopropane product. Hence, the [Co(MeTAA)] catalyst is much faster than [Co(PP)]. As is clear from the results summarized in Table 1, the [Co(MeTAA)] catalyst gave higher isolated yields of the cyclopropane products in a shorter amount of time, revealing the higher activity of this catalyst for the cyclopropanation of methyl acrylate with EDA. Moreover, the trans/cis ratio of 93:7 is superior to that of [Co(PP)] (88:12). Entry 8 shows the reaction in which EDA is added in excess (relative to methyl acrylate, being the limiting reagent) affording a similar yield of 87%. This means that both reagents, i.e. either the diazo compound or the alkene, can be interchangeably used as limiting reagents without a noticeable effect on the obtained yields. This has a net advantage over the well-established copper bis-oxazoline catalysts, for which the alkene always has to be present in excess and the diazo compound has to be added slowly to the reaction mixture. Not even traces of the dimerization products (maleates or fumarates) were observed when using [Co(MeTAA)] as the catalyst.

Several other Co\textsuperscript{II} complexes have been tested (Figure 3) in order to compare their activity to that of [Co(MeTAA)]. When comparing the activity of two catalysts belonging to the tetraazaannulene family (Table 1, entries 6-7), it is clear that all of them are active, with [Co(BzMeTAA)] (Table 1, entry 6) producing cyclopropanes in the highest isolated yield (97%). This is possibly due to the benzyl substituents slowing-down catalyst deactivation pathways (e.g. 1,4-addition of the alkene between the methine carbon of the 2,4-pentanediminato ring and the cobalt centre observed for the base catalyst).\[20\] Other complexes, such as [Co(salen)], proved to

**Scheme 2. Synthesis of cobalt(II) tetramethyltetraaza[14]annulene.**
be much slower and low yielding under the same applied reaction conditions (Table 1, entry 5).

**Table 1. Reaction conditions screening for the cyclopropanation of methylacrylate with EDA.**

<table>
<thead>
<tr>
<th>Ent.</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>time (h)</th>
<th>Yield (%)&lt;sup&gt;[b]&lt;/sup&gt;</th>
<th>trans: cis&lt;sup&gt;[e]&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>--</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>20</td>
<td>1</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>Co(OAc)&lt;sub&gt;2&lt;/sub&gt;*4H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>20</td>
<td>1</td>
<td>&lt;5</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>[Co(TPP)]</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>20</td>
<td>67</td>
<td>88:12</td>
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<td>20</td>
<td>58</td>
<td>88:12</td>
</tr>
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<td>18</td>
<td>43</td>
<td>70:30</td>
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<td>6</td>
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<td>PhMe</td>
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</tr>
<tr>
<td>7</td>
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<td>1</td>
<td>90</td>
<td>89:10</td>
</tr>
<tr>
<td>8&lt;sup&gt;[d]&lt;/sup&gt;</td>
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<td>1</td>
<td>87</td>
<td>93:7</td>
</tr>
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<td>[Co(MeTAA)]</td>
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<td>1</td>
<td>85</td>
<td>93:7</td>
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<td>94:6</td>
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<td>1</td>
<td>74</td>
<td>95:5</td>
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<tr>
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<td>[Co(MeTAA)]</td>
<td>PhCl</td>
<td>20</td>
<td>1</td>
<td>69</td>
<td>93:7</td>
</tr>
<tr>
<td>13</td>
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<td>CH&lt;sub&gt;3&lt;/sub&gt;CN : CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt; (4:1)</td>
<td>20</td>
<td>1</td>
<td>80</td>
<td>93:7</td>
</tr>
<tr>
<td>14</td>
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<td>CH&lt;sub&gt;3&lt;/sub&gt;OH : CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt; (4:1)</td>
<td>20</td>
<td>1</td>
<td>84</td>
<td>94:6</td>
</tr>
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<td>15</td>
<td>[Co(MeTAA)]</td>
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<td>10</td>
<td>1</td>
<td>80</td>
<td>93:7</td>
</tr>
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<td>2</td>
<td>74</td>
<td>97:3</td>
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<td>-78</td>
<td>5</td>
<td>67</td>
<td>99:1</td>
</tr>
<tr>
<td>18&lt;sup&gt;[e]&lt;/sup&gt;</td>
<td>[Co(MeTAA)]</td>
<td>PhMe</td>
<td>10</td>
<td>1</td>
<td>85&lt;sup&gt;[f]&lt;/sup&gt;</td>
<td>96:4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>75&lt;sup&gt;[b]&lt;/sup&gt;</td>
<td>95:5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6</td>
<td>14&lt;sup&gt;[i]&lt;/sup&gt;</td>
<td>95:5</td>
</tr>
</tbody>
</table>

<sup>[a]</sup> Reactions were carried out under N<sub>2</sub> with 1.0 equiv of EDA, 3.0 eq. of methylacrylate and 1.5 mol% catalyst. Concentration: 1.9 mmol EDA/5 mL solvent. <sup>[b]</sup> Isolated yields. <sup>[c]</sup> Determined by GC. <sup>[d]</sup> 1.0 eq. methylacrylate, 1.2 eq. EDA and 1.5 mol% catalyst. <sup>[e]</sup> Recyclability study performed, starting with 5.0 mol% catalyst <sup>[f]</sup> cycle 1 <sup>[g]</sup> cycle 2 <sup>[h]</sup> cycle 3 <sup>[i]</sup> cycle 4.
We decided to further explore the scope of the cyclopropanation reaction using the base catalyst [Co(MeTAA)], because it is simple, cheap and easier to synthesize in high quantities than [Co(Bz-MeTAA)]. Furthermore, when using nitrogen bases as additives the activity of this catalyst can be further improved to reach similar high yields as those obtained with [Co(Bz-MeTAA)] (vide infra), despite the latter being slightly more active than [Co(MeTAA)] in absence of additives.

Table 2. Additive screening for the cyclopropanation of acrylates with EDA and [Co(MeTAA)].

<table>
<thead>
<tr>
<th>Ent.</th>
<th>Olefin</th>
<th>Additive</th>
<th>Product</th>
<th>Yield (%)</th>
<th>trans: cis</th>
</tr>
</thead>
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<td></td>
<td>-</td>
<td><img src="image1.png" alt="Product 1" /></td>
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<td>97:3</td>
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<tr>
<td>2</td>
<td></td>
<td>N</td>
<td><img src="image2.png" alt="Product 2" /></td>
<td>94</td>
<td>97:3</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>P</td>
<td><img src="image3.png" alt="Product 3" /></td>
<td>90</td>
<td>97:3</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>-</td>
<td><img src="image4.png" alt="Product 4" /></td>
<td>52</td>
<td>93:7</td>
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<tr>
<td>5</td>
<td></td>
<td>S</td>
<td><img src="image5.png" alt="Product 5" /></td>
<td>45</td>
<td>94:6</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>N</td>
<td><img src="image6.png" alt="Product 6" /></td>
<td>70</td>
<td>94:6</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>P</td>
<td><img src="image7.png" alt="Product 7" /></td>
<td>79</td>
<td>93:7</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>N</td>
<td><img src="image8.png" alt="Product 8" /></td>
<td>81</td>
<td>93:7</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>N</td>
<td><img src="image9.png" alt="Product 9" /></td>
<td>83</td>
<td>94:6</td>
</tr>
</tbody>
</table>

[a] Performed at using 1.5 mol% [Co(MeTAA)] and 1.5 mol% additive under N2 with 1.0 eq. of EDA (0.48 M) and 2 eq. of olefin. [b] Performed using 1.5 mol% [Co(MeTAA)] and 25 mol% additive with 1.0 eq. of EDA (0.38 M) and 3 eq. of olefin. [c] Isolated yields. [d] Determined by GC.
After we determined that \([\text{Co(MeTAA)}]\) is capable of catalysing cyclopropanation reactions in both polar and nonpolar solvents, as well as at a wide range of temperatures, we decided to explore the effect of coordinating additives on the activity of the catalyst. Previous studies have shown that axial coordination of nitrogen donors to Co\textsuperscript{II} porphyrins increase the overall activity of the catalyst.\cite{21} Several additives, such as DMAP and N-methylimidazole were tested (Table 2), which showed that also for \([\text{Co(MeTAA)}]\) as the catalyst the yield increased from 78\% without additive (Table 2, entry 1) to 94\% in the presence of N-methylimidazole (1 eq. with respect to the catalyst; Table 2, entry 2).

To better illustrate the influence of the additive, the alkene has been changed to a more challenging one, such as methylmethacrylate (Table 2, entry 4), which without an additive affords the corresponding cyclopropane in only 52\% yield. On addition of an equimolar amount of N-methylimidazole w.r.t. the catalyst, the yield increases to 83\% (Table 2, entry 9). A positive effect is therefore observed upon coordination of a nitrogen donor on one face of the catalyst. Adding excess additive results in slightly reduced yields (Table 2, entries 6 and 8 vs entries 7 and 9), however still higher than without any additive. A partial blocking of both faces of the catalyst might play a role here. We hypothesise that the coordination of an additive to the cobalt(II) centre makes the catalyst more electron rich, thus more prone to carbene reduction and formation of the cobalt(III) carbene radical intermediate during catalysis, thus accelerating the reaction.

The increased yield of the cyclopropanation reaction due to coordination of additives to the catalyst led us to evaluate several other ligands, including chiral ones. These additives contain nitrogen donors that can coordinate to cobalt, as well as –OH and –NH groups which potentially stabilise intermediates during the catalytic cycle, through hydrogen bonding interactions. We hoped this could lead to chirality transfer as well. Additives such as 1-phenylethylamine, nicotine or ephedrine proved to be good additives for the cyclopropanation of methyl acrylate with EDA, increasing the yield up to 99\% (Table 3, entries 2, 4 and 5). Bulkier additives such as di-2-naphthylprolinol in combination with \([\text{Co(MeTAA)}]\) led to outstanding results in the cyclopropanation of styrene even at −78 °C (Table 3, entry 10), yielding the desired product almost quantitatively in a short reaction time. While the additives do have a beneficial effect on the overall yield and in shortening the reaction times, no chirality transfer was observed for any of the reactions using a chiral additive. Even when applying a high additive:catalyst ratio of 17:1 (25 mol\% additive) the products were isolated as racemic mixtures. This implies that the catalyst itself requires a chiral backbone for efficient chirality transfer.
Having optimized the reaction conditions, we decided to explore the substrate scope. Cyclopropanation of a total of 13 alkenes was tested including a variety of electron deficient acrylates (Table 4, entries 1-6) using a 1:1 mixture of [Co(MeTAA)] and N-methylimidazole in CH$_2$Cl$_2$ at room temperature under conditions in which the

**Table 3. (Chiral) additive screening in the [Co(MeTAA)]-catalysed cyclopropanation of methylacrylate and styrene.**

<table>
<thead>
<tr>
<th>Ent.</th>
<th>-R</th>
<th>Additive</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)$^b$</th>
<th>trans: cis $^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-COOMe</td>
<td>-</td>
<td>20</td>
<td>1</td>
<td>78</td>
<td>97:3</td>
</tr>
<tr>
<td>2</td>
<td>-COOMe</td>
<td>[diethylamine][PhCH$_3$]</td>
<td>20</td>
<td>1</td>
<td>99</td>
<td>94:6</td>
</tr>
<tr>
<td>3</td>
<td>-COOMe</td>
<td>[tert-butyl hydroxylamine][H$_2$C-$O$-$NH$-$NM$_e$]</td>
<td>20</td>
<td>1</td>
<td>81</td>
<td>95:5</td>
</tr>
<tr>
<td>4</td>
<td>-COOMe</td>
<td>[4-methylimidazole][N]</td>
<td>20</td>
<td>1</td>
<td>99</td>
<td>96:4</td>
</tr>
<tr>
<td>5</td>
<td>-COOMe</td>
<td>[1,2-dihydroxybenzylamine][H$_2$C-$O$-$NH$-$NM$_e$]</td>
<td>20</td>
<td>1</td>
<td>82</td>
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</tr>
<tr>
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<td>-COOMe</td>
<td>[d-aminophenylalanine][H$_2$C-$O$-$NH$-$NM$_e$]</td>
<td>0</td>
<td>2</td>
<td>83</td>
<td>97:3</td>
</tr>
<tr>
<td>7</td>
<td>-COOMe</td>
<td>[tert-butyl hydroxylamine][H$_2$C-$O$-$NH$-$NM$_e$]</td>
<td>-78</td>
<td>5</td>
<td>65</td>
<td>99:1</td>
</tr>
<tr>
<td>8</td>
<td>-Ph</td>
<td>-</td>
<td>20</td>
<td>1</td>
<td>85</td>
<td>85:15</td>
</tr>
<tr>
<td>9</td>
<td>-Ph</td>
<td>[1,2-dihydroxybenzylamine][H$_2$C-$O$-$NH$-$NM$_e$]</td>
<td>0</td>
<td>2</td>
<td>92</td>
<td>87:13</td>
</tr>
<tr>
<td>10</td>
<td>-Ph</td>
<td>[d-aminophenylalanine][H$_2$C-$O$-$NH$-$NM$_e$]</td>
<td>-78</td>
<td>5</td>
<td>98</td>
<td>89:11</td>
</tr>
<tr>
<td>11</td>
<td>-Ph</td>
<td>[octylphosphonic acid][O-$SiMe$_3][P$_n$]</td>
<td>-78</td>
<td>5</td>
<td>93</td>
<td>89:11</td>
</tr>
</tbody>
</table>

$^a$ Performed using 1.5 mol% [Co(MeTAA)] and 25 mol% additive with 1.0 eq. of EDA (0.38 M) and 3 eq. of olefin. $^b$ Isolated yields. $^c$ Determined by GC.
alkene is the limiting reagent. Reasonable yields in the range between 72-94% were obtained, as well as with good diastereoselectivities up to 97:3 favouring the trans isomer. A somewhat lower trans: cis ratio of 69:31 has been obtained for acrylonitrile, but this substrate is known to be more problematic, and previous catalysts did not achieve a higher ratio.\[22\] The yield could be significantly increased by using [Co(BzMeTAA)] instead of [Co(MeTAA)]. Substituted styrenes have also been tested (Table 4, entries 7-10), yielding around 80% of the isolated product, again the trans isomer being the favoured one. No general trend has been observed for the substitution pattern of styrene, being more consistent with a radical mechanism rather than a concerted one. As can be observed in entries 11-13, internal alkenes as well as electron rich alkenes are challenging substrates for [Co(MeTAA)].

Due to the intrinsic instability and explosive nature of diazo compounds in the absence of an electron withdrawing substituent, commercially available diazo compounds are mainly ester substituted ones. As such, only a few diazo compounds could be conveniently screened for these experiments (Table 4, entries 1, 14, 15), affording moderate to good yields, with a similar preference towards the trans-cyclopropane as the base reaction with EDA. The substrate scope can however be expanded by switching from the use of stable diazo compounds to tosylhydrazone salts as precursors for non-stabilized diazo compounds. Thermal decomposition of tosylhydrazone salts was developed in the group of Aggarwal as an attractive methodology to prepare substituted diazo compounds in situ.\[23\] They successfully applied this method in the catalytic synthesis of epoxides from ketones. However, with the rhodium and iron catalysts tested cyclopropane formation was much less successful using tosylhydrazone salts as carbene precursors, leading to poor yields and selectivities. As such, we wondered if [Co(MeTAA)] is more tolerant to (reaction conditions associated with) the use of tosylhydrazone salts as precursors to diazo compounds in one-pot catalytic transformations. Hence, we initially performed some screening experiments (Table 5) concerning the cyclopropanation of methyl acrylate with sodium benzyl tosylhydrazone salt, catalysed by [Co(MeTAA)] at 45 °C.
Table 4. Substrate Scope Varying both the Alkene and the Diazo compound.\[^{[a]}\]

\[
\begin{array}{cccccc}
\text{Ent.}^{[a]} & \text{-}R^1 & \text{Olefin} & \text{Product} & \text{Yield (\%)}^{[b]} & \text{trans: \textit{cis}}^{[c]} \\
0 & \text{-COOEt} & \text{-} & \text{-} & 94 & 97:3 \\
2 & \text{-COOEt} & \text{-} & \text{-} & 83 & 94:6 \\
3 & \text{-COOEt} & \text{-} & \text{-} & 75 & 90:10 \\
4 & \text{-COOEt} & \text{-} & \text{-} & 81 & 97:3 \\
5 & \text{-COOEt} & \text{-} & \text{-} & 79 & 69:31 \\
6 & \text{-COOEt} & \text{-} & \text{-} & 72 & 34:66 \\
7 & \text{-COOEt} & \text{-} & \text{-} & 93 & 86:14 \\
8 & \text{-COOEt} & \text{-} & \text{-} & 79 & 67:33 \\
9 & \text{-COOEt} & \text{-} & \text{-} & 79 & 78:22 \\
10 & \text{-COOEt} & \text{-} & \text{-} & 78 & 78:22 \\
11 & \text{-COOEt} & \text{-} & \text{-} & 9 & 5^{[d]} \\
12 & \text{-COOEt} & \text{-} & \text{-} & <1 & \text{n.d.} \\
13 & \text{-COOEt} & \text{-} & \text{-} & <2^{[d]} & \text{n.d.} \\
14 & \text{-COOEt} & \text{-} & \text{-} & 86 & 98:2 \\
15 & \text{-COOEt} & \text{-} & \text{-} & 72 & 82:18 \\
\end{array}
\]

\[^{[a]}\] Performed using 5 mol\% [Co(MeTAA)] and 5 mol\% N-methylimidazole with 1.0 eq. of olefin (0.47 M) and 1.2 eq. of EDA. \[^{[b]}\] Isolated yields. \[^{[c]}\] Determined by GC. \[^{[d]}\] [Co(BzMeTAA)] used instead of [Co(MeTAA)]
Table 5. Reaction conditions screening for the cyclopropanation of methylacrylate with sodium benzyl tosylhydrazone salt catalysed by [Co(MeTAA)].[{a}]

<table>
<thead>
<tr>
<th>Ent.</th>
<th>Solvent.</th>
<th>PTC [c]</th>
<th>Additive [d]</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>trans: cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃CN</td>
<td>--</td>
<td>--</td>
<td>45</td>
<td>18</td>
<td>80</td>
<td>74:26</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>--</td>
<td>--</td>
<td>45</td>
<td>18</td>
<td>67</td>
<td>76:24</td>
</tr>
<tr>
<td>3</td>
<td>PhMe</td>
<td>--</td>
<td>--</td>
<td>45</td>
<td>18</td>
<td>47</td>
<td>75:25</td>
</tr>
<tr>
<td>4</td>
<td>PhCl</td>
<td>--</td>
<td>--</td>
<td>45</td>
<td>18</td>
<td>52</td>
<td>76:24</td>
</tr>
<tr>
<td>5</td>
<td>Dioxane</td>
<td>--</td>
<td>--</td>
<td>45</td>
<td>18</td>
<td>13</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>1,2-dichloroethane</td>
<td>--</td>
<td>--</td>
<td>45</td>
<td>18</td>
<td>38</td>
<td>74:26</td>
</tr>
<tr>
<td>7</td>
<td>DMF</td>
<td>--</td>
<td>--</td>
<td>45</td>
<td>18</td>
<td>64</td>
<td>75:25</td>
</tr>
<tr>
<td>8b</td>
<td>MeOH</td>
<td>--</td>
<td>MeOH</td>
<td>45</td>
<td>18</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>9</td>
<td>THF</td>
<td>Aliquat®336</td>
<td>--</td>
<td>45</td>
<td>18</td>
<td>&gt;99</td>
<td>76:24</td>
</tr>
<tr>
<td>10</td>
<td>THF</td>
<td>Aliquat®336</td>
<td>--</td>
<td>45</td>
<td>4</td>
<td>&gt;99</td>
<td>76:24</td>
</tr>
<tr>
<td>11</td>
<td>THF</td>
<td>Aliquat®336</td>
<td>--</td>
<td>45</td>
<td>2</td>
<td>&gt;99</td>
<td>76:24</td>
</tr>
<tr>
<td>12</td>
<td>PhMe</td>
<td>Aliquat®336</td>
<td>--</td>
<td>45</td>
<td>18</td>
<td>&gt;99</td>
<td>76:24</td>
</tr>
<tr>
<td>13</td>
<td>PhCl</td>
<td>Aliquat®336</td>
<td>--</td>
<td>45</td>
<td>18</td>
<td>94</td>
<td>75:25</td>
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<tr>
<td>14</td>
<td>THF</td>
<td>Aliquat®336</td>
<td>--</td>
<td>20</td>
<td>18</td>
<td>85c</td>
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<tr>
<td>15</td>
<td>CH₂Cl₂</td>
<td>Aliquat®336</td>
<td>--</td>
<td>20</td>
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<td>16</td>
<td>CH₂Cl₂</td>
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</tr>
<tr>
<td>17</td>
<td>THF</td>
<td>--</td>
<td>1-methylimidazole</td>
<td>45</td>
<td>18</td>
<td>96</td>
<td>75:25</td>
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<tr>
<td>18</td>
<td>THF</td>
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<td>DMAP</td>
<td>45</td>
<td>18</td>
<td>86</td>
<td>74:26</td>
</tr>
<tr>
<td>19</td>
<td>THF</td>
<td>--</td>
<td>pyridine</td>
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<td>76:24</td>
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<tr>
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<td>THF</td>
<td>--</td>
<td>2,4,6-trimethylpyridine</td>
<td>45</td>
<td>18</td>
<td>&gt;99</td>
<td>76:24</td>
</tr>
</tbody>
</table>

[{a}] Reactions were carried out under N₂ with 1.0 equiv of sodium benzyl tosylhydrazone, 3.0 eq. of methylacrylate and 3 mol% [Co(MeTAA)]. Concentration: 0.675 mmol sodium benzyl tosylhydrazone /5 mL solvent; [{b}] methyl 3-methoxypropanoate is obtained as sole product; [{c}] 0.15 eq. Aliquat®336; [{d}] 0.5 eq. additive. [{f}] Aliquat®336 is a quaternary ammonium salt which contains a mixture of C8 (octyl) and C10 (decyl) chains with C8 predominating and a chloride counter ion.
We were happy to note that the catalyst is indeed tolerant to these reaction conditions, as this approach substantially broadens the substrate scope. Extended solvent screening was performed, testing eight different solvents (Table 5, entries 1-8). The highest yield was obtained in acetonitrile (80%) and THF (67%), while 1,2-dichloroethane (38%) and dioxane (13%) led to poor yields. Tosylhydrazone salts are insoluble in non-polar solvents such as toluene, and therefore are known to be troublesome for in situ diazo formation. This was confirmed in our studies. In toluene, the reaction afforded only 47% of the desired cyclopropane. However, phase transfer catalysts are known to enhance the rate of conversion of the tosylhydrazone salts into diazo compounds, even in non-polar solvents like toluene. Therefore, we tested Aliquat®336 in combination with a few solvents (Table 5, entries 9-15).

The effect is remarkable, the yield increasing to 99% (entry 9), even upon drastic reduction of the reaction time (entries 10-11) or lowering the reaction temperature to 20 °C (entry 14). Interestingly, solvents that are poor yielding in absence of this phase transfer catalyst, such as toluene, become viable solvents for this reaction in the presence of Aliquat®336 to afford almost quantitative yields of the desired cyclopropane product (entry 12).

Table 6. Substrate scope varying both the tosylhydrazone salt and the alkene.[a]

<table>
<thead>
<tr>
<th>Ent.</th>
<th>-R¹</th>
<th>Alkene</th>
<th>Product</th>
<th>Yield (%)</th>
<th>trans: cis</th>
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<td>1</td>
<td>-Ph</td>
<td>OMe</td>
<td><img src="image1" alt="Diagram" /></td>
<td>94</td>
<td>78:22</td>
</tr>
<tr>
<td>2</td>
<td>-CN</td>
<td>OMe</td>
<td><img src="image2" alt="Diagram" /></td>
<td>68</td>
<td>70:30</td>
</tr>
<tr>
<td>3</td>
<td>-NO₂</td>
<td>OMe</td>
<td><img src="image3" alt="Diagram" /></td>
<td>63</td>
<td>72:28</td>
</tr>
<tr>
<td>4</td>
<td>-OMe</td>
<td>OMe</td>
<td><img src="image4" alt="Diagram" /></td>
<td>94</td>
<td>74:26</td>
</tr>
</tbody>
</table>
Diastereoselective Radical-Type Cyclopropanation of Electron Deficient Alkenes

Since nitrogen donor additives have a positive influence on the activity of [Co(MeTAA)] (vide supra), we decided to test their effect in combination with tosylhydrazone salts as well (Table 5, entries 17-20), this time in the absence of Aliquat®336 as phase transfer catalyst. 1-methylimidazole performs again better than DMAP with a yield of 96% vs 86%. The best results were obtained with pyridine and 2,4,6-trimethylpyridine though, both of which leading to almost quantitative formation of the desired cyclopropane with a negligible effect on the diastereoselectivity. Due to high yields obtained using either a phase transfer catalyst (PTC) or a nitrogen-donor ligand additive, using both would be redundant for these specific reactions. However, the mechanisms of action of the quaternary ammonium salt Aliquat®336 and nitrogen-donor ligand additives are totally different, even it might seem that they lead to similar results. The PTC favours the in situ generation
of the diazo compound, while the nitrogen donor additive enhances the electron donating properties of the cobalt catalyst. Therefore, we decided to move forward in screening the substrate scope without adding any nitrogen-donor ligands, but in the presence of Aliquat®336 as a PTC. However, it might be beneficial to use a combination of both for more challenging substrates. Five substituted sodium tosylhydrazone salts were used in the cyclopropanation of methyl acrylate. Tosylhydrazone salts containing electron donating substituents afforded the desired products in high yields of 94-97%. Tosylhydrazone salts containing electron withdrawing substituents resulted in somewhat lower yields (Table 6, entries 2 and 3). The reaction of the iPr-substituted tosylhydrazone salt and four electron deficient alkenes, part of the acrylates family have been tested and afforded the desired cyclopropanes in yields up to 97% (Table 6, entries 5-8). Remarkably, acrylonitrile yielded the substituted cyclopropane in 96% yield with a 3:1 trans: cis selectivity (entry 7). Substituted styrenes (entries 9-11) are also easily cyclopropanated using [Co(MeTAA)] and tosylhydrazone salts (entries 1,4 and 5).

3. Conclusions

We have shown that cobalt(II) tetraaza[14]annulene complexes are highly active in catalytic cyclopropanation of electron deficient alkenes. These low spin cobalt(II) catalysts are cheap, easy to synthesize, afford high cyclopropanation yields and their activity is superior to that of [Co(PP)]. Fast and selective carbene transfer reactions are achieved by taking advantage of the radical mechanism involving discrete cobalt(III)-carbene radical species, with unwanted carbene-carbene dimerization and 1,3-dipolar addition reactions between the electron deficient alkene and the diazo reagent being almost completely suppressed. In addition, a new one-pot protocol was presented that uses in situ generated diazo compounds. This method substantially expands the substrate scope by taking advantage of the compatibility between the catalyst and the thermal decomposition of tosylhydrazone salts in one-pot transformations. This method yields substituted cyclopropanes in almost quantitative yield, using relative low catalyst loadings. All reactions described in this paper can be performed in a one-pot fashion, are practical and fast, tolerant to many solvents, can be performed in a broad temperature range and do not require slow addition of any of the components. The reaction is diastereoselective, the trans isomer being the one favoured in all cases. The formation of side-products is kept to a minimum. To fully elucidate the mechanism of the [Co(MeTAA)] complex during radical catalysis, in depth kinetic studies and DFT investigations are required. These studies are reported in the following chapter.
**4. Experimental Section**

**General Considerations.** All manipulations were performed under a nitrogen atmosphere using standard Schlenk techniques. All solvents used for catalysis were dried over and distilled from sodium (toluene, tetrahydrofuran, diethyl ether) or CaH₂ (dichloromethane, methanol, acetonitrile). Diazocompounds and alkenes have been degassed using the freeze-thaw-pump-method prior to use. Acrylates are passed through basic alumina before use, to remove radical scavengers. All other chemicals were purchased from commercial suppliers (Sigma Aldrich, Acros or Strem) and used without further purification. NMR spectra (¹H, and ¹³C{¹H}) were measured on a Bruker AV400, AV300, DRX 500 or DRX 300 spectrometer. Unless noted otherwise, the NMR spectra were measured in CDCl₃. Individual peaks are reported as: multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant in Hz. Mass spectra of the synthesized compounds were recorded on an Agilent-5973 GC-MS spectrometer, and the corresponding HRMS data were recorded on a JEOL AccuTOF 4G via direct injection probe using either EI or ESI. The GC used for isomer separation is a Shimadzu 17A with a Supelco SPB TM–1 Fused Silica Capillary Column with a length of 30 m, a diameter of 0.32 mm and a film thickness of 2.0 µm.

**Catalyst preparation.** [Co(MeTAA)], [Co(MePhTAA)] and [Co(Bz-MeTAA)] have been synthesized according to reported procedures.¹⁹ [Co(TPP)] and [Co(salen)] have been purchased from Sigma-Aldrich and used without further purification.

**General Procedure for Cyclopropanation using Diazo Compounds.** Under a nitrogen atmosphere, catalyst (0.05 eq.) was added to a flame-dried Schlenk tube. The tube was capped, evacuated, and backfilled with nitrogen. The solid was dissolved, followed by the addition of the additive (0.05 eq.) and alkene (1.0 eq., 0.48M). Then, diazo compound (1.2 eq.) was added, and the solution was left stirring for 1h. After the reaction finished, the resulting mixture was concentrated and the residue was purified by flash chromatography (silica gel) or extracted in pentane.

**General Procedure for Synthesis of the N-tosylhydrazone salts.**²⁹ An equimolar mixture of corresponding aldehyde and N-tosylhydrazide was placed in a round bottom flask and dissolved in methanol (2 mL/mmol). The reaction mixture was stirred overnight at room temperature. The white precipitate was collected by filtration, and washed with cold methanol and hexane to obtain the pure product. The formed N-tosylhydrazone was then deprotonated in methanol using 1 equivalent of sodium methoxide. After evaporation of methanol, the pure product was obtained as a white powder.

**General Procedure for Cyclopropanation using N-tosylhydrazone salts.** Under a nitrogen atmosphere, the respective N-tosylhydrazone salt (1.0 eq.), catalyst (0.03 eq.) and Aliquat@336 (0.15 eq.) were added to a flame-dried Schlenk tube in the glovebox. The tube was capped, evacuated, and backfilled with nitrogen. Then, alkene (3.0 eq., 0.405 M) and solvent were added. The Schlenk tube was then placed in an oil bath and heated to 50 °C under nitrogen for a set period. After the reaction finished, the resulting mixture was concentrated and the residue was purified by flash chromatography (silica gel) or extracted in pentane.
Catalyst characterization:

[Co(MeTAA)] :

**Elemental analysis** calcd. for C\textsubscript{22}H\textsubscript{22}CoN\textsubscript{4}: C, 65.83; H, 5.52; N, 13.96; calcd. for C\textsubscript{22}H\textsubscript{22}CoN\textsubscript{4}.1.5H\textsubscript{2}O: C, 61.68; H, 5.88; N, 13.08; Found: C, 61.46; H, 5.67; N, 12.58. **HRMS (EI):** Calcd. for C\textsubscript{22}H\textsubscript{22}CoN\textsubscript{4}, m/z 401.1176, Found m/z 401.1156

**EPR spectrum:**

[Co(MePhTAA)] :

**Elemental analysis** calcd. for C\textsubscript{32}H\textsubscript{26}CoN\textsubscript{4}: C, 73.14; H, 4.99; N, 10.66; calcd. for C\textsubscript{32}H\textsubscript{26}CoN\textsubscript{4}.H\textsubscript{2}O: C, 70.71; H, 5.19; N, 10.31; Found: C, 70.71; H, 5.25; N, 10.59. **HRMS (ESI):** Calcd. for C\textsubscript{32}H\textsubscript{26}CoN\textsubscript{4}, m/z 525.1489, Found m/z 525.1503

**EPR spectrum:**
[Co(Bz-MeTAA)] :

**Elemental analysis** calcd. for C\textsubscript{36}H\textsubscript{30}CoN\textsubscript{4}O\textsubscript{2}: C, 70.93; H, 4.96; N, 9.19; calcd. for C\textsubscript{36}H\textsubscript{30}CoN\textsubscript{4}O\textsubscript{2}·H\textsubscript{2}O: C, 68.90; H, 5.14; N, 8.93; Found: C, 68.72; H, 5.48; N, 8.57. **HRMS (ESI)**: Calcd. for C\textsubscript{36}H\textsubscript{30}CoN\textsubscript{4}O\textsubscript{2} m/z 609.1701, Found m/z 609.1699

**EPR spectrum**:

[Co(MeTAA)]: 1-Methylimidazole adduct:

According to literature studies\cite{26} even when using excess 1-methylimidazole only the 5-coordinate species (1:1 adduct) is formed, the 6 coordinate not being formed (1:2 adduct). We have observed identical behaviour as reported, see data below:

**HRMS (ESI)**: Calcd. for [Co(MeTAA)]-N-Mel (C\textsubscript{22}H\textsubscript{22}CoN\textsubscript{4})(C\textsubscript{4}H\textsubscript{6}N\textsubscript{2}) m/z 483.1707, Found m/z 483.1701.

**EPR spectrum**: 5-coordinate cobalt spectrum.
Chapter 2

[Co(MePhTAA)] : 1-Methylimidazole adduct :

**EPR spectrum**: 5-coordinate cobalt spectrum.

---

[Co(Bz-MeTAA)] : 1-Methylimidazole adduct :

**EPR spectrum**: 5-coordinate cobalt spectrum.
Product characterization:

**Ethyl methyl 1,2-cyclopropanedicarboxylate**

Trans-isomer: \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 4.06 (q, \(J = 7.1\) Hz, 2H), 3.61 (s, 3H), 2.14 – 2.01 (m, 2H), 1.38 - 1.30 (m, 2H), 1.18 (t, \(J = 7.2\) Hz, 3H). \(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta\) 172.20, 171.65, 61.04, 52.09, 22.37, 22.08, 15.28, 14.13. \(\text{HRMS (EI)}:\) Calcd. for C\(_8\)H\(_{12}\)O\(_4\) m/z 172.0736, Found m/z 172.0737. \(\text{GC analysis}:\) Supelco SPB-1 (Temp program: initial temp = 70° C, 7.00° C/min, final temp = 250° C, final time = 5.00 min) \(\text{trans-isomer: } t = 14.66\) min, \(\text{cis-isomer: } t = 14.93\) min.

**Ethyl tert-butyl 1,2-cyclopropanedicarboxylate**

Trans-isomer: \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 4.14 (q, \(J = 7.1\) Hz, 2H), 2.08 (tq, \(J = 7.0, 3.6\) Hz, 2H), 1.45 (s, 9H), 1.36 (t, \(J = 7.3\) Hz, 2H), 1.27 (t, \(J = 7.3\) Hz, 2H). \(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta\) 171.87, 170.70, 81.03, 60.82, 27.88, 23.27, 21.93, 15.07, 14.03. \(\text{HRMS (EI)}:\) Calcd. for C\(_9\)H\(_{15}\)O\(_4\) m/z 199.09703, Found m/z 199.09531. \(\text{GC analysis}:\) Supelco SPB-1 (Temp program: initial temp = 70° C, 7.00° C/min, final temp = 250° C, final time = 5.00 min) \(\text{trans-isomer: } t = 17.87\) min, \(\text{cis-isomer: } t = 18.15\) min.

**Diethyl-1,2-cyclopropanedicarboxylate**

Trans-isomer: \(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta\) 4.20 (q, \(J = 7.1\) Hz, 4H), 2.27 – 2.17 (m, 2H), 1.55 – 1.41 (m, 2H), 1.32 (t, \(J = 7.1\) Hz, 6H). \(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) \(\delta\) 171.77, 137.68, 126.91, 77.59, 77.14, 61.07, 22.36, 21.19, 15.31, 14.17. \(\text{HRMS (EI)}:\) Calcd. for C\(_9\)H\(_{14}\)O\(_4\) m/z 186.08921, Found m/z 186.08977. \(\text{GC analysis}:\) Supelco SPB-1 (Temp program: initial temp = 70° C, 7.00° C/min, final temp = 250° C, final time = 5.00 min) \(\text{cis-isomer: } t = 15.54\) min, \(\text{trans-isomer: } t = 15.84\) min.

**Ethyl 2-cyano cyclopropanecarboxylate**

Trans-isomer: \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 4.18 (q, \(J = 7.1\) Hz, 2H), 2.25 (ddd, \(J = 8.8, 6.0, 4.3\) Hz, 1H), 1.93 (dd, \(J = 9.2, 6.3, 4.3\) Hz, 1H), 1.49 (ddd, \(J = 14.9, 8.8, 6.2, 4.9\) Hz, 2H), 1.28 (t, \(J = 7.2\) Hz, 3H). \(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta\) 170.02, 119.14, 61.66, 20.94, 14.41, 13.97, 5.52. \(\text{HRMS (EI)}:\) Calcd. for C\(_7\)H\(_9\)N\(_2\)O\(_2\) m/z 139.06333, Found m/z 139.06263. \(\text{GC analysis}:\) Supelco SPB-1 (Temp program: initial temp = 70° C, 7.00° C/min, final temp = 250° C, final time = 5.00 min) \(\text{trans-isomer: } t = 12.38\) min, \(\text{cis-isomer: } t = 14.35\) min.
Ethyl 2-cyano 2-methyl cyclopropanecarboxylate

Cis-isomer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.28 (q, $J = 7.0$ Hz, 2H), 1.92 (dd, $J = 8.0$, 6.4 Hz, 1H), 1.84 (dd, $J = 6.4$, 5.1 Hz, 1H), 1.51 (s, 3H), 1.35 (t, $J = 7.2$, 3H), 1.25 (dd, $J = 8.1$, 5.0 Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 168.91, 120.06, 61.67, 27.92, 21.81, 20.97, 14.23, 13.91. Trans-isomer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.23 (q, $J = 7.1$ Hz, 2H), 2.37 - 2.32 (m, 1H), 1.63 (dd, $J = 8.9$, 5.4 Hz, 1H), 1.54 (s, 3H), 1.45 (dd, $J = 6.8$, 5.3 Hz, 1H), 1.3 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 168.70, 122.49, 61.62, 26.14, 19.81, 14.87, 14.26, 12.79. HRMS (EI): Calcd. for C$_8$H$_{11}$N$_1$O$_2$ m/z 153.07898, Found m/z 153.07948.

Ethyl 2-phenyl cyclopropanecarboxylate

Trans-isomer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.31 (t, 2H), 7.23 (t, 2H), 7.14 (d, 1H), 4.22 (q, $J = 7.1$ Hz, 2H), 2.57 (m, 1H), 1.96 (m, 1H), 1.65 (m, 1H), 1.36 (m, 1H), 1.33 (t, $J = 7.1$ Hz 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 173.49, 140.19, 128.54, 126.54, 126.22, 60.79, 26.27, 24.30, 17.18, 14.36. Cis-isomer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.31 (t, 2H), 7.23 (t, 2H), 7.14 (d, 1H), 3.91 (q, 2H), 2.61 (m, 1H), 2.11 (m, 1H), 1.75 (m, 1H), 1.35 (m, 1H), 1.01 (t, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 171.05, 136.63, 129.38, 127.95, 126.71, 60.25, 25.56, 21.89, 14.11, 11.20. GC analysis: Supelco SPB-1 (Temp program: initial temp = 70° C, 7.00° C/min, final temp = 250° C, final time = 5.00 min) trans-isomer: $t = 20.16$ min, cis-isomer: $t = 21.14$ min.

Ethyl 2-phenyl 2-methyl cyclopropanecarboxylate

Trans-isomer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36–7.31 (m, 4H), 7.28–7.22 (m, 1H), 4.29–4.20 (m, 2H), 2.01 (dd, $J = 8.3$, 6.0 Hz, 1H), 1.58 (s, 3H), 1.50–1.43 (m, 2H), 1.34 (t, $J = 7.1$ Hz, 3H). Cis-isomer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36–7.31 (m, 4H), 7.28–7.22 (m, 1H), 3.88 (p, $J = 7.1$ Hz, 2H), 1.95 (dd, $J = 7.8$, 5.4 Hz, 1H), 1.83 (t, $J = 5.1$ Hz, 1H), 1.51 (s, 3H), 1.19 (dd, $J = 7.8$, 4.7 Hz, 1H), 0.99 (t, $J = 7.1$ Hz, 3H). HRMS (EI): Calcd. for C$_{13}$H$_{16}$O$_2$ m/z 204.11503, Found m/z 204.11390. GC analysis: Supelco SPB-1 (Temp program: initial temp = 70° C, 7.00° C/min, final temp = 250° C, final time = 5.00 min) cis-isomer: $t = 20.04$ min, trans-isomer: $t = 21.05$ min.

Ethyl 2-(4-methoxyphenyl)cyclopropanecarboxylate

Trans-isomer: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.50–7.33 (m, 2H), 7.21–7.06 (m, 2H), 4.27 (q, $J = 7.1$ Hz, 2H), 3.85 (s, 3H), 2.68–2.53 (m, 1H), 1.98 (dd, $J = 6.4$, 1.6 Hz, 1H), 1.97–1.87 (m, 1H), 1.72–1.61 (m, 1H), 1.38 (t, $J = 7.1$ Hz, 3H). HRMS (EI): Calcd. for C$_{13}$H$_{16}$O$_3$ m/z 220.10994, Found m/z 220.10877. GC analysis: Supelco SPB-1 (Temp program: initial temp = 70° C, 7.00° C/min, final temp = 250° C, final time = 5.00 min) cis-isomer: $t = 24.69$ min, trans-isomer: $t = 26.90$ min.
Diastereoselective Radical-Type Cyclopropanation of Electron Deficient Alkenes

**Ethyl 2-(4-methylphenyl)cyclopropanecarboxylate**

*Trans*-isomer: *^1^H NMR* (300 MHz, CDCl$_3$) $\delta$ 7.23 – 7.08 (m, 4H), 4.30 (q, $J = 7.2$ Hz, 2H), 2.63 (m, 1H), 2.44 (s, 3H), 2.00 (m, 1H), 1.71 (m, 1H), 1.43 – 1.38 (m, 4H). *HRMS (EI)*: Calcd. for C$_{13}$H$_{16}$O$_2$, m/z 204.11503, Found m/z 204.11448. *GC analysis*: Supelco SPB-1 (Temp program: initial temp = 70° C, 7.00° C/min, final temp = 250° C, final time = 5.00 min) *trans*-isomer: $t = 16.26$ min, *cis*-isomer: $t = 16.53$ min.

**1-tert-butyl 2-methyl cyclopropane-1,2-dicarboxylate**

*Trans*-isomer: *^1^H NMR* (400 MHz, CDCl$_3$) $\delta$ 3.66 (s, 3H), 2.04 (m, 2H), 1.41 (s, 9H), 1.33 (m, 2H). *^13^C NMR* (101 MHz, CDCl$_3$) $\delta$ 172.53, 170.83, 81.29, 52.12, 28.08, 23.55, 21.93, 15.26. *HRMS (EI)*: Calcd. for C$_9$H$_{13}$O$_4$ [M – CH$_3$] $m/z = 185.08138$, found m/z = 185.08135. *GC analysis*: Supelco SPB-1 (Temp program: initial temp = 70° C, 7.00° C/min, final temp = 250° C, final time = 5.00 min) *trans*-isomer: $t = 20.76$ min, *cis*-isomer: $t = 21.03$ min.

**1-benzyl 2-methyl cyclopropane-1,2-dicarboxylate**

*Trans*-isomer: *^1^H NMR* (400 MHz, CDCl$_3$) $\delta$ 7.39 (m, 5H), 5.16 (s, 2H), 3.72 (s, 3H), 2.25 (m, 2H), 1.49 (m, 2H). *^13^C NMR* (101 MHz, CDCl$_3$) $\delta$ 172.12, 171.59, 135.57, 128.64, 128.42, 128.32, 66.92, 52.19, 22.40, 22.34, 15.54. *HRMS (EI)*: Calcd. for C$_{13}$H$_{14}$O$_4$, m/z = 234.0892, found m/z = 234.0900. *GC analysis*: Supelco SPB-1 (Temp program: initial temp = 70° C, 7.00° C/min, final temp = 250° C, final time = 5.00 min) *cis*-isomer: $t = 24.17$ min, *trans*-isomer: $t = 24.65$ min.

**Methyl 2-phenylcyclopropanecarboxylate**

*Trans*-isomer: *^1^H NMR* (400 MHz, Chloroform- $d$) $\delta$ 7.30 (d, $J = 4.6$ Hz, 2H), 7.26 – 7.21 (m, 1H), 7.17 – 7.10 (m, 2H), 3.75 (s, 3H), 2.61 – 2.53 (m, 1H), 1.95 (ddd, $J = 8.2$, 5.3, 4.1 Hz, 1H), 1.65 (dt, $J = 9.8$, 4.9 Hz, 1H), 1.38 – 1.32 (m, 1H); *^13^C NMR* (101 MHz, Chloroform- $d$) $\delta$ 173.75, 139.87, 128.38, 127.82, 126.09, 51.80, 26.18, 23.86, 16.94; *Cis*-isomer: *^1^H NMR* (400 MHz, Chloroform- $d$) $\delta$ 7.72 – 7.66 (m, 2H), 7.41 – 7.35 (m, 2H), 3.47 (s, 3H), 2.66 – 2.60 (m, 1H), 1.77 – 1.73 (m, 1H), 1.42 – 1.38 (m, 1H); *^13^C NMR* (101 MHz, Chloroform- $d$) $\delta$ 171.30, 136.34, 129.10, 126.58, 126.42, 51.34, 25.51, 21.56, 11.27; *HRMS (EI)*: Calcd. for C$_{11}$H$_{12}$O$_2$, m/z = 176.0837, found m/z = 176.0828.

**Methyl 2-(4-cyanophenyl)cyclopropanecarboxylate**

*Trans*-isomer: *^1^H NMR* (400 MHz, Chloroform- $d$) $\delta$ 7.60 – 7.57 (m, 2H), 7.22 – 7.18 (m, 2H), 3.75 (s, 3H), 2.59 – 2.51 (m, 1H), 1.98 (ddd, $J = 8.5$, 5.5, 4.2 Hz, 1H), 1.74 – 1.68 (m, 1H), 1.38 (ddd, $J = 8.6$, 6.4, 4.8 Hz, 1H); *^13^C NMR* (101 MHz, Chloroform- $d$) $\delta$ 172.90, 145.68, 132.51, 132.19, 126.70, 118.66, 106.50, 52.03, 25.83, 24.51, 17.41; *Cis*-isomer: *^1^H NMR* (400 MHz, Chloroform- $d$) $\delta$ 7.72 – 7.66 (m, 2H), 7.41 – 7.35 (m, 2H), 3.49 (s, 3H), 2.61 (d, $J = 8.8$ Hz, 1H), 2.21 (ddd, $J = 9.2$, 8.0, 5.7 Hz, 1H), 1.79 – 1.75 (m, 1H), 1.46 (td, $J = 8.3$, 5.3 Hz, 1H); *^13^C NMR* (101 MHz, Chloroform- $d$) $\delta$ 170.78, 142.07,
131.59, 130.19, 129.88, 129.35, 127.17, 110.15, 51.59, 25.32, 22.00, 11.68. **HRMS (EI):** Calcd. for C_{12}H_{11}NO_2, m/z = 201.0790, found m/z = 201.0784.

**Methyl 2-(4-nitrophenyl)cyclopropanecarboxylate**

*Trans-isomer: * $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 8.17 (dd, $J$ = 8.7, 3.3 Hz, 2H), 7.28 - 7.19 (m, 2H), 3.76 (s, 3H), 2.66 - 2.58 (m, 1H), 2.03 (ddd, $J$ = 9.2, 5.4, 4.1 Hz, 1H), 1.76 (dt, $J$ = 9.8, 5.1 Hz, 1H), 1.42 (ddd, $J$ = 8.5, 6.6, 5.0 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl_3) $\delta$ 172.80, 129.94, 126.64, 123.70, 123.05, 105.95, 99.87, 52.08, 27.77, 25.67, 17.70. **HRMS (EI):** Calcd. for C_{11}H_{11}NO_4, m/z = 221.0688, found m/z = 221.06773.

**Methyl 2-(4-methoxyphenyl)cyclopropanecarboxylate**

*Trans-isomer: * $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 7.06 (d, $J$ = 7.1 Hz, 2H), 6.85 (d, $J$ = 7.2 Hz, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 2.52 (ddd, $J$ = 9.9, 6.1, 3.6 Hz, 1H), 1.91 - 1.80 (m, 1H), 1.64 - 1.52 (m, 1H), 1.29 (ddd, $J$ = 8.3, 6.3, 4.4, 1.4 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl_3) $\delta$ 172.80, 129.94, 126.64, 123.70, 123.05, 105.95, 99.87, 52.08, 27.77, 25.67, 17.70. **HRMS (EI):** Calcd. for C_{12}H_{14}O_3, m/z = 206.0943, found m/z = 206.0940.

**Methyl 2-(4-isopropylphenyl)cyclopropanecarboxylate**

*Trans-isomer: * $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 7.18 (d, $J$ = 8.2 Hz, 2H), 7.07 (d, $J$ = 8.2 Hz, 2H), 3.75 (s, 3H), 2.93 - 2.83 (m, 1H), 2.57 - 2.48 (m, 1H), 1.92 (ddd, $J$ = 8.3, 5.3, 3.1 Hz, 1H), 1.62 (dt, $J$ = 9.5, 4.9 Hz, 1H), 1.36 - 1.33 (m, 1H), 1.27 (d, $J$ = 6.9 Hz, 6H); $^{13}$C NMR (101 MHz, CDCl_3) $\delta$ 177.21, 126.42, 126.08, 51.78, 33.63, 25.96, 23.89, 23.76, 21.57, 16.82. **Cis-isomer: * $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 7.25 - 7.14 (m, 4H), 3.75 (d, $J$ = 0.8 Hz, 3H), 2.98 - 2.89 (m, 1H), 2.80 (dd, $J$ = 9.2, 7.1 Hz, 1H), 1.71 (dd, $J$ = 9.3, 4.5 Hz, 1H), 1.27 (dd, $J$ = 6.9, 0.7 Hz, 6H), 1.20 - 1.15 (m, 1H), 1.03 (s, 3H); $^{13}$C NMR (101 MHz, CDCl_3) $\delta$ 176.05, 147.17, 134.01, 129.10, 126.11, 51.91, 33.60, 31.38, 24.90, 23.89, 23.87, 20.00, 14.45. **Cis-isomer: * $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 7.12 (s, 4H), 3.34 (d, $J$ = 0.7 Hz, 3H), 2.90 - 2.85 (m, 1H), 2.32 (t, $J$ = 8.0 Hz, 1H), 1.96 (dd, $J$ = 7.3, 4.9 Hz, 1H), 1.52 (s, 3H), 1.25 (d, $J$ = 7.1 Hz, 6H), 1.15 - 1.10 (m, 1H); $^{13}$C NMR (101 MHz, CDCl_3) $\delta$ 172.91, 146.84, 134.41, 128.74, 125.73, 51.16, 33.46, 27.63, 24.90, 23.91, 23.89, 21.19, 18.84. **HRMS (EI):** Calcd. for C_{15}H_{20}O_2, m/z = 232.1463, found m/z = 232.1464.
Diastereoselective Radical-Type Cyclopropanation of Electron Deficient Alkenes

2-(4-Isopropylphenyl)cyclopropanecarbonitrile

Trans-isomer: $^1$H NMR (400 MHz, Chloroform-d) δ 7.21 (d, $J = 8.1$ Hz, 2H), 7.07 (d, $J = 8.1$ Hz, 2H), 2.92 (p, $J = 6.9$ Hz, 1H), 2.64 (ddd, $J = 9.2$, 6.7, 4.7 Hz, 1H), 1.62 (dt, $J = 9.2$, 5.2 Hz, 1H), 1.55 (dd, $J = 8.8$, 5.0 Hz, 1H), 1.46 (ddd, $J = 8.7$, 6.7, 5.0 Hz, 1H), 1.27 (d, $J = 6.9$ Hz, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 148.14, 134.81, 126.71, 126.24, 121.09, 33.66, 24.58, 23.85, 15.05, 6.39. HRMS (EI): Calcd. for [M-CH$_2$]$^+$, C$_{14}$H$_{17}$N, m/z = 185.1204, found m/z = 185.1209.

2-(4-Isopropylphenyl)-N,N-dimethylcyclopropanecarboxamide

Trans-isomer: $^1$H NMR (400 MHz, Chloroform-d) δ 7.17 (d, $J = 8.1$ Hz, 2H), 7.11–7.04 (m, 2H), 3.15 (s, 3H), 3.01 (s, 3H), 2.89 (dq, $J = 13.7$, 7.0 Hz, 1H), 2.49–2.40 (m, 1H), 1.99 (ddd, $J = 9.2$, 5.3, 4.2 Hz, 1H), 1.25 (d, $J = 6.9$ Hz, 7H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.97, 146.77, 138.31, 126.36, 125.98, 37.21, 35.76, 33.58, 25.16, 23.91, 22.86, 16.08, 10.36. HRMS (EI): Calcd. for [M-CH$_2$]$^+$, C$_{15}$H$_{21}$NO, m/z = 231.1623, found m/z = 231.1629.

1-Isopropyl-4-(2-phenylcyclopropyl)benzene

Trans-isomer: $^1$H NMR (400 MHz, Chloroform-d) δ 7.40–7.33 (m, 2H), 7.32–7.20 (m, 5H), 7.17 (d, $J = 8.2$ Hz, 2H), 2.98 (p, $J = 6.9$ Hz, 1H), 2.31–2.14 (m, 2H), 1.60–1.47 (m, 2H), 1.34 (d, $J = 6.9$ Hz, 5H), 1.25 (d, $J = 6.9$ Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 146.34, 142.65, 139.83, 128.94, 128.85, 128.45, 128.32, 127.57, 127.01, 126.40, 125.70, 125.61, 33.68, 27.15, 27.04, 18.08, 11.72. HRMS (EI): Calcd. for [M-CH$_2$]$^+$, C$_{18}$H$_{20}$, m/z = 236.1565, found m/z = 236.1554.

1-Isopropyl-4-(2-(4-methoxyphenyl)cyclopropyl)benzene

Trans-isomer: $^1$H NMR (400 MHz, Chloroform-d) δ 7.24–7.17 (m, 2H), 7.16–7.08 (m, 4H), 6.91–6.86 (m, 2H), 3.84 (s, 3H), 2.93 (hept, $J = 7.0$ Hz, 1H), 2.14 (dd, $J = 19.6$, 8.2, 6.5, 4.5 Hz, 2H), 1.41 (ddd, $J = 8.3$, 6.1, 1.9 Hz, 2H), 1.30 (d, $J = 6.9$ Hz, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 157.70, 146.19, 139.98, 134.60, 130.00, 128.59, 126.79, 126.32, 125.57, 113.74, 55.23, 33.61, 27.15, 27.04, 23.98, 17.61. HRMS (EI): Calcd. for [M-CH$_2$]$^+$, C$_{19}$H$_{22}$O, m/z = 266.1670, found m/z = 266.1660.

1-Fluoro-4-(2-(4-isopropylphenyl)cyclopropyl)benzene

Trans-isomer: $^1$H NMR (400 MHz, Chloroform-d) δ 7.20 (d, $J = 8.0$ Hz, 2H), 7.16–7.05 (m, 4H), 7.04–6.97 (m, 2H), 2.93 (p, $J = 6.9$ Hz, 1H), 2.22–2.08 (m, 2H), 1.42 (ddt, $J = 17.8$, 8.5, 5.7 Hz, 2H), 1.29 (dd, $J = 6.9$, 0.8 Hz, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 162.29, 159.87, 146.40, 139.55, 138.13, 138.10, 128.64, 127.14.
54. Acknowledgements

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6. References

Diastereoselective Radical-Type Cyclopropanation of Electron Deficient Alkenes


