Activating Aldehyde C–H Bonds: Applications to Hydroacylation and Transfer Hydroformylation

by

Stephen K. Murphy

A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy

Department of Chemistry
University of Toronto

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Abstract

Cross-couplings that proceed via C–H bond activation streamline the synthesis of complex molecules. Rhodium complexes are promising catalysts for these reactions and they readily activate aldehyde C–H bonds to generate acyl-rhodium$^{III}$-hydrides. Developing strategies to control the reactivity of these oxidative addition products enables developments in hydroacylation and hydroformylation.

Chapter 1 describes a cooperative catalysis strategy for branched-selective hydroacylation of alkenyl alcohols with salicylaldehydes. A phosphinite ligand reversibly binds the alkenyl alcohol to promote an intermolecular coupling and override the inherent linear selectivity of hydroacylation. Chapter 2 expands branched-selective hydroacylation to non-chelating aldehydes through the advent of an electron rich rhodium catalyst with a small-bite angle diphosphine. This enabled an intermolecular olefin hydroacylation with the most broad substrate scope with respect to the aldehyde component reported to date. Mechanistic studies shed light on the rate limiting step of the reaction and the unique properties of the substrates and catalyst.

Chapter 3 describes the use of bifunctional ruthenium catalysts for intramolecular ketone hydroacylation. This strategy circumvents aldehyde C–H bond activation and avoids issues of
competitive aldehyde decarbonylation. γ-Butyrolactones and δ-valerolactones were generated with high enantiomeric excess by using Noyori’s asymmetric transfer hydrogenation catalyst. This overall-oxidative reaction is inhibited by oxidant (acetone) and autocatalytic in a reductant (iso-propanol).

Chapter 4 describes the development of a transfer hydroformylation protocol. Reactivity at room temperature was obtained with catalyst loadings as low as 0.15% by taking advantage of the unique ability of rhodium to activate typically inert C–H bonds. This method was applied to complex bioactive molecules, including macrolide antibiotics, indole alkaloids, steroids, and terpenes. Mechanistic studies revealed that a benzoate counterion acts a proton shuttle to enable transfer hydroformylation.
Acknowledgments

I give my sincere thanks to Prof. Vy M. Dong for her mentorship over the course of my doctoral studies. You have made the lab an engaging and supportive place to do chemistry and have provided me with many opportunities for scientific and professional growth. As well, I would like to extend my gratitude to Wilmer Alkhas for his help over the years.

I would also like to thank my committee members Doug Stephan and Mark Lautens for participating in various meetings and for their keen insight. As well, thank you to Jik Chin, Ron Kluger, and Clark Landis for participating in departmental examinations. I would also like to thank my undergraduate advisor, Prof. Suning Wang, for inspiring me to pursue organometallic chemistry.

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Thank you to my mom, Karen Ralley, and my stepdad, David Carpenter, for your unwavering support, love, and encouragement. I am so lucky to have the two of you as parents. To Monika and Josh, thank you for having me over so often in Toronto. I hope that Clara wasn’t too freaked out by the anteater stuffed animal that I got for her. Sorry. To Megan and Matt, thanks for always being up for a party and late night poutine. I am looking forward to being closer to all of you as I prepare for my move to the east coast.
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1 Branched-Selective Hydroacylation of Allylic and Homoallylic Alcohols*  

1.1 Introduction  

Hydroacylation is an atom-economical reaction that cross-couples aldehydes and olefins to generate ketones (Scheme 1.1). This reaction combines a chemoselective C–H bond activation step with C–C bond formation to rapidly build structural complexity. A variety of transition metals and organic molecules catalyze this transformation, with rhodium complexes being among the most studied.

\[
\begin{align*}
\text{R}_1\text{CHO} + \text{R}_2\text{=CH}_2 & \xrightarrow{\text{Rh, Ru, Ni, Co, NHC}} \text{R}_1\text{CH(OH)R}_2 \\
\text{linear} & \text{branched}
\end{align*}
\]

Scheme 1.1 Hydroacylation of olefins

The mechanism of rhodium-catalyzed hydroacylation (Scheme 1.2) is commonly referred to as a “black box” because the intermediates are often unobservable. Nonetheless, a mechanistic understanding has been gained through deuterium-labelling experiments, stoichiometric reactions and computational studies. The hydroacylation mechanism begins with oxidative addition of a Rh\(^{1}\) catalyst (I) to an aldehyde C–H bond. This key step generates an acyl-Rh\(^{III}\)-hydride intermediate (II) that has two potential fates. In the undesired reductive decarbonylation pathway, de-insertion of CO occurs followed by reductive elimination to form an alkane. This pathway produces a catalytically inactive Rh-carbonyl complex (VII) and consumes the aldehyde starting material. If acyl-Rh\(^{III}\)-hydride II follows along the hydroacylation pathway by olefin coordination, hydrometallation and reductive elimination, two regioisomeric ketones (linear and branched) can form. Thus, key challenges in hydroacylation methodology are to

---

promote aldehyde C–H bond activation while preventing reductive decarbonylation and to control regioselectivity in C–C bond formation.

Scheme 1.2 Mechanism of Rh-catalyzed olefin hydroacylation.

Cationic Rh-complexes, such as [Rh(dppe)][ClO₄], are state-of-the-art catalysts for intramolecular hydroacylation and they readily cyclize alkenals to produce ketones.¹ Intermolecular variants are more challenging and are often plagued by reductive decarbonylation. To address this, the majority of intermolecular couplings rely on the use of β-chelating aldehydes (Scheme 1.3).³⁻⁶ Coordination of a β-heteroatom to the Rh catalyst directs C–H bond activation and stabilizes the acyl-RhIII-hydride intermediate from de-insertion of CO. Within these limitations, several research groups have developed general methods to access linear ketones.³k,⁵e

Scheme 1.3 β-chelating aldehydes used in intermolecular hydroacylation.
The inherent linear-selectivity of Rh-catalyzed hydroacylation can be overturned to yield branched ketones by using a directing group on the olefin component. Suemune reported that 1,5-hexadienes undergo moderately branched-selective hydroacylation with salicylaldehydes (Scheme 1.4, top). In Suemune’s double-chelating approach, the phenolic group on the aldehyde promoted C–H activation and prevented decarbonylation, while the unusual branched-regioselectivity was enforced by the olefinic directing group. Our laboratory recently reported the enantioselective hydroacylation of homoallylic sulfides with salicylaldehydes (Scheme 1.4, bottom). In that case, the regioselectivities were generally >20:1 branched-to-linear. Although this approach formed the basis for a highly regioselective ketone synthesis, the analogous hydroxy olefins (homoallylic alcohols) were unreactive, perhaps due to the weaker coordinating ability of the hydroxyl group.


Scheme 1.4 Reactivity of 1,5-hexadienes and homoallylic sulfides towards hydroacylation.

1.2 Reaction Design

We targeted the hydroacylation of allylic and homoallylic alcohols as a means to generate β- and γ-hydroxyketone products within a common framework. To develop this reaction, we assessed phosphorus-based ligands that are known to reversibly bind alcohols and promote metal-catalyzed transformations. Breit applied this strategy to achieve branched-selective hydroformylation of homoallylic and bishomoallylic alcohols (Scheme 1.5). In Breit’s work, exchange of an alcohol with a catalytic amount of methyl diphenylphosphinite (Ph₂POMe) generated a homoallylphosphinite that was reactive toward regioselective hydroformylation.
Similarly, Tan developed a chiral phosphorus-based scaffolding ligand for enantioselective allylamine hydroformylation.\(^8\) Jun pioneered a related strategy, termed metal-organic cooperative catalysis, to achieve linear-selective olefin hydroacylation with non-chelating aldehydes by using a 2-amino-picoline co-catalyst.\(^9\) Bedford also developed ortho-arylation of phenols by using phosphinites as reversibly bound directing groups.\(^{10}\)

**Scheme 1.5** Phosphinites as catalytic directing groups in hydroformylation.

Inspired by these studies, we imagined that \(\text{Ph}_2\text{POMe}\) would form a covalent bond with a hydroxy olefin 2 to produce a substrate bound phosphinite 3 (Scheme 1.6). In the presence of salicylaldehyde 1 and a Rh catalyst, this intermediate could undergo substrate-directed hydroacylation to generate the phosphinite-bound hydroxy ketone 4. Finally, transesterification would release the phosphinite and the desired \(\beta\)-hydroxy ketone 5. This cooperative catalysis between Rh and phosphinite enables hydroacylation of hydroxy olefins with branched-selectivity, while overcoming the need for stoichiometric auxiliaries.\(^{11}\)

**Scheme 1.6** Proposed hydroacylation of allylic alcohols mediated by a phosphinite catalyst.
1.3 Hydroacylation of Allylic Alcohols

To begin testing this proposal, we subjected salicylaldehyde 1a and allyl alcohol 2a to hydroacylation conditions (Scheme 1.7, top). A catalytic amount of sodium acetate (NaOAc) was added to promote metalation of the salicylaldehyde. With Wilkinson’s catalyst, the γ-hydroxy ketone 5a' was obtained in only 4% yield with 16:1 regioselectivity in favour of the linear product. Competitive decarbonylation occurred to produce phenol in 28% yield. In contrast, a catalytic system comprised of [Rh(COD)Cl]_2 and Ph_2POMe provided the β-hydroxy ketone 5a in 74% yield as a single regioisomer according to ^1H NMR analysis (Scheme 1.7, bottom). Thus, adding the phosphinite improved reactivity and promoted a switch to branched-selectivity.

Scheme 1.7 Hydroacylation of allyl diphenylphosphinite with salicylaldehyde.

Using this strategy, we prepared β-hydroxy aryl ketones by coupling salicylaldehyde with five readily available allylic alcohols (Table 1.1). As 1,2-disubstituted olefins are often unreactive toward hydroacylation, we were pleased to find that these substrates efficiently coupled with salicylaldehyde to give β-hydroxy ketones as single regioisomers by ^1H NMR analysis (Table 1.1). Furthermore, the disubstituted olefins underwent hydroacylation using a reduced catalyst loading of 2.5 mol% [Rh(COD)Cl]_2 and 25 mol% Ph_2POMe, presumably because the products are less sensitive to dehydration. E- and Z-configured olefins were equally efficient coupling partners (entries 1 and 2). An allylic alcohol with a pendant olefin underwent chemoselective hydroacylation of the proximal 1,2-disubstituted olefin without any observable hydroacylation of the terminal olefin (entry 3). In contrast, methyl allyl ether did not undergo hydroacylation even with prolonged reaction time, probably because this substrate cannot undergo phosphinite exchange (entry 4). Our strategy allowed branched-selective hydroacylation
of 1,1-disubstituted olefin 2-methyl-2-propene-1-ol. The β-hydroxy ketone with an α-quaternary centre was isolated as one regioisomer in 90% yield after three hours of reaction. (entry 5). This transformation could be performed with a lower catalyst loading (1 mol% [Rh(COD)Cl]_2 and 10 mol% Ph_2POMe, 1 mmol scale) to produce the desired branched ketone in 93% yield after sixteen hours of reaction. To our knowledge, this is the first Rh-catalyzed hydroacylation to generate α-quaternary ketones, highlighting the power of phosphorus-based directing groups in hydroacylation.

Table 1.1 Regioselective hydroacylation of various allylic alcohols

<table>
<thead>
<tr>
<th>Entry</th>
<th>#</th>
<th>Olefin</th>
<th>Yield (%)</th>
<th>#</th>
</tr>
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<tr>
<td>1†</td>
<td>2b</td>
<td></td>
<td>88</td>
<td>5b</td>
</tr>
<tr>
<td>2</td>
<td>2c</td>
<td></td>
<td>86</td>
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<td>3</td>
<td>2d</td>
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<td>4</td>
<td>2e</td>
<td></td>
<td>0a</td>
<td>5e</td>
</tr>
<tr>
<td>5</td>
<td>2f</td>
<td></td>
<td>90 (93b)</td>
<td>5f</td>
</tr>
</tbody>
</table>

*a No products could be identified by GC-MS after 24 h. † [Rh(COD)Cl]_2 (1%), Ph_2POMe (10%), salicylaldehyde (1 mmol), 16 h. † Reaction and analysis performed by Matthew Coulter.*

With 2-methyl-2-propene-1-ol as the coupling partner, substitution at every position of salicylaldehyde was investigated and the corresponding α-quaternary ketones were obtained in 73–90% yields (Table 1.2). Salicylaldehydes bearing either electron-donating or electron-withdrawing substituents were transformed with similar efficiency. Substrates with increased steric bulk at the 3 or 6 positions underwent hydroacylation with slightly longer reaction times (entries 4, 5 and 6). Although phenols can undergo phosphinite exchange, they were tolerated and did not inhibit catalysis. For example, 4-hydroxysalicylaldehyde bears an additional hydroxy
group that can exchange with the phosphinite catalyst; nonetheless, the compound was coupled in 82% yield (entry 7).

Table 1.2 Regioselective hydroacylation of 2-methyl-2-propene-1-ol with various salicylaldehydes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>#</th>
<th>Aldehyde (R =)</th>
<th>Yield (%)</th>
<th>Time (h)</th>
<th>#</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>H</td>
<td>90</td>
<td>3</td>
<td>5g</td>
</tr>
<tr>
<td>2a</td>
<td>1b</td>
<td>5-Cl</td>
<td>73</td>
<td>5</td>
<td>5h</td>
</tr>
<tr>
<td>3†</td>
<td>1c</td>
<td>5-OMe</td>
<td>76</td>
<td>6</td>
<td>5i</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>3-Me</td>
<td>80</td>
<td>5</td>
<td>5j</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>6-Me</td>
<td>78</td>
<td>5</td>
<td>5k</td>
</tr>
<tr>
<td>6†</td>
<td>1f</td>
<td></td>
<td>86</td>
<td>18</td>
<td>5l</td>
</tr>
<tr>
<td>7‡†</td>
<td>1g</td>
<td>4-OH</td>
<td>82</td>
<td>3</td>
<td>5m</td>
</tr>
</tbody>
</table>

*NaOAc (5%)  † 2-Hydroxy-1-naphthaldehyde is used rather than a salicylaldehyde. ‡ THF was used instead of (CH₂Cl)₂ to solubilize the aldehyde. † Reaction and analysis performed by Matthew Coulter.

Because the phosphinite acts as both a ligand and reversibly-bound directing group, the efficiency of this transformation is closely related to the ratio of phosphinite to Rh, with 5:1 being optimal. However, the phosphinite can decompose to phosphine oxides through three pathways. In one pathway the phosphinite rearranges to form allyldiphenylphosphine oxide,
perhaps by a [2,3]-sigmatropic rearrangement.\textsuperscript{12} Two other pathways were identified during our initial optimization studies, where the pre-formed allylphosphinite 3 was subjected to hydroacylation conditions (Scheme 1.8, top). We observed the desired β-hydroxy ketone 5a in 33\% yield indicating that 3 is a competent intermediate as proposed in Scheme 1.6. In addition, enone 6 and chromanone 7 were isolated. Either β-elimination of phosphinite 4 to generate 6 or cyclization of 4 to generate 7 may occur with concomitant catalyst decomposition to form diphenylphosphine oxide (Scheme 1.8, bottom). To account for the higher yields obtained using sub-stoichiometric phosphinite (Scheme 1.7, 74\% yield) compared to stoichiometric amounts (Scheme 1.8, top), we suggest that transesterification of phosphinite 4 to generate β-hydroxy ketone 5a outcompetes enone and chromanone formation in the presence of alcohol. Indeed, hydroacylation of allylphosphinite 3 in the presence of methanol results in formation of 5a in 65\% yield (Scheme 1.8, top).

\[ \text{Scheme 1.8 Hydroacylation of allylphosphinite.} \]

1.4 Hydroacylation of Homoallylic Alcohols

To extend phosphinite-directed hydroacylation to homologated hydroxy olefins, we first studied the reaction of salicylaldehyde with homoallyl alcohol using [Rh(COD)Cl]\textsubscript{2} as the pre-catalyst in the presence of Ph\textsubscript{2}POMe and catalytic NaOAc (Table 1.3). By applying the conditions reported for hydroacylation of allyl alcohols (entry 1), we obtained the desired homoaldol product 9a in 60\% yield along with olefin migration products. Changing the solvent from (CH\textsubscript{2}Cl\textsubscript{2}) to THF gave 9a in 97\% yield as a single regioisomer (entry 2). Reducing the catalyst loading further to 1 mol\% [Rh(COD)Cl]\textsubscript{2} gave the product in 70\% yield (entry 3). No
catalytic activity was observed when the phosphinite ligand was replaced with triphenylphosphine (entry 4), which supports the role of Ph₂POMe as an exchangeable directing group.

**Table 1.3** Hydroacylation of homoallyl alcohol with salicylaldehyde.

<table>
<thead>
<tr>
<th>entry</th>
<th>x</th>
<th>y</th>
<th>ligand</th>
<th>solvent</th>
<th>yield (%)</th>
<th>time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>50</td>
<td>Ph₂POMe</td>
<td>(CH₂Cl)₂</td>
<td>54</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>25</td>
<td>Ph₂POMe</td>
<td>THF</td>
<td>97</td>
<td>2.5</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>10</td>
<td>Ph₂POMe</td>
<td>THF</td>
<td>70</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>20</td>
<td>PPh₃</td>
<td>THF</td>
<td>0⁹</td>
<td>48</td>
</tr>
</tbody>
</table>

Stoichiometry: salicylaldehyde (0.25 mmol, 1.0 equiv), olefin (1.5 equiv). The branched-to-linear selectivity was >20:1 by ¹H NMR analysis of the crude reaction mixtures for entries 1-3. Yields are of isolated and purified products. a salicylaldehyde (1 mmol, 1 equiv) b No product could be detected by GC-MS. † Reaction and analysis performed by Matthew Coulter. ‡ Reaction and analysis performed by David Petrone.

Nine stERICALLY and electronically diverse salicylaldehydes were investigated as coupling partners for homoallyl alcohol under our optimized conditions (Table 1.3, entry 2). The corresponding α-branched ketones were obtained as single regioisomers in 75–98% yields (Table 1.4). Both fluoro and chloro substituents were tolerated (entries 1 and 2), and 5-iodosalicylaldehyde produced the desired hydroacylation product in good yield without any observable Mizoroki-Heck coupling or proto-deiodination (entry 3). Electron-rich methoxysalicylaldehydes (entries 5-7) and substrates with increased steric bulk at the 3 or 6 positions (entries 7 and 8) reacted well. The Lewis basic nitrogen in 5-(4-pyridyl)salicylaldehyde did not inhibit catalysis despite its potential to bind the metal catalyst (entry 9).
Table 1.4 Regioselective hydroacylation of homoallyl alcohol with salicylaldehydes.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>#</th>
<th>R</th>
<th>yield (%)</th>
<th>time (h)</th>
<th>#</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>H</td>
<td>97</td>
<td>2.5</td>
<td>9a</td>
</tr>
<tr>
<td>2†</td>
<td>1h</td>
<td>5-F</td>
<td>88</td>
<td>3.5</td>
<td>9b</td>
</tr>
<tr>
<td>3†</td>
<td>1b</td>
<td>5-Cl</td>
<td>92</td>
<td>3.5</td>
<td>9c</td>
</tr>
<tr>
<td>4</td>
<td>1i</td>
<td>5-I</td>
<td>75</td>
<td>3.5</td>
<td>9d</td>
</tr>
<tr>
<td>5†</td>
<td>1j</td>
<td>4-OMe</td>
<td>92</td>
<td>3</td>
<td>9e</td>
</tr>
<tr>
<td>6</td>
<td>1c</td>
<td>5-OMe</td>
<td>86</td>
<td>2.5</td>
<td>9f</td>
</tr>
<tr>
<td>7</td>
<td>1k</td>
<td>3-OMe</td>
<td>83</td>
<td>4</td>
<td>9g</td>
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<tr>
<td>8†</td>
<td>1e</td>
<td>6-Me</td>
<td>98</td>
<td>3</td>
<td>9h</td>
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<tr>
<td>9†</td>
<td>1l</td>
<td>5-(4-py)</td>
<td>75</td>
<td>4</td>
<td>9i</td>
</tr>
</tbody>
</table>

Stoichiometry: salicylaldehyde (0.25 mmol, 1.0 equiv), olefin (1.5 equiv). The branched-to-linear selectivity was >20:1 by $^1$H NMR analysis of the crude reaction mixtures in all cases. Yields are of isolated and purified products. † Reaction and analysis performed by David Petrone.

A series of γ-hydroxyketones were prepared by coupling salicylaldehyde with homoallyl alcohols (Table 1.5). Disubstituted olefins are difficult substrates for intermolecular hydroacylation; however, cis- and trans-3-hexen-1-ol underwent coupling to yield the desired branched ketones (entries 2 and 3). Substitution at the α and β positions of homoallyl alcohol (entries 4 and 5) was tolerated, although the secondary alcohol (entry 5) required a longer reaction time. Diastereoselectivities were moderate and not improved when an olefin with increased allylic strain was employed (entry 6). Homoallylbenzylether did not furnish any hydroacylation products, probably because this substrate cannot undergo phosphinite exchange.
Additionaly, a further homologated alcohol transformed only to trace amounts of the hydroacylation product, along with products of olefin isomerization (entry 8).

Table 1.5 Regioselective hydroacylation of homoallyl alcohols with salicylaldehyde.

<table>
<thead>
<tr>
<th>entry</th>
<th>#</th>
<th>olefin</th>
<th>yield (%)</th>
<th>time (h)</th>
<th>#</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8a</td>
<td></td>
<td>97 (70(^a))</td>
<td>2.5</td>
<td>9j</td>
</tr>
<tr>
<td>2</td>
<td>8b</td>
<td></td>
<td>50</td>
<td>24</td>
<td>9k</td>
</tr>
<tr>
<td>3</td>
<td>8c</td>
<td></td>
<td>53</td>
<td>24</td>
<td>9k</td>
</tr>
<tr>
<td>4</td>
<td>8d</td>
<td></td>
<td>92(^b)</td>
<td>2.5</td>
<td>9l</td>
</tr>
<tr>
<td>5(^i)</td>
<td>8e</td>
<td></td>
<td>98(^c)</td>
<td>16</td>
<td>9m</td>
</tr>
<tr>
<td>6</td>
<td>8f</td>
<td></td>
<td>53(^d)</td>
<td>20</td>
<td>9n</td>
</tr>
<tr>
<td>7(^i)</td>
<td>8g</td>
<td></td>
<td>0(^e)</td>
<td>18</td>
<td>9o</td>
</tr>
<tr>
<td>8</td>
<td>8h</td>
<td></td>
<td>trace</td>
<td>20</td>
<td>9p</td>
</tr>
</tbody>
</table>

Stoichiometry: salicylaldehyde (0.25 mmol, 1.0 equiv), olefin (1.5 equiv). The branched-to-linear selectivity was >20:1 by \(^1\)H NMR analysis of the crude reaction mixtures in all cases. Yields are of isolated and purified products. \(^a\) [Rh(COD)Cl]\(_2\) (1 mol%), Ph\(_2\)POMe (10 mol %), salicylaldehyde (1 mmol), 9 h. \(^b\) \(dr = 64:36\). \(^c\) \(dr = 71:29\). \(^d\) \(dr = 63:37\). \(^e\) No products could be identified by GC-MS after 24 h. \(^i\) Reaction and analysis performed by David Petrone.

We next explored 2-vinylphenol substrates and found that they are highly reactive towards hydroacylation under our optimized conditions (Table 1.6). 2-Vinylphenol coupled to give the \(\alpha\)-aryl ketone as a single regioisomer (entry 1). We considered that the phenolic group of 2-vinylphenol could coordinate to Rh under basic reaction conditions and promote a background reaction. The fact that no products were formed when Ph\(_2\)POMe was replaced with PPh\(_3\).
suggests that the phosphinite undergoes exchange with the phenolic group and promotes the reaction. The effects of olefin electronics and substitution on reaction efficiency were investigated next. The electron deficient olefin 5-fluoro-2-vinylphenol (entry 2) underwent rapid hydroacylation, whereas the electron rich olefin 4-methoxy-2-vinylphenol (entry 3) was slightly less efficient. The disubstituted olefin 2-hydroxy-β-methylstyrene underwent efficient hydroacylation to yield the α-aryl ketone (entry 4).

Table 1.6 Regioselective hydroacylation of 2-vinylphenols with salicylaldehyde.

<table>
<thead>
<tr>
<th>entry</th>
<th>#</th>
<th>olefin</th>
<th>yield (%)</th>
<th>time (h)</th>
<th>#</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8i</td>
<td></td>
<td>88 (0)</td>
<td>4</td>
<td>9q</td>
</tr>
<tr>
<td>2‡</td>
<td>8j</td>
<td></td>
<td>98</td>
<td>4</td>
<td>9r</td>
</tr>
<tr>
<td>3‡</td>
<td>8k</td>
<td></td>
<td>68</td>
<td>7</td>
<td>9s</td>
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<tr>
<td>4</td>
<td>8l</td>
<td></td>
<td>86</td>
<td>18</td>
<td>9t</td>
</tr>
</tbody>
</table>

Stoichiometry: salicylaldehyde (0.25 mmol, 1.0 equiv), olefin (1.5 equiv). The branched-to-linear selectivity was >20:1 by $^1$H NMR analysis of the crude reaction mixtures in all cases. Yields are of isolated and purified materials. *no product was detected under the conditions in Table 1, entry 4.* ‡Reaction and analysis performed by David Petrone.

During our scope studies, we found that the products of homoallyl alcohol hydroacylation equilibrate with hemiketals upon storage. This cyclization prompted us to search for conditions to synthesize substituted heterocycles. We found that reduction of 9a using
sodium borohydride and treatment of the resulting diol with aqueous HCl afforded tetrahydrofuran 10 in 78% yield with 33:1 diastereoselectivity in favor of the trans stereoisomer (Scheme 1.9).

\[ \text{Scheme 1.9 Synthesis of a di-substituted tetrahydrofuran.} \]
\[ (Ar = 2\text{-hydroxyphenyl}). \] † Reaction and analysis performed by David Petrone.

1.5 Mechanism of Phosphinite-Directed Hydroacylation

We developed a rationale for the high regioselectivity of phosphinite-directed hydroacylation through a combination of deuterium labelling studies and competition experiments. We first tested the reversibility of oxidative addition and hydrometallation by reacting \( d_1 \)-salicylaldehyde (\( d\text{-1a} \)) and \( h_1 \)-5-methoxysalicylaldehyde (\( h\text{-1c} \)) with 2-methyl-2-propene-1-ol (2f) (Scheme 1.10, top). Extensive deuterium scrambling occurred resulting in the formation of unlabeled 5g and labelled 5i. An analogous experiment using homoallylic alcohol as the coupling partner gave similar results (Scheme 1.10, bottom).
Scheme 1.10 Deuterium cross-over experiment with deuterio- and protio-salicylaldehydes. Yields are of isolated materials. The deuterium content was quantified by mass spectrometry and deuterium NMR analysis.

To explain this scrambling, we propose that oxidative addition and hydrometallation are reversible (Scheme 1.11). The Rh catalyst can under oxidative addition to the C–D bond of aldehyde \textit{d-1a} to give complex \textbf{VIII}, which undergoes deuterometallation to generate \textbf{IX}. Subsequent C–C bond rotation and β-hydride elimination generates complex \textbf{X}. Reductive elimination of the C–H bond generates unlabeled aldehyde \textit{h-1a} and labeled allylphosphinite \textit{d-3b}. These compounds couple with unlabeled olefin and aldehyde, respectively, to generate the
scrambled ketones. In agreement with previous studies on the mechanism of intermolecular hydroacylation,\textsuperscript{1} we propose that branched-selective hydroacylation occurs by a reversible oxidative addition and hydrometallation followed by a turnover-limiting C–C bond reductive elimination.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme11.png}
\caption{Proposed mechanism of deuterium scrambling.}
\end{figure}

To probe the selectivity determining step of this reaction, we compared the reactivity of 2-buten-1-ol (2\textsuperscript{g}) and 3-buten-1-ol (8\textsuperscript{a}) under identical reaction conditions (Scheme 1.12). The allylic alcohol underwent hydroacylation to generate the β-hydroxyketone exclusively. However, the homoallylic alcohol underwent sluggish hydroacylation to yield a mixture of the γ- and β-hydroxyketones.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme12.png}
\caption{Comparison of the products obtained by the reactions of 2-buten-1-ol and 3-buten-1-ol.}
\end{figure}

Because these reactions yield the same β-hydroxyketone product, they are likely joined by a common intermediate XII as shown in Scheme 1.13. The intermediate XII can arise from either hydrometallation of the allylic alcohol in the linear manifold or by hydrometallation of the homoallylic alcohol in the branched-manifold. This intermediate has three potential fates: 1)
reductive elimination to form the $\gamma$-hydroxyketone 9a; 2) $\beta$-hydride elimination to form XI containing a homoallylic alcohol moiety; or 3) $\beta$-hydride elimination to yield XIII containing an allylic alcohol moiety. For the reaction of homoallylic alcohol 8a, the higher yield of 9a over 5n indicates that XII undergoes reductive elimination to form 9a more rapidly than $\beta$-hydride elimination to XIII. Thus, hydrometallation is likely the rate-limiting step in the linear-manifold of allylic alcohol hydroacylation. Furthermore, linear-selective hydrometallation of allylic alcohols has a significantly higher barrier than any step in the branched-selective pathway.

Scheme 1.13 Linear and branched manifolds for hydroacylation of 2-buten-1-ol and their connection to the mechanism for hydroacylation of 3-buten-1-ol.

We propose that linear-selective hydrometallation is disfavored due to an accumulation of ring-strain in the transition state. As shown in Scheme 1.14, linear-selective hydrometallation would proceed through a 6-membered ring with a highly distorted geometry. Conversely, branched-selective hydride insertion could occur through a 5-membered ring intermediate in an envelope conformation.
Scheme 1.14 Transition states for hydride insertion in either the branched or linear manifolds.

Based on the above model, the branched-to-linear selectivity should decrease with increasing chelate size. Indeed, we observed lower regioselectivities when homologated alkenyl alcohols were used as coupling partners (Scheme 1.15). 2-Allylphenol (11) underwent hydroacylation with 4:1 branched-to-linear selectivity. Products of olefin isomerization and hydroacylation were also observed.

Scheme 1.15 Hydroacylation of allylphenol.
† Reaction and analysis performed by David Petrone.

1.6 Conclusions

We have developed an atom economical method for synthesizing β- and γ-hydroxy aryl ketones with α-tertiary and -quaternary centers. The high reactivity and regioselectivity of this C–H bond functionalization can be attributed to cooperative catalysis between the Rh and phosphinite. We have demonstrated that branched-selective hydroacylation occurs by reversible oxidative addition and hydrometallation followed by a turnover limiting reductive elimination. Conversely, the linear manifold is disfavored due to ring strain in the transition state leading to linear hydrometallation.
1.7 Experimental

1.7.1 Substrate Preparation

(3a) Allylphosphinite

\[ \text{Allyl alchohol (0.395 mL, 6.8 mmol)} \]

\[ \text{was added dropwise to a stirring solution of triethylamine (0.688 g, 6.8 mmol) and chlorodiphenylphosphine (1.500 g, 6.8 mmol) in toluene (15 mL). A white precipitate formed immediately. The solution was stirred for two hours, and then transferred to a round bottom flask via cannula filtration. The remaining precipitate was washed with 2x15 mL toluene and the washings were transferred to the round bottom flask in the same manner. The solvent was removed under reduced pressure. The residual oil was passed through a short plug of neutral alumina to yield the pure product as a colourless oil. 78% yield. The title compound was confirmed by comparison the }^{1} \text{H NMR data to literature values.}^{14} \]

\[ {^{1} \text{H NMR}} (400 MHz, CDCl}_{3}) \delta 4.16 (ddt, J = 9.7, 5.2, 1.7 Hz, 2H), 4.89-4.95 (m, 1H), 5.12-5.20 (m, 1H), 5.70-5.80 (m, 1H), 6.97-7.10 (m, 6H), 7.53-7.60 (m, 4H). \]

(2d) 1,5-heptadien-7-ol

\[ \text{Triethylphosphonoacetate (1.190 mL, 6 mmol) was added to a stirring solution of NaH (0.240 g, 6 mmol) in anhydrous THF at 0°C. After 15 minutes, 4-pentenal (0.592 mL, 6 mmol) was added dropwise and the reaction was stirred for 30 minutes at 0°C, and then 30 minutes at room temperature. The solution was diluted with diethyl ether and washed sequentially with a saturated Na}_{2}CO_{3(aq)} \text{solution, water, and brine. The organic layer was separated and dried over MgSO}_{4}. \text{ The solvent was removed in vacuo to yield the desired ester as a clear colourless oil (0.8836 g, 96%) which was used in the next step without further purification. The crude ester was dissolved in THF and the solution was cooled to -10 °C. DIBAL-H (1.0 M in hexanes, 12.61 mL, 12.61 mmol) was added dropwise. The solution was stirred for two hours while gradually warming to 10°C. The solution was diluted with diethyl ether and quenched by the addition of methanol followed by 1M HCl solution. The solution was washed sequentially with} \]
water and brine. The organic layer was separated and dried over MgSO₄, and the solvent was removed in vacuo. The residual oil was purified via flash chromatography (4:1 Hx:EtOAc mixture) to afford the desired allylic alcohol as a clear colourless oil (0.3511 g, 57%). ¹H NMR (300 MHz): δ 2.08-2.23 (m, 4H), 4.05-4.13 (m, 2H), 4.91-5.08 (m, 2H), 5.61-5.89 (m, 3H). ¹³C NMR (75 MHz) δ 31.55, 33.27, 63.76, 114.87, 120.41, 132.45, 138.07. HRMS (ESI+): calculated for [C₇H₁₆O₁N₁]⁺ [M+NH₄]⁺ 130.12319, found 130.12308.

(8f) 2-methyl-3-penten-1-ol
2-Methyl-1,3-propanediol (1.802 g, 20 mmol) was added to a vigorously stirred suspension of NaH (60 wt% in mineral oil, 0.840 g, 21 mmol) in THF (40 mL). The solution was stirred for 45 minutes at room temperature. TBSCl (3.165 g, 21 mmol) was then added and the solution was stirred for 1 hour at room temperature. The solution was diluted with diethyl ether and washed sequentially with a saturated Na₂CO₃(aq) solution, water, and brine. The organic layer was separated and dried over MgSO₄. The solvent was removed in vacuo to yield the desired monoprotected alcohol as a clear colourless oil (3.847 g, 94%) which was used without purification in the next step. ¹H NMR (400 MHz, CDCl₃) δ 3.74 (dd, J = 9.8, 4.4 Hz, 1H), 3.68 – 3.51 (m, 3H), 2.80 (s, 1H), 2.01 – 1.88 (m, 1H), 0.90 (s, 9H), 0.84 (d, J = 7.0 Hz, 3H), 0.08 (s, 6H). The ¹H NMR values agree with the literature values.

DMSO (3.21 mL, 45.23 mmol) was added dropwise to a stirring solution of oxalyl chloride (1.94 mL, 22.61 mmol) in 50 mL CH₂Cl₂ at -78°C. The solution was stirred for 10 minutes. The monoprotected alcohol (3.847 g, 18.84 mmol) dissolved in 4 mL CH₂Cl₂ was then added dropwise. The solution was stirred to 20 minutes. Triethylamine (13.14 mL, 94.22 mmol) was added and the reaction was stirred for 20 minutes, and then allowed to warm to room temperature over another 20 minutes. The solution was diluted with CH₂Cl₂, quenched with a saturated NH₄Cl solution, and extracted three times with brine. The organic layer was separated
and dried over MgSO_4. The solvent was removed *in vacuo* and then the resulting residue was suspended in Et_2O and filtered through celite. The solvent was removed *in vacuo* to yield the desired aldehyde as a yellow oil (3.6210 g, 95%) which was used without purification in the next step. \(^1\)H NMR (200 MHz, CDCl_3) \(\delta 9.74 (d, J = 1.6\ Hz, 1H), 3.83 (dd, J = 5.8, 3.9\ Hz, 2H), 2.64 – 2.42 (m, 2H), 1.09 (d, J = 7.0\ Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H). The \(^1\)H NMR values agree with the literature values.\(^{15}\)

n-BuLi (2.1 M in Hx, 2.91 mL, 6.1 mmol) was added dropwise to a stirring suspension of ethyltriphenylphosphonium iodide (2.551 g, 6.1 mmol) in THF (30 mL) at 0°C. The solution was stirred for 10 minutes, and then the aldehyde (1.214 g, 6 mmol) dissolved in 2 mL THF was added dropwise. The solution was stirred for 1 hour at room temperature. The solution was diluted with Et_2O and then extracted sequentially with water and brine. The organic layer was separated and dried over MgSO_4. The solvent was removed in vacuo to afford a residue which was suspended in hexanes and triturated. After filtration through paper, the solution was concentrated *in vacuo* and the residue was filtered through a plug of silica gel and eluted with 2% ethyl acetate in hexanes to afford the product as a clear and colourless oil (650 mg, 51%). \(^1\)H NMR (400 MHz, CDCl_3) \(\delta 5.48 – 5.36 (m, 1H), 5.16 – 5.07 (m, 1H), 3.47 – 3.38 (m, 1H), 3.35 – 3.27 (m, 1H), 2.68 – 2.55 (m, 1H), 1.59 (dd, J = 6.8, 1.8\ Hz, 3H), 0.93 – 0.88 (m, 3H), 0.85 (s, 9H), 0.00 (s, 6H).

The silyl ether was dissolved in 3:1:1 AcOH:H_2O:THF (15 mL) and stirred at room temperature for 4 hours. The solution was diluted with Et_2O and extracted twice with saturated Na_2CO_3 solution. The organic layer was separated and dried over MgSO_4. The solution was concentrated *in vacuo* and subjected to silica gel chromatography (4:1 pentane:diethyl ether) to afford the product as a clear, colourless oil (0.105 g, 35%, 4:1 cis:trans). The \(^1\)H and \(^13\)C NMR data agree with the literature values.\(^{16}\)

(8j) 2-hydroxy-5-fluoro-styrene

\[
\text{n-BuLi (7.2 mL, 1.9 M in Hx, 11.9 mmol) was added dropwise to a stirring suspension of triphenylmethylphosphonium bromide (4.25 g, 11.9 mmol) THF (55 mL) at -78°C. The solution was stirred for 15 minutes at this temperature. This}
\]
solution was then warmed to room temperature, and then re-cooled to -78°C, at which time the aldehyde (6 mmol) dissolved in 20 mL THF was added drop wise. The solution was stirred for 4 hours at room temperature. The solution was quenched with a saturated solution of NH₄Cl(aq), and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The crude mixture was purified via flash column chromatography eluting with 4:1 hexanes/ethyl acetate to give a white solid MP 55-57 °C (657 mg, 80%). ¹H NMR (400 MHz, CDCl₃) δ 7.09 (dd, J = 9.4, 3.1 Hz, 1H), 6.95 – 6.80 (m, 2H), 6.73 (dd, J = 8.8, 4.6 Hz, 1H), 5.73 (dd, J = 17.7, 1.0 Hz, 1H), 5.40 (dd, J = 11.1, 1.0 Hz, 1H), 4.89 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 158.47, 156.11, 148.73, 148.71, 130.58, 130.56, 126.08, 126.01, 116.81, 116.76, 116.73, 115.32, 115.08, 113.18, 112.94. HRMS (ESI+), calculated for [C₈H₈F₁O₁]⁺ [M+H]⁺ 139.05592 found 139.05547.

(8k) 2-hydroxy-4-methoxy-styrene

n-BuLi (7.2 mL, 1.9 M in Hx, 11.9 mmol) was added dropwise to a stirring suspension of triphenylmethylphosphonium bromide (4.25 g, 11.9 mmol) THF (55 mL) at -78°C. The solution was stirred for 15 minutes at this temperature. This solution was then warmed to room temperature, and then re-cooled to -78°C, at which time the aldehyde (6 mmol) dissolved in 20 mL THF was added drop wise. The solution was stirred for 4 hours at room temperature. The solution was quenched with a saturated solution of NH₄Cl(aq), and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The crude mixture was purified via flash column chromatography eluting with 4:1 hexanes/ethyl acetate to give a white solid MP 62-64 °C (610 mg, 71%). ¹H NMR (400 MHz, CDCl₃) δ 7.29 (d, J = 8.6 Hz, 1H), 6.85 (dd, J = 17.7, 11.2 Hz, 1H), 6.50 (dd, J = 8.6, 2.4 Hz, 1H), 6.37 (d, J = 2.4 Hz, 1H), 5.62 (dd, J = 17.7, 1.0 Hz, 1H), 5.26 (dd, J = 11.2, 1.0 Hz, 1H), 5.22 (s, 1H), 3.78 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 160.29, 153.89, 131.15, 128.23, 117.78, 113.80, 106.81, 101.62, 55.33. HRMS (ESI+), calculated for [C₉H₁₁O₂]⁺ [M+H]⁺ 151.07590 found 151.07576.
(II) 5-(4-pyridyl)-salicylaldehyde

5-iodosalicylaldehyde (200 mg, 0.806 mmol), 4-pyridylboronic acid (198 mg, 1.61 mmol), tetrakistriphenylphosphino palladium (O) (56 mg, 0.048 mmol), and potassium carbonate (55.7 mg, 4.03 mmol) were combined in a 2-neck round bottom flask in a glove-box. The flask was then equipped with a stirbar and sealed with septa and removed from the glove-box. The solid composition was then dissolved in a 1:1 mixture of THF:H2O. The reaction vessel was fitted with a reflux condenser and a glass stopper and was heated at a gentle reflux for 26 hours. At this time the vessel was cooled to room temperature and its contents were transferred to a separatory funnel with EtOAc. The organic layers were washed with water, dried over anhydrous MgSO4 for 2 hours, and concentrated. The crude mixture was then purified on silica gel using gradient elution (2:1 hexanes: ethyl acetate → 100% ethyl acetate), providing the desired product as a yellow solid MP 170-171°C (66 mg, 41% yield).

\[ ^1H \text{NMR} \ (400 \text{ MHz, CDCl}_3) \delta 11.14 \ (s, 1H), 10.01 \ (s, 1H), 8.68 \ (d, J = 6.0 \text{ Hz, } 2H), 7.84 \ (dt, J = 8.6, 2.3 \text{ Hz, } 2H), 7.48 \ (dd, J = 4.5, 1.6 \text{ Hz, } 2H), 7.13 \ (d, J = 8.6 \text{ Hz, } 1H). \]

\[ ^{13}C \text{NMR} \ (100 \text{ MHz, CDCl}_3) \delta 196.33, 162.27, 150.49, 146.39, 135.27, 131.99, 130.05, 120.92, 120.84, 118.74. \]

**HRMS (ESI+), calculated for [C_{12}H_{10}N_{1}O_{2}]^{+} [M+H]^{+} 200.07115 found 200.07143.**

1.7.2 Ketone Synthesis

**Method 1.1 Phosphinite-Directed Hydroacylation with Liquid Aldehydes**

In a glovebox, [Rh(COD)Cl]2 (0.01 mmol, 2.5 mol %) and sodium acetate (0.08 mmol, 20 mol %) were weighed into a vial. 1.0 mL of either degassed dichloroethane or THF was added. Methyl diphenylphosphinite (0.01 mmol, 25 mol %), aldehyde (0.4 mmol, 1.0 equiv.), and the alcohol (0.6 mmol, 1.5 equiv.) were added via syringe. The vial was charged with a stir bar, sealed with a Teflon-lined screw-cap, and heated at 67 °C for the indicated period of time. The product was isolated by Si gel or thin layer chromatography. Some reactions were performed with 0.2 mmol of the aldehyde. In these cases, the amounts of the other reaction components were adjusted to maintain the ratios given in the standard procedure.

**Method 1.2 Phosphinite-Directed Hydroacylation with Solid Aldehydes**

In a glovebox, [Rh(COD)Cl]2 (0.01 mmol, 2.5 mol %) and sodium acetate (0.08 mmol, 20 mol %), and the aldehyde (0.4 mmol, 1.0 equiv.) were weighed into a vial. 1.0 mL of degassed
dichloroethane was added. Methyl diphenylphosphinite (0.01 mmol, 25 mol %) and the alcohol (0.6 mmol, 1.5 equiv.) were added via syringe. The vial was charged with a stir bar, sealed with a Teflon-lined screw-cap and heated at 67 °C for the indicated period of time. The product was isolated by Si gel or thin layer chromatography. Specified reactions were performed with 0.2 mmol of the aldehyde. In these cases, the amounts of the other reaction components were adjusted to maintain the ratios given in the standard procedure.

**Method 1.3 Hydroacylation of Allylic Alcohol with Wilkinson’s Complex**

In a glovebox, RhCl(PPh₃)₃ (18.5 mg, 0.02 mmol) and sodium acetate (3.3 mg, 0.04 mmol) were weighed into a vial. 1.0 mL of degassed dichloroethane was added. Allyl alcohol (17.4 mg, 0.3 mmol) and salicylaldehyde (24.4 mg, 0.2 mmol) were added via syringe. The vial was charged with a stir bar, sealed with a Teflon-lined screw-cap and heated at 70 °C for the 3 hours. The reaction was then cooled to room temperature and the solvent was removed in vacuo. ¹H NMR analysis of the crude material with 1,3,5-trimethoxybenzene as the internal standard showed that reaction reached 32% conversion with 28% yield of the decarbonylation product, and 4% yield of the linear product with a 16:1 linear to branched ratio.

**(Scheme 1.7, 5a)**

**2-(2-hydroxybenzoyl)propan-1-ol**

![Chemical structure](image)

The title compound was prepared from salicylaldehyde (0.4 mmol) and allyl alcohol according to Method 1.1 (3 h reaction time) with the exception that [Rh(COD)Cl]₂ (0.02 mmol, 9.9 mg) and Ph₂POMe (0.24 mmol, 51.9 mg) were used and the temperature was set to 70°C. Purification via silica gel column chromatography (gradient 15:1 → 7:3 hexanes:ethyl acetate) afforded the title compound as a light yellow oil (47.5 mg, 66%). ¹H NMR (400 MHz, CDCl₃): δ 1.30 (d, J = 7.0 Hz, 3H), 3.69-3.79 (m, 1H), 3.82 (dd, J = 11.0, 4.3 Hz, 1H), 3.98 (dd, J = 11.0, 4.0 Hz, 1H), 6.93 (t, 7.7 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.81 (d, J = 8.3 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 15.0, 42.5, 64.43, 118.6, 118.9, 119.1, 130.1, 136.8, 163.2, 210.0. HRMS (ESI+), calculated for [C₁₀H₁₂O₃]⁺ [M+H]⁺ 180.0786, found 180.0787.
(Table 1.1, entry 1, 5b)

2-(2-hydroxybenzoyl)pentan-1-ol

The title compound was prepared from salicylaldehyde (0.4 mmol), and cis-2-penten-1-ol according to Method 1.1 (3 h reaction time). Purification via Si gel chromatography (15:1 → 7:3 hexanes:ethyl acetate) afforded the product as a yellow oil (73.3 mg, 88%). \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta\) 0.93 (t, \(J = 7.3\) Hz, 3H), 1.30-1.49 (m, 2H), 1.59-1.77 (m, 2H), 2.11 (br s, 1H), 3.67 (dddd, \(J = 7.0, 7.0, 7.0, 4.0\) Hz, 1H), 3.85 (dd, \(J = 11.0, 4.0\) Hz, 1H), 3.97 (dd, \(J = 11.0, 7.1\) Hz, 1H), 6.92 (ddd, \(J = 8.3, 7.2, 1.2\) Hz, 1H), 7.00 (dd, \(J = 8.4, 1.1\) Hz, 1H), 7.49 (ddd, \(J = 8.7, 7.2, 1.6\) Hz, 1H), 7.80 (dd, \(J = 8.1, 1.6\) Hz, 1H), 12.39 (br s, 0.9H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 14.3, 20.8, 30.8, 31.9, 47.7, 63.2, 118.9, 119.2, 119.4, 130.3, 136.9, 163.2, 210.4; HRMS (ESI+) Calcd. for [C\(_{12}\)H\(_{17}\)O\(_3\)]\(^+\) [M+H]\(^+\) 209.11777, found 209.11824.

(Table 1.1, entry 2, 5c)

2-(2-hydroxybenzoyl)pentan-1-ol

The title compound was prepared from salicylaldehyde (0.4 mmol) and trans-2-penten-1-ol according to Method 1.1 (3 h reaction time). Purification via Si gel chromatography (gradient 15:1 → 7:3 hexanes:ethyl acetate) afforded the product as a yellow oil (71.0 mg, 85%). The title compound was confirmed of the \(^1\)H NMR data to product 5ab.

(Table 1.1, entry 3, 5d)

2-(2-hydroxybenzoyl)-6-hepten-1-ol

The title compound was prepared from salicylaldehyde (0.4 mmol) and 1,5-heptadiene-7-ol according to Method 1.1 (3 h reaction time). Purification via Si gel chromatography (gradient 15:1 → 7:3 hexanes:ethyl acetate) afforded the product as a yellow oil (88.2 mg, 94%). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 1.35-1.55 (m, 2H), 1.59-1.83 (m, 2H), 2.06 (q, 7.2 Hz, 2H), 2.31 (br s, 1H), 3.62-3.71 (m, 1H), 3.83 (dd, \(J = 11.0, 4.0, 1\) H), 3.96 (dd, \(J = 11.1, 7.3\) Hz, 1H), 4.91-5.03 (m, 2H), 5.69-5.81 (m, 1H), 6.92 (t, \(J = 7.4, 1\) H), 7.00 (d, \(J = 7.0\) Hz, 1H), 7.49 (t, 7.9 Hz, 1H), 7.80 (d, \(J = 7.9, 1\) H), 12.40 (s, 1H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 26.77, 29.24, 33.90, 47.90, 63.33, 115.31, 118.98, 119.29, 119.62, 130.44,
137.01, 138.19, 163.26, 210.27. HRMS (ESI+), calculated for [C\textsubscript{14}H\textsubscript{19}O\textsubscript{3}]\textsuperscript{+} [M+H]\textsuperscript{+} 235.13342, found 235.13306.

(Table 1.1, entry 5, 5f)

2-(2-hydroxybenzoyl)-2-methylpropan-1-ol

The title compound was prepared from salicylaldehyde (0.4 mmol) and 2-methylallyl alcohol according to Method 1.1 (3 h reaction time). Purification via Si gel chromatography (35% diethyl ether in hexanes) afforded the product as a yellow oil (69.5 mg, 90%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 1.53 (s, 6H), 2.53 (t, J = 7.3 Hz, 1H), 3.69 (d, J = 8.3, 7.2, 1.3 Hz , 1H), 7.02 (dd, J = 8.5, 1.2 Hz , 1H), 7.45 (ddd, J = 8.6, 7.2, 1.6 Hz , 1H), 8.00 (dd, J = 8.3, 1.6 Hz , 1H), 12.43 (br s, 0.9H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 23.8, 49.4, 71.5, 117.7, 118.2, 119.6, 130.8, 136.1, 163.9, 212.8; HRMS (ESI+) Calcd. for [C\textsubscript{11}H\textsubscript{15}O\textsubscript{3}]\textsuperscript{+}[M+H]\textsuperscript{+} 195.10212, found 195.10242.

(Table 1.2, entry 2, 5h)

2-(2-hydroxy-5-chlorobenzoyl)-2-methylpropan-1-ol

The title compound was prepared from 5-chlorosalicylaldehyde (0.2 mmol) and 2-methylallyl alcohol according to Method 1.1 (5 h reaction time) except that NaOAc (0.01 mmol, 0.8 mg) was used. Purification via thin layer chromatography (gradient 15:1 → 7:3 hexanes:ethyl acetate) afforded the product as a yellow oil (33.5 mg, 73%). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 1.50 (s, 6H), 3.70 (s, 2H), 6.97 (d, J = 8.9 Hz, 1H), 7.39 (dd, J = 8.9, 2.6 Hz, 1H), 7.93 (d, J = 2.5 Hz, 1H). \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ 23.8, 49.4, 71.5, 117.7, 118.2, 119.6, 130.8, 136.1, 162.29, 211.95. HRMS (ESI), calculated for [C\textsubscript{11}H\textsubscript{14}ClO\textsubscript{3}]\textsuperscript{+}[M+H]\textsuperscript{+} 229.06315, found 229.06263.

(Table 1.2, entry 3, 5i)

3-hydroxy-1-(2-hydroxy-5-methoxyphenyl)-2,2-dimethylpropan-1-one

The title compound was prepared from 2-hydroxy-5-methoxybenzaldehyde (0.2 mmol)and 2-methylallyl alcohol according to Method 1.1 (4h reaction time). Purification was performed via preparative thin layer chromatography (3:2 hexanes:ethyl acetate). The Si gel was extracted via sonication with ethyl
acetate (2 extractions), to give the product as a yellow oil (33.8 mg, 76%). $^1$H NMR (400 MHz, CDCl$_3$) δ 1.52 (s, 6H), 2.56 (t, $J = 7.1$ Hz, 1H), 3.69 (d, $J = 7.1$ Hz, 2H), 3.80 (s, 3H), 6.97 (d, $J = 9.1$ Hz, 1H), 7.11 (dd, $J = 9.1$, 3.0 Hz, 1H), 7.45 (d, $J = 3.0$ Hz, 1H), 11.95 (br s, 0.9H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 23.7, 49.3, 56.1, 71.5, 114.2, 117.2, 120.2, 123.8, 151.0, 158.2, 212.3; HRMS (ESI+) Calcd. for [C$_{12}$H$_{17}$O$_4$]$^+$ [M+H]$^+$ 225.11268, found 225.11295.

(Table 1.2, entry 4, 5j)

2-(2-hydroxy-3-methylbenzoyl)-2-methylpropan-1-ol

The title compound was prepared from 3-methylsalicylaldehyde (0.4 mmol) and 2-methylallyl alcohol according to Method 1.1 (5 h reaction time). Purification via Si gel chromatography (gradient 15:1 → 7:3 hexanes:ethyl acetate) afforded the product as a yellow oil (66.5 mg, 80%). $^1$H NMR (300 MHz, CDCl$_3$): δ 1.51 (s, 6H), 2.26 (s, 3H), 2.66 (br s, 1H), 3.68 (s, 2H), 6.77 (t, $J = 7.9$ Hz, 1H), 7.32 (d, $J = 7.1$ Hz, 1H), 7.85 (d, $J = 8.3$ Hz, 1H), 12.77 (s, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 16.13, 23.96, 49.48, 71.66, 117.01, 117.59, 128.53, 128.65, 136.89, 162.57, 213.20. HRMS (ESI+): calculated for [C$_{12}$H$_{17}$O$_3$]$^+$ [M+H]$^+$ 209.11777; found 209.11798.

(Table 1.2, entry 5, 5k)

2-(2-hydroxy-6-methylbenzoyl)-2-methylpropan-1-ol

The title compound was prepared from 6-methylsalicylaldehyde (0.4 mmol) and 2-methylallyl alcohol according to Method 1.1 (5 h reaction time). Purification via Si gel chromatography (gradient 15:1 → 7:3 hexanes:ethyl acetate) afforded the product as a yellow oil (65.0 mg, 78%). $^1$H NMR (300 MHz, CDCl$_3$): δ 1.50 (s, 6H), 2.25 (s, 3H), 2.73 (br s, 1H), 3.67 (s, 2H), 6.76 (t, $J = 7.5$ Hz, 1H), 7.31 (d, $J = 7.5$ Hz, 1H), 7.84 (d, 8.2 Hz, 1H), 12.77 (s, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 16.13, 23.95, 49.49, 71.62, 116.02, 117.60, 128.53, 128.63, 136.56, 162.56, 213.18. HRMS (ESI), calculated for [C$_{12}$H$_{17}$O$_3$]$^+$ 209.11777, found 209.11682.
3-hydroxy-1-(2-hydroxynaphthalen-1-yl)-2,2-dimethylpropan-1-one

The title compound was prepared from 2-hydroxy-1-naphthaldehyde (0.2 mmol) and 2-methylallyl alcohol according to Method 1.2 (16 h reaction time). Purification was performed via preparative thin layer chromatography (hexanes:ethyl acetate). The Si gel was extracted via sonication with tetrahydrofuran (2 extractions), to give the product as a white solid (39.0 mg, 80%, MP 153-154 °C). \( ^1H \) NMR (400 MHz, DMSO-\( \text{d}_6 \)) \( \delta \) 1.16 (s, 6H), 3.60 (s, 2H), 4.98 (bs, 0.9H), 7.16 (d, \( J = 8.9 \) Hz, 1H), 7.29 (ddd, \( J = 8.0, 6.8, 1.2 \) Hz, 1H), 7.38 (ddd, \( J = 8.4, 6.8, 1.4 \) Hz, 1H), 7.55 (d, \( J = 8.4 \) Hz, 1H), 7.78-7.81 (m, 2H), 10.05 (br s, 1H); \( ^{13}C \) NMR (101 MHz, DMSO-\( \text{d}_6 \)) \( \delta \) 21.9, 50.3, 68.6, 118.0, 122.2, 122.9, 123.8, 126.5, 127.5, 127.9, 129.8, 131.0, 150.2, 214.7; HRMS (ESI+) Calcd. for \([\text{C}_{15}\text{H}_{17}\text{O}_3]^+\) [M+H]^+ 245.11777, found 245.11800.

1-(2,4-dihydroxyphenyl)-3-hydroxy-2,2-dimethylpropan-1-one

The title compound was prepared from 2,4-dihydroxybenzaldehyde (0.2 mmol) and 2-methylallyl alcohol using tetrahydrofuran as solvent according to Method 1.2 (4 h reaction time). Purification was performed via preparative thin layer chromatography (3:2 hexanes:tetrahydrofuran). The Si gel was extracted via sonication with tetrahydrofuran (2 extractions). The isolated product was washed twice with chloroform and concentrated to give a white solid (34.5 mg, 82%, MP 140-142 °C). \( ^1H \) NMR (400 MHz, DMSO-\( \text{d}_6 \)) \( \delta \) 1.25 (s, 6H), 3.66 (s, 2H), 4.84 (br s, 0.9H), 6.25 (d, \( J = 2.4 \) Hz, 1H), 6.32 (dd, \( J = 8.9, 2.5 \) Hz, 1H), 7.80 (d, \( J = 8.9 \) Hz, 1H), 10.35 (br s, 0.9H), 12.51 (br s, 0.7H); \( ^{13}C \) NMR (101 MHz, DMSO-\( \text{d}_6 \)) \( \delta \) 23.5, 49.7, 69.1, 102.9, 107.0, 112.8, 132.2, 162.9, 163.7, 209.7; HRMS (ESI+) Calcd. for \([\text{C}_{11}\text{H}_{15}\text{O}_4]^+\) [M+H]^+ 211.09703, found 211.09674.

3-(2-hydroxybenzoyl)-1-butanol

The title compound was prepared from salicylaldehyde (0.25 mmol) and 3-buten-1-ol according to Method 1.1 (2.5 h reaction time). Purification via silica gel column chromatography (gradient 10:1 → 7:3 hexanes:ethyl acetate)
acetate) afforded the title compound as a light yellow oil (47.2 mg, 97%). \textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta\) 12.50 (s, 1H), 7.86 (d, \(J = 8.0\) Hz, 1H), 7.47 (t, \(J = 7.8\) Hz, 1H), 6.99 (d, \(J = 8.4\) Hz, 1H), 6.91 (t, \(J = 7.6\) Hz, 1H), 3.78 (dt, \(J = 10.2, 5.1\) Hz, 1H), 3.74 – 3.65 (m, 2H), 2.14 (td, \(J = 13.4, 6.6\) Hz, 1H), 1.72 (td, \(J = 12.2, 6.1\) Hz, 1H), 1.62 (s, 1H), 1.27 (d, \(J = 7.0\) Hz, 3H). \textbf{\textsuperscript{13}C NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta\) 210.59, 163.17, 136.43, 130.02, 118.95, 118.73, 118.58, 60.41, 36.70, 36.09, 17.77. \textbf{HRMS} (ESI+), calculated for [C\textsubscript{11}H\textsubscript{15}O\textsubscript{3}]\(^{+}\) [M+H]\(^{+}\) 195.10212 found 195.10278.

(\textit{Table 1.4}, entry 2, 9b)
\textbf{3-(2-hydroxy-5-fluorobenzoyl)-1-butanol}

\begin{figure}[h]
\centering
\includegraphics[width=0.2\textwidth]{figure.png}
\caption{Structure of 3-(2-hydroxy-5-fluorobenzoyl)-1-butanol}
\end{figure}

The title compound was prepared according to Method 1.2, 4 hour reaction time. Purification via preparative TLC (4:1 hexanes:ethyl acetate) afforded the title compound as a light yellow oil (46.7 mg, 88%). \textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta\) 12.20 (s, 1H), 7.54 (dd, \(J = 9.2, 3.1\) Hz, 3H), 7.25 – 7.19 (m, 1H), 6.96 (dd, \(J = 9.1, 4.6\) Hz, 1H), 3.78 – 3.62 (m, 3H), 2.18 – 2.08 (m, 1H), 1.71 (dd, \(J = 14.1, 11.7\), 6.1 Hz, 1H), 1.54 (s, 1H), 1.27 (d, \(J = 6.9\) Hz, 3H). \textbf{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) \(\delta\) 209.74, 196.20, 159.26, 156.05, 153.68, 124.09, 123.85, 119.97, 119.89, 118.04, 115.05, 114.81, 60.24, 36.91, 35.97, 17.57. \textbf{HRMS} (ESI+), calculated for [C\textsubscript{11}H\textsubscript{14}F\textsubscript{1}O\textsubscript{3}]\(^{+}\) [M+H]\(^{+}\) 213.09270 found 213.09312.

(\textit{Table 1.4}, entry 3, 9c)
\textbf{3-(2-hydroxy-5-chlorobenzoyl)-1-butanol}

\begin{figure}[h]
\centering
\includegraphics[width=0.2\textwidth]{figure.png}
\caption{Structure of 3-(2-hydroxy-5-chlorobenzoyl)-1-butanol}
\end{figure}

The title compound was prepared from 5-chlorosalicylaldehyde (0.25 mmol) and 3-buten-1-ol according to Method 1.2 (4 hour reaction time). Purification by preparative TLC (4:1 hexanes:ethyl acetate) afforded the title compound as a clear oil (52.5 mg, 92%). \textbf{\textsuperscript{1}H NMR} (300 MHz, CDCl\textsubscript{3}) \(\delta\) 12.37 (s, 1H), 7.82 (d, \(J = 2.5\) Hz, 1H), 7.41 (dd, \(J = 8.9, 2.5\) Hz, 1H), 6.97 – 6.92 (m, 1H), 3.77 – 3.62 (m, 3H), 2.13 (ddd, \(J = 20.0, 13.4, 6.9\) Hz, 1H), 1.71 (ddd, \(J = 14.0, 11.8, 5.9\) Hz, 1H), 1.56 (s, 1H), 1.26 (d, \(J = 7.0\) Hz, 3H). \textbf{\textsuperscript{13}C NMR} (100 MHz, CDCl\textsubscript{3}) \(\delta\) 209.75, 196.20, 153.68, 124.09, 123.85, 119.97, 119.89, 118.04, 115.05, 114.81, 136.22, 129.19, 123.62, 120.29, 119.11, 60.25, 36.85, 35.92, 17.71. \textbf{HRMS} (ESI+), calculated for [C\textsubscript{11}H\textsubscript{14}Cl\textsubscript{1}O\textsubscript{3}]\(^{+}\) [M+H]\(^{+}\) 229.06315 found 229.06363.
(Table 1.4, entry 4, 9d)

3-(2-hydroxy-5-iodobenzoyl)-1-butanol

The title compound was prepared from 5-iodosalicylaldehyde (0.25 mmol) and 3-buten-1-ol according to Method 1.2 (3.5 h reaction time). Purification via silica gel column chromatography (gradient 11:1 → 4:1 hexanes:ethyl acetate) afforded the title compound as a light yellow oil (60.0 mg, 75%). $^1$H NMR (400 MHz, CDCl$_3$) δ 12.41 (s, $J = 8.0$ Hz, 1H), 8.14 (d, $J = 2.1$ Hz, 1H), 7.70 (dd, $J = 8.8$, 2.2 Hz, 1H), 6.79 (d, $J = 8.8$ Hz, 1H), 3.77 – 3.61 (m, 3H), 2.17 – 2.07 (m, 1H), 1.72 (dq, $J = 14.1$, 6.0 Hz, 1H), 1.40 (s, $J = 10.0$ Hz, 1H), 1.26 (d, $J = 7.0$ Hz, 3H). $^{13}$C NMR (10 MHz, CDCl$_3$) δ 209.61, 162.68, 144.63, 138.34, 121.16, 120.67, 79.79, 60.30, 36.84, 35.94, 17.81. HRMS (ESI+), calculated for [C$_{11}$H$_{14}$IO$_3$]$^+$ [M+H]$^+$ 320.99876, found 320.99949.

(Table 1.4, entry 5, 9e)

3-(2-hydroxy-4-methoxybenzoyl)-1-butanol

The title compound was prepared from 2-hydroxy-4-methoxy benzaldehyde and 3-buten-1-ol according to Method 1.1 (3 hour reaction time). Purification by preparative TLC (10:3 hexanes:ethyl acetate) provided the desired product as a yellow oil (51.6 mg, 92 %). $^1$H NMR (400 MHz, CDCl$_3$) δ 13.00 (s, 1H), 7.76 (d, $J = 8.4$ Hz, 1H), 6.46 – 6.43 (m, 2H), 3.84 (s, 3H), 3.74 – 3.60 (m, 3H), 2.19 – 2.02 (m, 1H), 1.78 – 1.66 (m, 1H), 1.57 (s, 1H), 1.25 (d, $J = 6.9$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 208.62, 166.09, 166.05, 131.59, 112.67, 107.64, 101.09, 60.40, 55.54, 36.36, 36.13, 17.84. HRMS (ESI+), calculated for [C$_{12}$H$_{17}$O$_4$]$^+$ [M+H]$^+$ 225.11268, found 225.11204.

(Table 1.4, entry 6, 9f)

3-(2-hydroxy-5-methoxybenzoyl)-1-butanol

The title compound was prepared from 2-hydroxy-5-methoxy benzaldehyde (0.25 mmol) and 3-buten-1-ol according to Method 1.1 (2.5 h reaction time). Purification via silica gel column chromatography (gradient 10:1 → 3:2 hexanes:ethyl acetate) afforded the title compound as a light yellow oil
(48.0 mg, 86%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 12.09 (s, 1H), 7.34 (d, $J = 3.0$ Hz, 1H), 7.11 (dd, $J = 9.1, 3.0$ Hz, 1H), 6.93 (d, $J = 9.1$ Hz, 1H), 3.80 (s, 3H), 3.77 – 3.67 (m, 3H), 2.19 – 2.08 (m, 1H), 1.82 – 1.64 (m, 2H), 1.27 (d, $J = 6.9$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 210.09, 157.48, 151.77, 124.20, 119.47, 118.07, 112.89, 60.31, 56.02, 36.75, 36.19, 17.55. HRMS (ESI+), calculated for [C$_{12}$H$_{17}$O$_4$]$^+$ [M+H]$^+$ 225.11268, found 245.11310.

(Table 1.4, entry 7, 9g)
3-(2-hydroxy-3-methoxybenzoyl)-1-butanol

![Structure] The title compound was prepared from 2-hydroxy-3-methoxy benzaldehyde (0.25 mmol) and 3-buten-1-ol according to Standard Method 1.1 (4 h reaction time). Purification via silica gel column chromatography (gradient 10:1 $\rightarrow$ 1:1 hexanes:ethyl acetate) afforded the title compound as a light yellow oil (46.2 mg, 83%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 12.81 (s, 1H), 7.46 (dd, $J = 8.3, 1.2$ Hz, 1H), 7.06 (dd, $J = 8.0, 1.2$ Hz, 1H), 6.85 (t, $J = 8.1$ Hz, 1H), 3.90 (s, 3H), 3.81 – 3.64 (m, 3H), 2.19 – 2.07 (m, 1H), 1.77 – 1.63 (m, 2H), 1.26 (d, $J = 6.9$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 211.20, 153.76, 149.34, 121.42, 118.83, 118.43, 117.15, 60.56, 56.41, 37.29, 36.30, 17.92. HRMS (ESI+), calculated for [C$_{12}$H$_{17}$O$_4$]$^+$ [M+H]$^+$ 225.11268, found 245.11354.

(Table 1.4, entry 8, 9h)
3-(2-hydroxy-6-methylbenzoyl)-1-butanol

![Structure] The title compound was prepared from 2-hydroxy-6-methyl benzaldehyde to Method 1.1 (3 hour reaction time). Purification by preparative TLC (10:3 hexanes:ethyl acetate) afforded the title compound as a yellow oil (51.02 mg, 98 %). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 12.81 (s, 1H), 7.71 (d, $J = 7.8$ Hz, 1H), 7.33 (d, $J = 7.2$ Hz, 1H), 6.82 – 6.77 (m, 1H), 3.83 – 3.71 (m, 1H), 3.71 – 3.60 (m, 2H), 2.25 (s, 3H), 2.20 – 2.02 (m, 1H), 1.79 (s, 1H), 1.70 (ddd, $J = 14.0, 12.1, 6.1$ Hz, 1H), 1.25 (d, $J = 6.9$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 210.78, 161.55, 137.09, 127.65, 127.53, 118.19, 117.75, 60.34, 36.67, 36.10, 17.82, 15.51. HRMS (ESI+), calculated for [C$_{12}$H$_{17}$O$_4$]$^+$ [M+H]$^+$ 209.11777, found 209.117943.
(Table 1.4, entry 9, 9i)

4-hydroxy-1-(2-hydroxy-5-pyridin-5-yl)-phenyl-2-methylbutan-1-one

The title compound was prepared from 5-(4-pyridyl)-salicylaldehyde (0.157 mmol) and 3-buten-1-ol according to Method 1.2 (3 hour reaction time) Purification by preparative TLC (100% ethyl acetate) afforded the title compound as a colourless oil (31.9 mg, 75%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 12.64 (s, 1H), 8.55 (dd, $J = 4.7, 1.4$ Hz, 2H), 8.24 (d, $J = 2.2$ Hz, 1H), 7.74 (dd, $J = 8.7, 2.2$ Hz, 1H), 7.45 (dd, $J = 4.6, 1.6$ Hz, 2H), 7.10 (d, $J = 8.7$ Hz, 1H), 3.93 (h, $J = 6.7$ Hz, 1H), 3.80 – 3.70 (m, 2H), 2.17 (ddd, $J = 13.8, 12.5, 6.8$ Hz, 1H), 1.78 – 1.68 (m, 1H), 1.30 (d, $J = 6.8$ Hz, 3H), 1.24 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 210.63, 163.86, 150.01, 147.20, 134.46, 128.76, 128.61, 121.01, 119.63, 118.83, 59.86, 36.66, 36.63, 17.17. 

HRMS (ESI+), calculated for [C$_{16}$H$_{18}$N$_{1}O$_3]+ [M+H]+ 272.12867 found 272.12838.

(Table 1.5, entry 2 and 3, 9k)

3-(2-hydroxybenzoyl)-1-hexanol

The title compound was prepared from salicylaldehyde (0.25 mmol) and (E)-3-penten-1-ol or (Z)-3-pentene-1-ol according to Method 1.1 (21 hour reaction time). Purification by preparative TLC (10:3 hexanes:ethyl acetate) afforded the title compound as a clear oil (29 mg, 52% - (E) alkene, 28 mg, 50% - (Z) alkene). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 12.60 (s, 1H), 7.87 (dd, $J = 8.1, 1.5$ Hz, 1H), 7.47 (ddd, $J = 8.6, 7.3, 1.6$ Hz, 1H), 6.98 (dd, $J = 8.4, 0.9$ Hz, 1H), 6.92 – 6.87 (m, 1H), 3.73 (dd, $J = 8.0, 5.5$ Hz, 1H), 3.61 (tdd, $J = 10.7, 8.9, 5.1$ Hz, 2H), 2.13 – 2.02 (m, 1H), 1.86 – 1.72 (m, 2H), 1.66 (s, 1H), 1.59 – 1.47 (m, 1H), 1.37 – 1.25 (m, 3H), 0.89 (t, $J = 7.3$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 210.82, 162.98, 136.44, 130.01, 119.56, 118.90, 118.83, 60.59, 41.80, 35.08, 34.84, 20.62, 14.14. HRMS (ESI+), calculated for [C$_{13}$H$_{19}$O$_3$]+ [M+H]+ 223.13342 found 223.13384.

(Table 1.5, entry 4, 9l)

3-(2-hydroxybenzoyl)-2-methyl-1-butanol

The title compound was prepared from salicylaldehyde (0.25 mmol), and 2-methyl-3-buten-1-ol according to Method 1.1 (2.5 h reaction time).
Purification via Si gel chromatography (10:1 → 3:2 hexanes:ethyl acetate) afforded the product as a yellow oil (47.7 mg, 92 %), which was found to be a 64:36 mixture of diastereomers by $^1$H NMR analysis.

Major: $^1$H NMR (400 MHz, CDCl$_3$): 12.55 (s, 1H), 7.89 (dd, $J$ = 8.1, 1.6 Hz, 1H), 7.49 – 7.44 (m, 1H), 6.99 (dd, $J$ = 8.4, 0.8 Hz, 1H), 6.92 – 6.88 (m, 1H), 3.76 (p, $J$ = 6.7 Hz, 1H), 3.68 – 3.49 (m, 2H), 2.29 – 2.18 (m, 1H), 1.76 – 1.57 (br s, 1H), 1.16 (d, $J$ = 6.9 Hz, 1H), 0.91 (d, $J$ = 7.0 Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 211.02, 163.19, 136.51, 130.04, 119.15, 118.88, 118.77, 64.85, 42.00, 38.12, 15.83, 14.62. HRMS (ESI+), calculated for [C$_{12}$H$_{17}$O$_3$]$^+$ [M+H]$^+$ 209.11777 found 209.11699.

Minor: $^1$H NMR (400 MHz, CDCl$_3$) δ 12.54 (s, 1H), 7.84 (dd, $J$ = 8.1, 1.5 Hz, 1H), 7.51 – 7.46 (m, 1H), 7.00 (dd, $J$ = 8.4, 1.2 Hz, 1H), 6.93 – 6.88 (m, 1H), 3.68 – 3.49 (m, 1H), 2.18 – 2.10 (m, 2H), 1.66 (s, 1H), 1.25 (d, $J$ = 7.0 Hz, 3H), 1.00 (d, $J$ = 6.9 Hz, 5H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 210.74, 163.18, 136.28, 130.08, 118.87, 118.72, 118.66, 66.10, 40.85, 38.23, 12.58, 12.38. HRMS (ESI+), calculated for [C$_{12}$H$_{17}$O$_3$]$^+$ [M+H]$^+$ 209.11777 found 209.11714.

(Table 1.5, entry 5, 9m)

3-(2-hydroxybenzoyl)-1-phenyl-1-butanol

The title compound was prepared from salicylaldehyde (0.25 mmol) and 1-phenyl-3-butene-1-ol according to Method 1.1 (17 hour reaction time). Purification by preparative TLC (10:2.5 hexanes:ethyl acetate) afforded the product as a clear oil (76.3 mg, 98 %), which was found to be a 68:32 mixture of diastereomers by $^1$H NMR analysis. HRMS (ESI+), calculated for [C$_{17}$H$_{18}$O$_3$Na]$^+$ [M+Na]$^+$ 293.1148 found 293.1146.

Major: $^1$H NMR (400 MHz, CDCl$_3$) δ 12.54 (s, 1H), 7.75 (dd, $J$ = 8.1, 1.4 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.37 – 7.27 (m, 5H), 7.00 (dd, $J$ = 8.4, 0.9 Hz, 1H), 6.92 – 6.85 (m, 1H), 4.67 (dd, $J$ = 9.0, 4.2 Hz, 1H), 3.88 – 3.79 (m, 1H), 2.32 (ddd, $J$ = 13.7, 7.8, 4.1 Hz, 1H), 2.00 (s, 1H), 1.88 (ddd, $J$ = 13.8, 9.0, 4.4 Hz, 1H), 1.27 (d, $J$ = 7.0 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ
210.60, 163.14, 144.47, 136.42, 130.05, 128.54, 127.71, 125.58, 118.87, 118.76, 118.62, 72.29, 42.75, 36.64, 18.94.

Minor: $^1$H NMR (400 MHz, CDCl$_3$) δ 12.47 (s, 1H), 7.81 (dd, $J = 8.1, 1.4$ Hz, 1H), 7.51 – 7.44 (m, 1H), 7.37 – 7.27 (m, 5H), 6.99 (dd, $J = 8.4, 0.9$ Hz, 2H), 6.93 – 6.85 (m, 4H), 4.77 (dd, $J = 9.1, 4.6$ Hz, 1H), 3.79 – 3.70 (m, 1H), 2.41 – 2.35 (m, 1H), 2.00 (s, 1H), 1.78 (ddd, $J = 14.1, 7.2, 4.6$ Hz, 1H), 1.29 (d, $J = 6.9$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 210.23, 163.14, 144.47, 136.26, 129.99, 128.58, 127.84, 125.74, 118.86, 118.76, 118.63, 72.45, 42.59, 37.16, 17.54.

(Table 1.5, entry 6, 9n)

3-(2-hydroxybenzoyl)-2-methyl-1-pentanol

The title compound was prepared from salicylaldehyde (0.25 mmol) and 2-methyl-3-penten-1-ol (4:1 cis:trans) according to Method 1.1 (20 h reaction time). Purification via silica gel column chromatography (gradient 10:1 → 4:1 hexanes:ethyl acetate) afforded the title compound as a light yellow oil (29.4 mg, 53%).

Major: $^1$H NMR (400 MHz, CDCl$_3$) δ 12.70 (s, 1H), 7.89 (dd, $J = 8.1, 1.5$ Hz, 1H), 7.48 (ddd, $J = 8.6, 7.3, 1.6$ Hz, 1H), 7.00 (dd, $J = 8.4, 1.0$ Hz, 1H), 6.94 – 6.87 (m, 1H), 3.68 – 3.52 (m, 3H), 2.17 – 2.05 (m, 1H), 1.89 (ddq, $J = 14.6, 9.6, 7.3$ Hz, 1H), 1.76 – 1.63 (m, 1H), 1.50 (s, 1H), 0.98 (d, $J = 7.0$ Hz, 3H), 0.86 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 211.12, 162.92, 136.52, 130.31, 120.77, 118.85, 118.66, 65.26, 48.31, 38.02, 22.87, 15.29, 12.14. HRMS (ESI+), calculated for [C$_{13}$H$_{19}$O$_3$]$^+$ [M+H]$^+$ 223.13342, found 223.13247.

Minor: $^1$H NMR (400 MHz, CDCl$_3$) δ 12.66 (s, 1H), 7.92 (dd, $J = 8.1, 1.5$ Hz, 1H), 7.47 (ddd, $J = 8.6, 7.3, 1.6$ Hz, 1H), 6.99 (dd, $J = 8.4, 1.0$ Hz, 1H), 6.93 – 6.88 (m, 2H), 3.62 (ddd, $J = 9.7, 5.9, 3.5$ Hz, 1H), 3.54 (dd, $J = 13.1, 7.8$ Hz, 2H), 2.23 – 2.11 (m, 1H), 1.87 (ddq, $J = 14.6, 9.9, 7.3$ Hz, 1H), 1.65 – 1.54 (m, 2H), 0.94 (d, $J = 7.0$ Hz, 3H), 0.85 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 210.76, 163.01, 136.36, 130.29, 119.98, 118.87, 118.67, 66.07, 48.20, 37.99, 20.83, 13.33, 12.07. HRMS (ESI+), calculated for [C$_{13}$H$_{19}$O$_3$]$^+$ [M+H]$^+$ 243.13342, found 223.13269.
(Table 1.6, entry 1, 9q)

1,2-bis(2-hydroxybenzoyl)-1-propanone

The title compound was prepared from salicylaldehyde (0.25 mmol) and 2-vinylphenol according to Method 1.1 (4 h reaction time). Purification via silica gel column chromatography (gradient 12:1 → 9:1 hexanes:ethyl acetate) afforded the title compound as a white solid (53.3 mg, 88%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 12.33 (s, 1H), 7.94 (dd, \(J = 8.1, 1.5\) Hz, 1H), 7.42 (ddd, \(J = 8.6, 7.3, 1.6\) Hz, 1H), 7.20 – 7.06 (m, 2H), 6.96 (dd, \(J = 8.4, 1.0\) Hz, 1H), 6.91 – 6.78 (m, 3H), 6.33 (s, 1H), 5.06 (q, \(J = 7.0\) Hz, 1H), 1.55 (d, \(J = 7.0\) Hz, 3H).; \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 208.77, 163.37, 153.21, 136.89, 130.73, 129.34, 128.87, 127.14, 121.57, 119.35, 118.83, 118.76, 116.84, 42.02, 17.46. HRMS (ESI+), calculated for [C\(_{15}\)H\(_{15}\)O\(_3\)]\(^+\) [M+H]\(^+\) 243.10212, found 243.10278.

(Table 1.6, entry 2, 9r)

1-(2-hydroxyphenyl)-2-(2-hydroxy-5-fluorophenyl)-1-propanone

The title compound was prepared from salicylaldehyde (0.25 mmol) and 2-vinyl-4-fluoro phenol according to Method 1.1 (4 hour reaction time). Purification by preparative TLC (10:3 hexanes:ethyl acetate) afforded the title compound as a white solid MP (130-132 °C) (63.7 mg, 98%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 12.20 (s, 1H), 7.91 (dd, \(J = 8.1, 1.5\) Hz, 1H), 7.50 – 7.41 (m, 1H), 6.98 (dd, \(J = 8.4, 0.9\) Hz, 1H), 6.87 (ddd, \(J = 14.7, 6.0, 2.1\) Hz, 2H), 6.81 (dd, \(J = 7.7, 3.0\) Hz, 1H), 6.77 (dd, \(J = 8.8, 4.7\) Hz, 1H), 5.96 (s, 1H), 5.01 (q, \(J = 7.0\) Hz, 1H), 1.56 (d, \(J = 7.0\) Hz, 3H). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 175.66, 158.47, 156.11, 148.73, 148.71, 130.58, 130.56, 126.08, 126.01, 116.81, 116.76, 116.73, 115.32, 115.08, 113.18, 112.94. HRMS (ESI+), calculated for [C\(_{15}\)H\(_{14}\)F\(_1\)O\(_3\)]\(^+\) [M+H]\(^+\) 261.09270, found 261.09279.
(Table 1.6, entry 3, 9s)

1-(2-hydroxyphenyl)-2-(2-hydroxy-4-methoxyphenyl)-1-propanone

The title compound was prepared from salicylaldehyde (0.25 mmol) and 2-vinyl-5-methoxy phenol according to Method 1.1 (7 hour reaction time). Purification by preparative TLC (10:4 hexanes:ethyl acetate) provided the desired product as a white solid MP 119-120 °C, (37.3 mg, 68%). $^1$H NMR (400 MHz, CDCl$_3$) δ 12.30 (s, 1H), 7.96 – 7.92 (m, 1H), 7.47 – 7.41 (m, 1H), 7.05 (d, $J = 8.4$ Hz, 1H), 6.97 (d, $J = 8.3$ Hz, 1H), 6.85 (t, $J = 7.5$ Hz, 1H), 6.65 (s, 1H), 6.45 – 6.40 (m, 2H), 4.97 (q, $J = 7.0$ Hz, 1H), 3.73 (s, 3H), 1.55 (d, $J = 7.0$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 208.87, 163.24, 159.99, 154.32, 136.71, 130.43, 129.92, 119.09, 119.00, 118.64, 118.40, 106.68, 102.88, 55.26, 41.63, 17.21. HRMS (ESI+), calculated for [C$_{16}$H$_{17}$O$_4$]$^+$ [M+H]$^+$ 273.11268, found 273.11328.

(Table 1.6, entry 4, 9t)

1,2-bis(2-hydroxybenzoyl)-1-butanone

The title compound was prepared from salicylaldehyde (0.25 mmol) and 2-propenylphenol according to Method 1.1 (4 h reaction time). Purification via silica gel column chromatography (gradient 11:1 → 4:1 hexanes:ethyl acetate) afforded the title compound as a white solid (53.3 mg, 88%). $^1$H NMR (400 MHz, CDCl$_3$) δ 12.32 (s, 1H), 8.01 (dd, $J = 8.1$, 1.4 Hz, 1H), 7.47 – 7.39 (m, 1H), 7.16 (dd, $J = 7.5$, 1.4 Hz, 1H), 7.11 (td, $J = 7.7$, 1.6 Hz, 1H), 6.96 (dd, $J = 8.4$, 0.8 Hz, 1H), 6.89 – 6.82 (m, 3H), 6.78 (s, 1H), 4.84 (t, $J = 7.5$ Hz, 1H), 2.24 – 2.12 (m, 1H), 2.04 – 1.91 (m, 1H), 0.92 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 208.64, 163.28, 153.84, 136.91, 130.60, 129.86, 124.85, 121.19, 119.21, 119.11, 118.68, 116.96, 49.53, 25.21, 12.26. HRMS (ESI+), calculated for [C$_{16}$H$_{17}$O$_3$]$^+$ [M+H]$^+$ 257.11777, found 257.11793.

(Scheme 1.12, 5n)

2-(2-hydroxybenzoyl)pentan-1-ol

The title compound was prepared from salicylaldehyde (0.25 mmol), and cis-2-buten-1-ol according to Method 1.1 (3 h reaction time). Purification via Si gel chromatography (15:1 → 7:3 hexanes:ethyl acetate) afforded the product as a
yellow oil (44.6 mg, 92 %). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 12.41 (s, 1H), 7.80 (d, $J = 8.0$ Hz, 1H), 7.49 (t, $J = 7.8$ Hz, 1H), 6.99 (d, $J = 8.4$ Hz, 1H), 6.92 (t, $J = 7.6$ Hz, 1H), 3.98 (dd, $J = 11.0$, 7.2 Hz, 1H), 3.84 (dd, $J = 11.0$, 4.0 Hz, 1H), 3.65 – 3.53 (m, 1H), 2.31 (s, 1H), 1.89 – 1.62 (m, 2H), 0.97 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 210.16, 163.07, 136.76, 130.25, 119.42, 119.04, 118.78, 62.73, 49.21, 22.82, 11.81. LRMS (EI+), calculated for [C$_{11}$H$_{14}$O$_3$]$^+$ [M]$^+$ 194.09, found 194.10.

1.7.3 Ketone Derivatization

(Scheme 1.9, 10)

2-(3-methyl-tetrahydrofuran-2-yl)-phenol

3-(2-hydroxybenzoyl)-1-butanol (44.5 mg, 0.25 mmol) and NaBH$_4$ (37.8 mg, 1 mmol) were weighed into a 10 mL round bottom flask. These solids were dissolved in 2.2 mL of MeOH added via syringe, and the reaction vessel was immediately fitted with a reflux condenser. This solution was heated to reflux and magnetically stirred for 3 hours. The reaction vessel was then cooled and all volatiles are removed in vacuo. At this time, 2.2 mL of 1M aqueous HCl was added via syringe and the resulting grey solution was stirred for 3 hours. The aqueous solution was extracted with ether (3 x 30 mL) and the combined organic layers were dried over anhydrous MgSO$_4$ and concentrated in vacuo. The crude mixture was purified via Si gel chromatography (4:1 hexanes:ethyl acetate) to afforded the title compound as a clear oil (35.1 mg, 78%), which was found to be a 33:1 mixture of diastereomers (trans:cis) based on analogy to the $^1$H coupling constants reported in the literature. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.43 (s, 1H), 7.21 – 7.15 (m, 1H), 6.96 (dd, $J = 7.6$, 1.7 Hz, 1H), 6.88 (dd, $J = 8.1$, 1.1 Hz, 1H), 6.83 (ddd, $J = 7.4$, 6.0, 1.2 Hz, 1H), 4.39 – 4.33 (m, 1H), 4.14 (ddd, $J = 10.9$, 8.2, 4.9 Hz, 1H), 4.01 (td, $J = 9.0$, 4.3 Hz, 1H), 2.32 – 2.19 (m, 2H), 1.80 – 1.68 (m, 1H), 1.13 – 1.07 (m, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 155.73, 128.87, 127.49, 123.48, 119.35, 117.03, 89.27, 67.16, 40.21, 34.14, 016.01. HRMS (ESI+), calculated for [C$_{11}$H$_{13}$O$_2$]$^+$ [M+H]$^+$ 177.09155, found 177.09183.
1.7.4  Mechanistic Studies

Scheme 1.8:

In a glovebox, \([\text{Rh(COD)Cl}]_2\) (9.9 mg, 0.02 mmol) and sodium acetate (3.3 mg, 0.04 mmol) were weighed into a vial. A stir bar and 0.500 mL of degassed 1,2-dichloroethane were added. Allyl diphenylphosphinite (73.0 mg, 0.3 mmol) and salicylaldehyde (24.0 mg, 0.2 mmol) were added via syringe. The vial was sealed with a Teflon-lined screw-cap, and heated at 40 °C for 3 hours. The products were isolated by Si gel chromatography (gradient 15:1 → 7:3 hexanes:ethyl acetate). 5a was obtained as a light yellow oil (33%, 11.9 mg). (see Section 4iii for characterization). 6 was obtained as a white solid (21%, 6.8 mg). \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 2.08-2.12 (m, 3H), 5.43-5.45 (m, 1H), 5.73-5.75 (m, 1H), 6.89 (t, J = 7.6 Hz, 1H), 7.02 (d, J = 8.3 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 11.90 (s, 1H); \(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta\) 19.5, 118.4, 118.6, 123.1, 132.8, 136.3, 142.7, 144.2, 163.1, 203.5; \text{HRMS (ESI+)} Calcd. for \([\text{C}_{10}\text{H}_{11}\text{O}_2]^{+}\) [M+H]\(^{+}\) 163.07590, found 163.07571. 7 was obtained as light yellow liquid (27%, 8.7 mg), which was confirmed by comparison to the \(^1\text{H NMR}\) values from the literature. \(^{18}\) \(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta\) 1.23 (d, J = 6.9, 3H), 2.82-2.93 (m, 1H), 4.17 (t, J = 11.0 Hz, 1H), 4.51 (dd, J = 11.3 Hz, 5.3 Hz, 1H), 6.97 (d, J = 8.8 Hz, 1H), 7.02 (t, J = 7.9 Hz, 1H), 7.44-7.51 (m, 1H), 7.91 (d, 7.9 Hz, 1H).

Scheme 1.10 (top):

In a glovebox, \([\text{Rh(COD)Cl}]_2\) (3.0 mg, 6.17 μmol) and sodium acetate (2.0 mg, 24.7 μmol) were weighed into a vial. 0.300 mL of degassed 1,2-dichloroethane was added. Methyl
diphenylphosphinite (13.3 mg, 61.7 μmol), $d_1$-salicylaldehyde (prepared according to a literature procedure, see Ref 2.) (7.6 mg, 61.7 μmol), 5-methoxysalicylaldehyde (9.4 mg, 61.7 μmol) and 2-methyl-2-propen-1-ol (8.9 mg, 123.5 μmol) were added via syringe. The vial was charged with a stir bar, sealed with a Teflon-lined screw-cap, and heated at 67 °C for 5 hours. The products were isolated by thin layer chromatography (4:1 hexanes:ethyl acetate, 3 elutions). $h/d$-5g was obtained as a colourless liquid (7.4 mg, 61%) and $h/d$-5i was obtained as a yellow liquid (10.0 mg, 72%). The isolated products were analyzed using DART-TOF-MS. The table below shows the intensities of the relevant peaks. From these values, the ratios of the various isotopologues were calculated. For product $h/d$-5g, the ratio of non-deuterated:monodeuterated:dideuterated was 24:66:10. For product $h/d$-5i, the ratio of non-deuterated:monodeuterated:dideuterated was 82:18:0. The reaction was repeated in the absence of alkene and no deuterium incorporation into 1c was observed by GC-MS.

Isotope ratios for the isolated products.

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</table>

**Scheme 1.10 (bottom):**

In a glovebox, [Rh(COD)Cl]$_2$ (2.0 mg, 4.06 μmol) and sodium acetate (2.7 mg, 32.86 μmol) were weighed into a vial. 0.200 mL of degassed tetrahydrofuran was added. Methyl diphenylphosphinite (8.8 mg, 40.61 μmol), $d_1$-salicylaldehyde (prepared according to a literature procedure, see Ref 2.) (10.0 mg, 81.2 μmol), 3-methoxysalicylaldehyde (12.4 mg, 81.2 μmol) and homoallylalcohol (11.7 mg, 164.4 μmol) were added via syringe. The vial was charged with a stir bar, sealed with a Teflon-lined screw-cap, and heated at 70 °C for 4 hours. The products
were isolated by thin layer chromatography (3:2 hexanes:ethyl acetate, 2 elutions). \textit{h/d/d$_3$-9a} was obtained as a colourless liquid (8.4 mg, 53%) and \textit{h/d/d$_2$-9g} was obtained as a yellow liquid (13.1 mg, 72%). The isolated products were analyzed using DART-TOF-MS. From the intensities of the relevant peaks, the ratios of the various isotopologues were calculated. For product \textit{h/d/d$_3$-9a}, the ratio of non-deuterated:monodeuterated:dideuterated:trideuterated was 51:38:10:1. For product \textit{h/d/d$_2$-9g}, the ratio of non-deuterated:monodeuterated was 76:22:3. The reaction was repeated in the absence of alkene and no deuterium incorporation into \textit{1c} was observed by GC-MS.

1.8 References


4. 2-aminobenzaldehydes have very recently been demonstrated to undergo efficient coupling with alkynes under Rh-catalysis, see: Castaing, M.; Wason, S. L.; Estepa, B.; Hooper, J. F.; Willis, M. C. Angew. Chem. Int. Ed. 2013, 52, 13280.


2 Hydroacylation of 2-Vinylphenols with Non-chelating Aldehydes*

2.1 Introduction

Strategies for controlling chemo-, regio-, and stereo-selectivity in hydroacylation have been developed by studying reactions with aldehydes that contain β-coordinating heteroatoms. However, few methods address the challenges of using aldehydes that lack a β-coordinating group, such as their less favourable metal-binding properties and tendency to undergo reductive decarbonylation. This section summarizes mechanistic studies on C–H bond activation of aldehydes that lack a β-coordinating group and the reactions of the resulting acyl-rhodium(III)-hydrides. The majority of work on this topic concerns the stoichiometric reactions of aldehydes with Rh-complexes. The findings from this survey are then applied to develop a method for catalytic hydroacylation of 2-vinylphenols with aldehydes that lack a β-coordinating group, hereafter referred to as non-chelating aldehydes.

Milstein reported the first acyl-rhodium(III)-hydride complexes that were not stabilized by chelation (Scheme 2.1).1 Coordinatively saturated complexes I were obtained by reacting RhCl(PMe3)3 with either aliphatic or aromatic aldehydes. The stability of these complexes was attributed to the lack of a vacant coordination site on the rhodium center and the slow dissociation of the PMe3 ligands. Using the relatively electron deficient ligand PPh3, C–H activation did not occur. Complexes I were unstable at 60 °C and underwent either reductive elimination to generate aldehydes or reductive decarbonylation to generate alkanes/arenes. Both processes were inhibited by PMe3, indicating that phosphine dissociation is a key step. This observation confirms that a vacant site is required for carbonyl de-insertion and that reductive elimination of aldehyde occurs from a 5-coordinate intermediate. By the principle of microscopic reversibility, we can conclude that oxidative addition of Rh to an aldehyde C–H bond occurs

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* Portions of the following discussion, including text, figures, tables and schemes, are reproduced with modifications. Adapted from Murphy, S. K.; Bruch, A.; Dong, V. M. Substrate-Directed Hydroacylation: Rh-Catalyzed Coupling of Vinyl Phenols and Non-Chelating Aldehydes. Angew. Chem. Int. Ed. 2014, 53, 2455, with permission from John Wiley & Sons. Adapted from Murphy, S. K.; Bruch, A.; Dong, V. M. Mechanistic Insights into Hydroacylation with Non-chelating Aldehydes and 2-Vinylphenols. Chem. Sci. 2015, 6, 174 with permission from The Royal Society of Chemistry.
from RhL₂X complexes. Abstracting the halide counterion of I with AgPF₆ led to immediate formation of an alkane and a Rh¹-carbonyl complex.

Scheme 2.1 Reactivity of a saturated acyl-Rh(III)-hydride complex.

Goldman studied aldehyde C–H bond activation with RhL₂X complexes (Scheme 2.2).² Pentacoordinate acyl-Rh³⁺-hydrides III were formed within ten minutes of mixing [RhCl(P(iPr)₃)₂] with alkyl or aryl aldehydes. Crystallographic analysis of these complexes revealed a Y-type distorted trigonal bipyramidal structure where the acyl, hydride and chloride ligands occupied the equatorial positions. Based on calorimetry, the oxidative addition of Rh to aldehydes was exothermic in the range of -10.5 to -15.2 kcal/mol. Aliphatic aldehydes such as 1-octanal underwent more exothermic reactions compared to aromatic aldehydes. Electron withdrawing groups on aromatic aldehydes favoured oxidative addition while donating groups increased the enthalpy of reaction. Complexes III underwent quantitative reductive decarbonylation at room temperature within two hours of formation. This process was inhibited by excess P(iPr)₃; however, no hexacoordinate Rh complexes were observed. Thus, dissociation of a phosphine from III probably occurs either prior to or during the rate limiting step of reductive decarbonylation. Milstein later studied analogous rhodium complexes with triflate counterions (Scheme 1.2).³ Within 30 minutes of mixing [Rh(PiPr₃)₂OTf] with aldehydes, acyl-rhodium³⁺-hydride complexes IV formed quantitatively. These complexes adopted a square-based pyramidal structure with the acyl group in the apical position. In contrast to Goldman’s studies, complexes IV were stable toward reductive decarbonylation, remaining unchanged after stirring in benzene for 24 hours. This stability was attributed to the lack of a vacant coordination site cis to the acyl ligand, which would be necessary for decarbonylation to occur.
The groups of Stille and Casey each performed kinetic analyses on the de-insertion of CO in metal-acyl complexes. Stille studied the products of oxidative addition of Wilkinson’s complex to acid chlorides (Scheme 2.3). Stille determined that the equilibrium between RCO-Rh\textsuperscript{III} and R-Rh\textsuperscript{III}-CO complexes varies dramatically with the nature of the R group. For alkyl groups, the equilibrium lies towards RCO-Rh\textsuperscript{III} complexes, whereas for aryl groups, the equilibrium falls far towards R-Rh\textsuperscript{III}-CO complexes, presumably due to stronger Ar-Rh bonds compared to alkyl-Rh bonds. For benzyl groups, the equilibrium constant for insertion of CO was highly solvent dependent. Casey came to similar conclusions studying bis(acyl)rhenium(I) complexes. Kinetic analysis showed that acyl groups with an alkyl chain undergo de-insertion of CO 28-29 times faster than those with aryl groups. Stille also found that de-insertion of CO from pentacoordinate RhCl\textsubscript{2}(ArCO)(PPh\textsubscript{3})\textsubscript{2} complexes XII is not inhibited by phosphine; however, the subsequent reductive elimination step is inhibited by phosphine. This suggests that reductive elimination takes place following phosphine dissociation, which gives RhCl\textsubscript{2}(Ar)(CO)(PPh\textsubscript{3}) (XIV). This result is consistent with the general phenomenon that pentacoordinate complexes undergo reductive elimination faster than hexacoordinate complexes. Although no data were provided for the rates of the final reductive elimination steps, it is likely that aryl-hydride reductive elimination would be faster than the alkyl-hydride reductive elimination.

Scheme 2.2 Thermodynamics for formation of unsaturated acyl-Rh\textsuperscript{III}-hydride complexes.

\[ \Delta H = -10.5 \text{ to } -15.2 \text{ kcal/mol} \]
Scheme 2.3 Decarbonylation of acid chlorides with Wilkinson’s complex.

Brookhart developed a hydroacylation catalyst (V) with pentamethycyclopentadienyl (Cp*) and vinyl trimethylsilane (VTMS) ligands (Scheme 2.4). This catalyst was effective for hydroacylation of a variety of olefins including norbornene, cyclopentene and 1-hexene. Changing the Cp* ligand to a (trifluoromethyl)tetramethylcyclopentadienyl ligand (complex VI) provided faster reaction rates by accelerating rate-limiting reductive elimination. Electron-rich benzaldehydes are ideal substrates for this reaction, while electron-deficient benzaldehydes provide lower yields even at elevated catalyst loadings and temperatures.

Scheme 2.4 Hydroacylation of olefins with aromatic aldehydes.

Detailed mechanistic studies (Scheme 2.5) showed that the Rh(Cp*)(VTMS)₂ catalyst (VI) is highly reactive toward oxidative addition to aldehydes. The major resting state X arises from olefin dissociation, oxidative addition to the aldehyde C–H bond, hydrometallation of the olefin and de-insertion of carbon monoxide (CO). Each of these steps is reversible, and hydrometallation is un-selective on the basis of deuterium-labelling experiments. Benzaldehydes...
with either electron-donating or electron-withdrawing substituents react to form $X$ with near equal rates. However, the reaction to form $X$ is more exergonic for benzaldehydes with electron-withdrawing substituents, presumably because electron-withdrawing substituents strengthen the aryl-Rh bond. These results suggest an early transition state for oxidative addition to the aldehyde C-H bond. Although acyl-Rh$^{\text{III}}$-alkyl complex $\text{IX}$ is slow to undergo reductive elimination of the linear ketone, it rearranges via carbonyl de-insertion and re-insertion to yield acyl-Rh$^{\text{III}}$-aryl complex $\text{XI}$, which reductively eliminates the same product. Alkyl aldehydes are unsuitable substrates because the reductive elimination would require C(sp$^3$)-C(sp$^2$) bond formation, which is disfavored compared to reductive decarbonylation. Furthermore, alkyl aldehydes undergo isomerization to mixtures of $n$ and $i$ aldehydes via a related mechanism.$^9$

![Scheme 2.5 Mechanism for hydroacylation with Brookhart's catalyst system.](image)

Tanaka reported the hydroacylation of mono and di-substituted N,N-dialkylacrylamides with both aliphatic and aromatic aldehydes using a cationic rhodium diphosphine complex (Scheme 1.7).$^{14}$ Tanaka later reported an asymmetric variant of this reaction for hydroacylation of 1,1-disubstituted N,N-dialkylacrylamides with aliphatic aldehydes using QuinoxP* as a
Although no mechanistic studies were performed, the authors suggest that this substrate combination results in an acyl-Rh$^\text{III}$-hydride intermediate that is coordinatively saturated and stable toward reductive decarbonylation. Alkyl aldehydes are ideal substrates for this reaction and no products of aldehyde isomerization were reported. Aromatic aldehydes can also be used in this reaction but require higher catalyst loadings.

Scheme 2.6 Hydroacylation of N,N-dialkylacrylamides.

Our laboratory recently developed a method for enantioselective hydroacylation of α-ketoamides with aldehydes that lack a β-coordinating heteroatom (Scheme 2.7). Kinetic studies revealed a second order dependence of the reaction rate on catalyst concentration, a positive non-linear effect with regard to the ligand and a large kinetic isotope effect at the aldehyde C–H bond. Taken together, these data suggest that the rate-limiting step involves homobimetallic oxidative addition to the aldehyde C–H bond. Although intermediates of this type could not be observed spectroscopically, the authors identified a Rh(diphosphine)(solvent)$_2^+$ complex as the catalyst resting state by $^1$H and $^{31}$P NMR spectroscopy. This finding is consistent with the popular “black box” description of the hydroacylation mechanism with cationic Rh complexes, where steady-state intermediates cannot be observed.
2.2 Reaction Design

All currently isolable acyl-Rh$^{III}$-hydrides are derived from neutral rhodium complexes with trialkylphosphine ligands. However, cationic Rh complexes are the most common catalysts for hydroacylation, despite results that indicate aldehyde C–H bond activation with cationic Rh is thermodynamically uphill. Thus, the literature on stoichiometric aldehyde activation and the literature on catalytic hydroacylation appear disconnected. I decided to bridge this gap by investigating neutral rhodium complexes for catalytic aldehyde functionalization. By combining this strategy with the use of a directing group on the olefin component, I sought to develop a general method for branched-selective hydroacylation with non-chelating aldehydes.

Developing new catalysts for branched-selective hydroacylation of olefins with aldehydes that lack a β-coordinating group is challenging. And the few Rh-catalyzed reactions that successfully use these aldehydes provide only linear ketones. As alternatives to Rh-catalysis, Krische and Ryu applied Ru-hydrides for branched-selective addition of aldehydes to enones and 1,3-dienes. Recently, Glorius reported an NHC-catalyzed method for linear selective coupling of benzaldehydes and electron deficient styrenes. In addition, a few promising examples of branched-selective coupling with electron rich styrenes were reported albeit with low-to-moderate yields. To address this challenge, I proposed that an anionic directing group on the olefin could enable branched-selective hydroacylation with broad aldehyde scope (Scheme 2.8).
Scheme 2.8 Proposed regioselective hydroacylation of olefins bearing an anionic directing group.

The choice of an anionic directing group allows the use of a neutral Rh catalyst, which is highly electron-rich compared to the commonly used cationic catalysts and more reactive toward C–H bond activation. On the basis of double-chelating hydroacylations with salicylaldehydes, the anionic group should also promote olefin binding and guide formation of the branched ketone. Bidentate phosphines were favored in order to make the acyl-Rh\textsuperscript{III}-hydride coordinatively saturated and therefore resistant to decarbonylation.

In principle, a wide range of acidic functional groups could be used to generate the requisite anionic directing group by reaction with a Brønsted base. Due to the prevalence of phenols and their wide range of acidity, 2-vinylphenols were chosen as the olefins for initial studies (Scheme 2.9). Furthermore, the products of 2-vinylphenol hydroacylation may be cyclized to a wide variety of benzofurans, including biologically relevant eupomatenoids.

Scheme 2.9 Hydroacylation of vinyl phenols with alkyl, alkenyl, and aryl aldehydes.

2.3 Hydroacylation of 2-Vinylphenols

The coupling of hydrocinnamaldehyde 1a with 4-chloro-2-vinylphenol 2a was examined in the presence of a base, Rh and various ligands (Table 2.1). A 2:1 P:Rh ratio was maintained
to generate the proposed saturated acyl-Rh\textsuperscript{III}-hydride intermediate (Scheme 2.8). Both P(OMe)\textsubscript{3} and bis(diphenylphosphino)methane (dppm) are effective ligands and provide the branched product 3a with >20:1 b:l selectivity (entries 1 and 2). Weller and Willis used similar small bite-angle diphosphines for hydroacylation of alkenes and alkynes with β-sulfur substituted aldehydes and they suggested that the small bite-angle promotes reductive elimination.\textsuperscript{16} A more sterically demanding and electron-rich ligand, bis(dicyclohexylphosphino)methane (dcpm), provides a faster reaction rate and higher yield (entry 3, 99% yield). Diphosphines with larger bite-angles are completely ineffective and the lack of chiral small bite-angle diphosphines precludes an enantioselective process. Changing the solvent from 1,2-DCE to THF and increasing the vinylphenol concentration to 1 M further increases reaction rates. In line with Bergman’s observation that Rh-alkoxide complexes undergo rapid exchange with phenols,\textsuperscript{17} [Rh(cod)OMe]\textsubscript{2} is an effective catalyst in the absence of added base (entry 4, 99% yield). This protocol uses commercially available catalyst components and does not require hydrogenation to activate the catalyst, unlike the cationic Rh diphosphine catalysts currently used for hydroacylation.

Table 2.1 Optimization of reaction conditions.

<table>
<thead>
<tr>
<th>#</th>
<th>Rh</th>
<th>Ligand</th>
<th>Additive</th>
<th>T [°C]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{a,*}</td>
<td>[Rh(cod)Cl]\textsubscript{2}</td>
<td>P(OMe)\textsubscript{3}</td>
<td>K\textsubscript{3}PO\textsubscript{4}</td>
<td>80</td>
<td>75</td>
</tr>
<tr>
<td>2\textsuperscript{b}</td>
<td>[Rh(cod)Cl]\textsubscript{2}</td>
<td>dppm</td>
<td>K\textsubscript{3}PO\textsubscript{4}</td>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>3\textsuperscript{b}</td>
<td>[Rh(cod)Cl]\textsubscript{2}</td>
<td>dcpm</td>
<td>K\textsubscript{3}PO\textsubscript{4}</td>
<td>60</td>
<td>99</td>
</tr>
<tr>
<td>4\textsuperscript{c}</td>
<td>[Rh(cod)OMe]\textsubscript{2}</td>
<td>dcpm</td>
<td>none</td>
<td>60</td>
<td>99</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Branched-to-linear ratios were >20:1 in all cases as determined by NMR analysis of the crude reaction mixtures. \textsuperscript{b} 5 mol % Rh dimer, 20 mol % ligand, 10 mol % K\textsubscript{3}PO\textsubscript{4}, 1,2-DCE solvent, 0.4 M in vinyl phenol. \textsuperscript{c} 2.5 mol % Rh dimer, 5 mol % ligand, 10 mol % K\textsubscript{3}PO\textsubscript{4}, 1,2-DCE solvent, 0.4 M in vinyl phenol. \textsuperscript{*} 2 mol % Rh dimer, 4 mol % ligand, THF solvent, 1 M in vinyl phenol. \textsuperscript{*} Reaction and analysis performed by Achim Bruch.

Aldehydes with diverse structures are excellent coupling partners for 2-vinylphenols (Table 2.2). Primary and secondary aliphatic aldehydes are transformed to ketones with yields
above 90% (entries 1-8) and acidic α-protons (entry 4) and potentially labile β-silyloxy groups (entry 5) are tolerated. Alkenyl aldehydes are traditionally challenging substrates in hydroacylation due to issues of chemoselectivity and their tendency to form π-complexes with Rh. Nonetheless, this method enables the first Rh-catalyzed hydroacylations with alkenyl aldehydes in the absence of a β-coordinating group on the aldehyde (entries 9-11). Alkenyl aldehydes react at a slightly elevated temperature and catalyst loading (100 °C, 4 mol % [Rh(cod)OMe]$_2$ and 8 mol % dcpm). Electron-rich benzaldehydes (entries 12 and 13) react to maintain the >20:1 b:l ratio that is observed for most other substrates, while electron-neutral and electron-deficient variants gave slightly lower regioselectivities (entries 14 and 15). Vanillin was effectively transformed in 82% yield to its corresponding α-arylketone product (entry 16). This protocol encompasses one of the broadest ranges of the aldehydes reported to date, highlighting the unique reactivity of neutral [Rh(X)(dcpm)] fragments towards activating aldehydic C–H bonds.

Vinylphenols with highly varied pK$_a$’s (Table 2.3) were coupled with hydrocinnamaldehyde in 50-93% yields and >20:1 b:l regioselectivity (entries 1-4). Sterically demanding vinylphenols are suitable substrates (entries 5-7) but the 6-Me substrate gives only 11% yield due to competitive aldol condensation. An increased yield of 50% was obtained upon diluting the reaction five-fold, suggesting a concentration-dependent chemoselectivity for hydroacylation and aldol condensation. Disubstituted vinyl phenols (2-propenylphenol) and further homologated substrates (2-allylphenol) do not react well with hydrocinnamaldehyde. Secondary aldehydes generally provided higher yields than primary aldehydes, presumably because they undergo aldol condensation more sluggishly under the reaction conditions (entries 8-11, 74-95% yields). These bulkier substrates exhibited slightly diminished regioselectivity with electron rich vinylphenols. The third substrate class, alkenyl aldehydes, gave almost identical results to hydrocinnamaldehyde (entries 12-15). Transformations with benzaldehyde displayed varied regioselectivity (from 9:1 to >20:1, entries 16-20). Sterically hindered olefins, including a bulky 4,6-(t-Bu)$_2$ substituted vinylphenol, are excellent coupling partners for benzaldehyde (entries 18-20).
Table 2.2 Aldehyde scope.

<table>
<thead>
<tr>
<th>Entry</th>
<th>#</th>
<th>Aldehyde</th>
<th>Yield (%)</th>
<th>b:l</th>
<th>#</th>
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<td>1*</td>
<td>1a</td>
<td>R = Bn</td>
<td>96</td>
<td>&gt;20:1</td>
<td>3b</td>
</tr>
<tr>
<td>2*</td>
<td>1b</td>
<td>Bu</td>
<td>99</td>
<td>&gt;20:1</td>
<td>3c</td>
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<td>3</td>
<td>1c</td>
<td>'Pr</td>
<td>91</td>
<td>&gt;20:1</td>
<td>3d</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>Ph</td>
<td>98</td>
<td>&gt;20:1</td>
<td>3e</td>
</tr>
<tr>
<td>5*</td>
<td>1e</td>
<td>CH₂-OTBS</td>
<td>68</td>
<td>&gt;20:1</td>
<td>3f</td>
</tr>
<tr>
<td>6a</td>
<td>1f</td>
<td></td>
<td>99</td>
<td>&gt;20:1</td>
<td>3g</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td></td>
<td>94</td>
<td>&gt;20:1</td>
<td>3h</td>
</tr>
<tr>
<td>8</td>
<td>1h</td>
<td></td>
<td>91</td>
<td>&gt;20:1</td>
<td>3i</td>
</tr>
<tr>
<td>9*</td>
<td>1i</td>
<td>R¹ = Ph; R², R³ = H</td>
<td>95</td>
<td>&gt;20:1</td>
<td>3j</td>
</tr>
<tr>
<td>10*</td>
<td>1j</td>
<td>R¹, R² = Me, R³ = H</td>
<td>62</td>
<td>10:1</td>
<td>3k</td>
</tr>
<tr>
<td>11*</td>
<td>1k</td>
<td>R¹, R² = H, R³ = Me</td>
<td>31</td>
<td>&gt;20:1</td>
<td>3l</td>
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<tr>
<td>12</td>
<td>1l</td>
<td>R = NMe₂</td>
<td>77</td>
<td>&gt;20:1</td>
<td>3m</td>
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<td>13</td>
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<td>16:1</td>
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<td>15</td>
<td>1o</td>
<td>R = CO₂Me</td>
<td>94</td>
<td>12:1</td>
<td>3p</td>
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<tr>
<td>16</td>
<td>1p</td>
<td></td>
<td>82</td>
<td>19:1</td>
<td>3q</td>
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Branched-to-linear ratios were determined by NMR analysis of the crude reaction mixtures. Conditions for alkyl aldehydes: 2 mol % [Rh(cod)OMe]₂ and 4 mol % dcpm, THF, 60 °C. Conditions for alkenyl and aryl aldehydes: 4 mol % [Rh(cod)OMe]₂ and 8 mol % dcpm, 1,4-dioxane, 100 °C. All reactions were carried out at 1 M with respect to vinylphenol. * 1:1 d.r. * Reaction and analysis performed by Achim Bruch.
Table 2.3 Olefin scope.

<table>
<thead>
<tr>
<th>Entry</th>
<th>#</th>
<th>R²</th>
<th>Product</th>
<th>Yield [%]</th>
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</thead>
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<td>2c</td>
<td>6-OMe</td>
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<td>&gt;20:1</td>
<td>3r</td>
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<tr>
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<td>2d</td>
<td>5-OMe</td>
<td><img src="product2.png" alt="Product" /></td>
<td>50</td>
<td>&gt;20:1</td>
<td>3s</td>
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<tr>
<td>3</td>
<td>2e</td>
<td>4-OMe</td>
<td><img src="product3.png" alt="Product" /></td>
<td>55</td>
<td>&gt;20:1</td>
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<tr>
<td>4</td>
<td>2f</td>
<td>4-F</td>
<td><img src="product4.png" alt="Product" /></td>
<td>93</td>
<td>&gt;20:1</td>
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<tr>
<td>5*</td>
<td>2g</td>
<td>6-Me</td>
<td><img src="product5.png" alt="Product" /> (R¹ = BnCH₂)</td>
<td>11 (50°)</td>
<td>&gt;20:1</td>
<td>3v</td>
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<tr>
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<td>2h</td>
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<td><img src="product6.png" alt="Product" /></td>
<td>93</td>
<td>&gt;20:1</td>
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<td>&gt;20:1</td>
<td>3x</td>
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<td>6-OMe</td>
<td><img src="product8.png" alt="Product" /></td>
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<td>11:1</td>
<td>3y</td>
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<tr>
<td>9</td>
<td>2e</td>
<td>4-OMe</td>
<td><img src="product9.png" alt="Product" /></td>
<td>74</td>
<td>10:1</td>
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<tr>
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<td>6-Me</td>
<td><img src="product10.png" alt="Product" /> (R¹ = Cy)</td>
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<td>&gt;20:1</td>
<td>3aa</td>
</tr>
<tr>
<td>11</td>
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<td>3-Me</td>
<td><img src="product11.png" alt="Product" /> (R¹ = Cy)</td>
<td>95</td>
<td>&gt;20:1</td>
<td>3ab</td>
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<td>12</td>
<td>2c</td>
<td>6-OMe</td>
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<td>6-Me</td>
<td><img src="product14.png" alt="Product" /></td>
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<td>&gt;20:1</td>
<td>3ae</td>
</tr>
<tr>
<td>15</td>
<td>2h</td>
<td>3-Me</td>
<td><img src="product15.png" alt="Product" /> (R¹ = PhCHCH₂)</td>
<td>96</td>
<td>&gt;20:1</td>
<td>3af</td>
</tr>
<tr>
<td>16</td>
<td>2c</td>
<td>6-OMe</td>
<td><img src="product16.png" alt="Product" /></td>
<td>88</td>
<td>19:1</td>
<td>3ag</td>
</tr>
<tr>
<td>17</td>
<td>2e</td>
<td>4-OMe</td>
<td><img src="product17.png" alt="Product" /></td>
<td>53</td>
<td>9:1</td>
<td>3ah</td>
</tr>
<tr>
<td>18*</td>
<td>2g</td>
<td>6-Me</td>
<td><img src="product18.png" alt="Product" /></td>
<td>81</td>
<td>&gt;20:1</td>
<td>3ai</td>
</tr>
<tr>
<td>19</td>
<td>2h</td>
<td>3-Me</td>
<td><img src="product19.png" alt="Product" /> (R¹ = Ph)</td>
<td>77</td>
<td>&gt;20:1</td>
<td>3aj</td>
</tr>
<tr>
<td>20</td>
<td>2i</td>
<td>4,6-(t-Bu)₂</td>
<td><img src="product20.png" alt="Product" /></td>
<td>84</td>
<td>&gt;20:1</td>
<td>3ak</td>
</tr>
</tbody>
</table>

Branched-to-linear ratios were determined by NMR analysis of the crude reaction mixtures. Conditions for alkyl aldehydes: 2 mol % [Rh(cod)OMe]₂ and 4 mol % dcpm, THF, 60 °C. Conditions for alkenyl and aryl aldehydes: 4 mol % [Rh(cod)OMe]₂ and 8 mol % dcpm, 1,4-dioxane, 100 °C. All reactions were carried out at 1 M with respect to vinylphenol unless otherwise noted. * Reaction and analysis performed by Achim Bruch.

This method provides an alternative approach to ortho-substituted α-aryl ketones, which are typically difficult to access by ketone α-arylation. The products of this hydroacylation were further elaborated in a straightforward manner. For example, the phenol component was triflated and used in Suzuki-Miyaura cross coupling (Scheme 2.10, top). Alternatively,
treating the resulting ketones with trifluoroacetic acid (TFA) induced cyclocondensation to the corresponding benzofurans (Scheme 2.10, bottom).[21]

![Scheme 2.10 Derivatization of hydroacylation products.](image)

Considering the success of this benzofuran synthesis, we targeted the eupomatenoid class of neolignans, (Table 2.4) which exhibit insecticidal, antimicrobial, antioxidant and antitumor activity.[22] Most recent syntheses of these compounds establish the benzofuran core first and rely on either Stille or Kumada coupling to append propenyl or allyl units.[23] Here, a fully functionalized vinylphenol was derived from eugenol and then hydroacylation and cyclocondensation were used to forge the benzofuran core. This approach enabled three-step syntheses of eupomatenoids 17 and 18, and four-step syntheses of eupomatenoids 12 and 16. The olefin proximal to the phenol reacted chemoselectively in the presence of distal allyl and propenyl units (depicted as R²).
Table 2.4 Eupomatenoid natural product synthesis.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Name</th>
<th>R¹</th>
<th>R²</th>
<th>T [°C]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>4e eupomatenoid 12</td>
<td>OMe</td>
<td>1-propenyl</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>4f eupomatenoid 16</td>
<td>H</td>
<td>1-propenyl</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>4g eupomatenoid 17</td>
<td>H</td>
<td>allyl</td>
<td>70</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>4h eupomatenoid 18</td>
<td>OMe</td>
<td>allyl</td>
<td>70</td>
<td>82</td>
</tr>
</tbody>
</table>

* Reaction and analysis performed by Achim Bruch.

2.4 Mechanism of 2-Vinylphenol Hydroacylation

To identify potential reaction intermediates, the $^{31}$P NMR spectrum of a catalytic hydroacylation involving hydrocinnamaldehyde (1a) and 4-nitro-2-vinylphenol (3b) was monitored (Table 2.5). At 12% conversion, four different phosphorus-containing complexes were detected in an approximately 3:3:1:1 ratio based on integration of the $^{31}$P NMR spectrum. Over the course of catalysis, complexes XVI and XVII decreased in concentration while only complexes XV and XVIII remained at the end of the reaction.
Table 2.5 $^{31}$P NMR spectrum of a catalytic reaction at 12% conversion.

<table>
<thead>
<tr>
<th>Complex</th>
<th>δ (ppm)</th>
<th>J_{Rh-P} (Hz)</th>
<th>J_{P-P} (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XV</td>
<td>−17.0</td>
<td>111</td>
<td>—</td>
</tr>
<tr>
<td>XVI</td>
<td>0.7, −26.9</td>
<td>125, 148</td>
<td>92</td>
</tr>
<tr>
<td>XVII</td>
<td>1.7, −9.9</td>
<td>126, 117</td>
<td>69</td>
</tr>
<tr>
<td>XVIII</td>
<td>−26.4</td>
<td>126</td>
<td>—</td>
</tr>
</tbody>
</table>

The major complex XV was prepared by reacting [Rh(cod)OMe]$_2$ with dcpm and 4-nitro-2-vinylphenol in a 1:2:2 molar ratio in THF (Scheme 2.11, top). A cationic [Rh(dcpm)$_2$]$^+$ fragment was identified by ESI$^+$ MS and by comparison of the NMR data with [Rh(dcpm)$_2$]BF$_4$. The synthesis of XV was accompanied by quantitative formation of 1,5-cyclooctadiene, MeOH and another Rh complex XIX containing a coordinated vinylphenolate anion as judged by $^1$H NMR analysis. The aromatic protons of the vinylphenolate were shifted upfield and the vinylic peaks appeared between 2 and 4 ppm—within the range for coordinated olefins. The $^{13}$C NMR spectrum showed coupling between the vinylic carbon atoms and the Rh center ($J_{Rh-C} = 11$ Hz and 15 Hz). Based on these data and ESI MS, we propose that this complex is an anionic 2:1 vinylphenolate-to-Rh complex. To test our proposal, the [(18-crown-6)K][Rh(nitrovinylphenolate)$_2$] salt (XX) was synthesized by treating two equivalents of 4-nitro-2-vinylphenol with [Rh(cod)OMe]$_2$, $t$-BuOK and 18-crown-6 (Scheme 2.11, middle). The solid
state structure of this salt (Scheme 2.11, bottom) contains two vinylphenolate anions bound to a Rh atom in a cis orientation, where the phenolate oxygen atoms bind to the potassium centre. Only small differences in chemical shift were noted between XX and XIX, which are probably due to potassium-coordination in XX. In addition, small shoulder-peaks were noted in the $^1$H NMR spectrum of XIX, which may indicate the presence of geometrical isomers.

**Scheme 2.11** Synthesis of $[\text{Rh(vinylphenolate)}_2]^+$ complexes. X-ray structure obtained by Dr. Joe Ziller of the UCI X-ray Crystallography Facility.

Given that the salt of XV and XIX account for nearly 60% of the Rh during catalysis, we expected that the reactivity of these species would correlate with the activity of the overall catalyst system. We examined the reactivity of each ion independently by studying the complexes $[\text{Rh(dcpm)}_2] \text{BF}_4$ and XX ([(18-crown-6)K][Rh(nitrovinylphenolate)$_2$]) (Table 2.6). While $[\text{Rh(diphosphine)}_2]^+$ complexes catalyse the cyclization of 4-pentenals at elevated temperatures,$^{24}$ $[\text{Rh(dcpm)}_2] \text{BF}_4$ did not catalyse vinylphenol hydroacylation even in the presence of base ($t$-BuOK, entries 2 and 3). Salt XX also did not catalyse hydroacylation (entry 4). However, it could be activated by dcpm to give an initial turnover frequency (TOF$_\text{init}$) that is four times lower than in the optimized reaction (entries 1 and 5, $15 \text{ h}^{-1}$ versus $4 \text{ h}^{-1}$ based on total
rhodium concentration, respectively). Although this rate is low, the observation of catalysis supports the intermediacy of phosphine ligated species and suggests that XV and XIX are not directly on the catalytic cycle. The combination of [Rh(dcpm)₂]BF₄, XX, and 1,5-cyclooctadiene resulted in slow catalysis (entries 6 and 7, approx. 50% conv. after 24 hours). The 1,5-cyclooctadiene probably converts the double salt back to a catalytically active species, although this effect is likely smaller than the inhibitory effect of 1,5-cyclooctadiene that occurs due to binding of the active catalyst.

Table 2.6 Hydroacylation with various Rh complexes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Additive</th>
<th>Yield (%)</th>
<th>Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Rh(cod)OMe]₂</td>
<td>dcpm</td>
<td>&gt;95</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>([Rh(dcpm)₂]BF₄</td>
<td>–</td>
<td>n.r.</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>[Rh(dcpm)₂]BF₄</td>
<td>t-BuOK</td>
<td>n.r.</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>XX</td>
<td>–</td>
<td>80</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>XX</td>
<td>dcpm</td>
<td>80</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>[Rh(dcpm)₂]BF₄/XX</td>
<td>–</td>
<td>n.r.</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>[Rh(dcpm)₂]BF₄/XX</td>
<td>cod</td>
<td>50</td>
<td>24</td>
</tr>
</tbody>
</table>

*a*only 4 mol% catalyst; *b*n.r. = no reaction

Complex XVIII is the next most abundant Rh complex during catalysis, and was identified as a cationic [Rh(dcpm)(cod)]⁺ fragment by comparison of its ³¹P NMR spectrum to that of [Rh(dcpm)(cod)]BF₄. The latter complex is a kinetically competent catalyst precursor in the presence of t-BuOK and provides a similar initial turnover frequency to the optimized reaction (18 h⁻¹ versus 15 h⁻¹, respectively).²⁵ When a suspension of 4-nitro-2-vinylphenol and t-BuOK was vigorously stirred with complex [Rh(dcpm)(cod)]BF₄ a nearly quantitative exchange reaction occurred to generate substrate-bound XVI (Scheme 2.12). In the presence of excess aldehyde, the olefin ligand of complex XVI exchanges with the aldehyde to generate
intermediate XVII. XVII is observed during catalysis but we could only characterize this complex by $^{31}$P NMR spectroscopy due to its low concentration at steady state. Complex XVII is only observed transiently and undergoes hydroacylation and a substitution reaction at room temperature to form cation XVIII and anion 3b', which aggregate with excess phenols as judged by ESI-MS.

![Scheme 2.12](image-url)  
**Scheme 2.12** Formation of olefin bound complex and its behavior in the presence of aldehyde.

Our investigation of catalyst resting states suggests that XVI and XVII are directly on the catalytic cycle, while a variety of off-cycle intermediates can re-enter the cycle via pathways mediated by 1,5-cyclooctadiene or 2-vinylphenol. The strong coordination of the 2-vinylphenol compared to the aldehyde is likely a key to promoting hydroacylation over competitive decarbonylation. Of the observed Rh complexes, oxidative addition would only be possible from XVII, which already contains the $O$-coordinated 2-vinylphenolate moiety. Formation of the acyl-Rh$^{II}$-hydride would likely be followed by rapid coordination of the olefin to generate a coordinatively saturated intermediate that is resistant to decarbonylation.$^{26}$

To identify kinetic parameters, hydroacylation of 4-nitro-2-vinylphenol with various amounts of hydrocinnamaldehyde was studied (Figure 2.1). The coupling reaction with 1.5 equiv of hydrocinnamaldehyde followed a curved reaction profile with an initial turnover frequency of 15 h$^{-1}$ and no induction period. Decreasing the aldehyde concentration by half decreased the
initial turnover frequency by half (8 h\(^{-1}\)), a result that suggests a first order dependence of the rate on aldehyde concentration. Using a large excess of aldehyde (8 equiv) yielded a reaction profile that was linear up to 80% conversion with an initial turnover frequency of only 23 h\(^{-1}\). Analysing the \(^{31}\)P spectrum under these highly concentrated conditions reveals that the equilibrium between XVI and XVII was completely shifted toward XVII. The formation of XVII, which contains both a coordinated aldehyde and phenolate, leads to saturation kinetics with respect to both substrates. Under typical catalytic conditions, however, this kinetic data and the assignment of catalyst resting states supports a first order dependence of the rate on aldehyde concentration and a zeroth order dependence on 2-vinylphenol concentration.

Figure 2.1 Kinetic data for hydroacylation with various amounts of hydrocinnamaldehyde.

These kinetic studies corroborate the concentration-dependent selectivity for hydroacylation over competitive aldol dehydration (Scheme 2.13). The substrate 6-methyl-2-vinylphenol (2g) undergoes slow hydroacylation due to its steric bulk, which allows the aldehyde to be consumed by dimerization. However, greater chemoselectivity for hydroacylation over aldol dehydration was observed upon five-fold dilution. Diluting the reaction slows down aldol
dehydration (second order in aldehyde)\textsuperscript{27} more dramatically than vinylphenol hydroacylation (first order in aldehyde, zeroth order in vinylphenol).

\begin{center}
\includegraphics[width=0.6\textwidth]{reaction_scheme}
\end{center}

\textbf{Scheme 2.13} Concentration-dependent chemoselectivity for hydroacylation over aldol dehydration. Reaction and analysis performed by Achim Bruch.

The turnover-limiting step of the reaction was probed by tracking the deuterium label for hydroacylation with deuterated 2-naphthaldehyde (Table 2.7, entry 1). This substrate coupled with 4-nitro-2-vinylphenol in 78\% yield and 12:1 b:l selectivity. \textsuperscript{1}H and \textsuperscript{2}D NMR analysis revealed that deuterium was incorporated into only the β-positions of the resulting ketones. Analysis of the products by mass spectrometry revealed that they were exclusively monodeuterated. Analogous results were obtained for the reaction of deuterated hydrocinnamaldehyde with 4-nitro-2-vinylphenol (Table 2.7, entry 2). Because we observed a lack of deuterium scrambling and multiply-deuterated products and we found that the on-cycle catalyst resting states are those that precede C–H bond activation, we can rule out reductive elimination as the turnover-limiting step. This conclusion suggests that at least one of the earlier steps in the catalytic cycle is irreversible.

This observation contrasts almost all other olefin hydroacylation studies where extensive deuterium-scrambling is observed as a result of rate-limiting reductive elimination.\textsuperscript{28,29} When larger bite-angle diphosphines were used in the test for deuterium scrambling (Table 2.7, entries 3-5), the reaction rates were significantly reduced and deuterium scrambling still did not occur. These results suggest that reductive elimination is not rate-determining for this substrate combination, regardless of ligand bite-angle. Accordingly, the fact that smaller bite-angle diphosphines provide faster rates can be attributed to their ability to promote earlier steps in the catalytic cycle.
Table 2.7 Deuterium labelling studies (olefin = 4-nitro-2-vinylphenol)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>R</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>b:l</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>dcpm</td>
<td>2-nap</td>
<td>24</td>
<td>78</td>
<td>12:1</td>
</tr>
<tr>
<td>2</td>
<td>dcpm</td>
<td>CH₂Bn</td>
<td>2</td>
<td>90</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>3</td>
<td>dcpe</td>
<td>CH₂Bn</td>
<td>12</td>
<td>45</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>4</td>
<td>dcpp</td>
<td>CH₂Bn</td>
<td>12</td>
<td>41</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>5</td>
<td>dcpb</td>
<td>CH₂Bn</td>
<td>12</td>
<td>35</td>
<td>&gt;20:1</td>
</tr>
</tbody>
</table>

Branched-to-linear ratios were determined by NMR analysis of the crude reaction mixtures. Entry 1: 1,4-dioxane, 100 °C. Entries 2-5: THF, 60 °C. Deuterium content measured by 

1H and 2D NMR, and ESI MS. * Reaction and analysis performed by Achim Bruch.

To further probe the turnover limiting step, we performed intermolecular competition experiments with aldehyde isotopologues. With 4-nitro-2-vinylphenol as the coupling partner, a kinetic isotope effect of 2.5 ± 0.2 was observed for the reaction with hydrocinnamaldehyde and 2.4 ± 0.2 for the reaction with 2-naphthaldehyde. The similar magnitudes of the KIE data indicate that these reactions proceed by similar mechanisms. Madsen reported a predicted KIE of 2.85 for oxidative addition of aldehydes to Rh(dppp)⁺. Our group has also previously reported a KIE of 1.7 for an intramolecular ketone hydroacylation protocol in which oxidative addition was reversible and migratory insertion was rate limiting. Weller and Willis have also observed a small KIE of ~1.4 for alkene hydroacylation with small bite angle diphosphines in which oxidative addition of a β-sulfur aldehyde was reversible and reductive elimination was implicated as rate limiting. The large primary KIE’s observed in the present case suggests that irreversible oxidative addition is likely the turnover limiting step.

We studied substituent effects by reacting different para-substituted benzaldehydes with 4-nitro-2-vinylphenol (Figure 2.2). Aldehydes with electron withdrawing substituents reacted faster than those with electron donating groups. The ρ value of 0.79 suggests a partial build-up of negative charge at the carbonyl carbon either prior to or during the turnover limiting step.
Brookhart previously found that oxidative addition of Rh to aldehydic C–H bonds occurs with an early transition state and that electron-deficient aldehydes reacting only slightly faster than electron-rich substrates. Contrastingly, Goldman found that the exothermicity of aldehyde C–H bond activation varied by several kcal/mol depending on the para-substituent of benzaldehydes. The moderate and positive $\rho$ value observed in this study suggests that oxidative addition is not a rapid pre-equilibrium but rather the turnover limiting step with an early transition state.

![Figure 2.2 Hammett study for para-substituted benzaldehydes.](image)

Having established the catalyst resting states and the turnover limiting step, we conclude that the rate of 2-vinylphenol hydroacylation is dictated predominantly by the rate of oxidative addition. Thus, the ligand dcpm likely accelerates this key step relative to its wide bite-angle counterparts. To better understand the steric component of this effect, we examined the reactivity of the ligand $(t\text{Bu})_2\text{PCH}_2\text{P}(t\text{Bu})(\text{Me})$, which has a larger steric profile than dcpm but similar electronic properties and bite-angle. This ligand did not provide an active catalyst. We thus propose that the small size of dcpm reduces steric interactions in the transition state for oxidative addition. An electronic effect is also apparent based on the comparison of dcpm with dppm: faster rates were observed with the more basic diphosphine dcpm despite its increased steric bulk. Our results contrast findings on the addition of H$_2$ to Rh(diphosphine)$_2^+$ complexes, and the hydroacylation of alkenes with $\beta$-sulfur substituted aldehydes. In the first case, wider bite angles favoured oxidative addition as a result of an electronic bite-angle effect, and in the latter case, small-bite angle diphosphines promoted a rate-limiting reductive elimination.
On the basis of experimental evidence and literature precedents, we propose the mechanism shown in Figure 2.3. The catalyst precursor $[\text{Rh(cod)OMe}]_2$ reacts with dcpm and vinylphenol 2 to form either the catalytically inactive double salt of XV and XIX or the major catalyst resting state XVI. Exchange of the olefin ligand for aldehyde 1 leads to intermediate XVII. Both complexes XVI and XVII are catalyst resting states and they decrease in concentration as the reaction progresses. Supported by kinetic isotope effects and a study of substituent effects, we propose that oxidative addition is turnover limiting. The resulting acyl-Rh$^{\text{III}}$-hydride XXI does not reductively decarbonylate to any measurable extent but instead undergoes migratory insertion to yield intermediate XXII. Reductive elimination and displacement of the product 3 with substrate 2 completes the catalytic cycle. Alternatively, 1,5-cyclooctadiene can displace either the vinylphenol (2) or product (3) to form the off-cycle intermediate XVIII, which increases in concentration during catalysis. The counterion of XVIII is a dissociated phenolate anion that can hydrogen bond with excess substrate or product.

Figure 2.3 Proposed mechanism for vinylphenol hydroacylation. (4-nitro group omitted from the vinylphenol, R = CH$_2$Bn).
2.5 Conclusions

We have developed a catalyst system for branched selective hydroacylation of olefins bearing anionic directing groups with a wide range of aryl, alkenyl, and alkyl aldehydes. High branched-selectivity and reactivity were generally observed. In combination with a cyclocondensation, we applied this method to access four neolignan natural products. We disclosed a mechanistic study on the branched-selective hydroacylation of 2-vinylphenols. Analysis of the catalyst resting states revealed that most of the catalyst is sequestered as an inactive double salt of Rh while the active catalyst consists of a Rh(dcpm)(vinylphenolate) fragment. Oxidative addition of Rh to the aldehyde C–H bond occurs even at room temperature followed by rapid hydroacylation. Strong binding of the vinylphenolate is likely a key to promoting hydroacylation over competitive aldehyde decarbonylation and aldol dehydration. KIE measurements and a Hammett plot support oxidative addition as the turnover limiting step. The high reactivity of [Rh(X)(dcpm)] fragments likely arises from the electron rich character of the complex and small-bite angle of the diphosphine, which both promote oxidative addition. In contrast, previous studies that use chelating aldehydes involve a fast and reversible C–H bond activation. This difference in mechanism highlights the challenge of C–H bond activation of aldehydes that lack a β-coordinating group. Given the mild reaction conditions, neutral [Rh(X)(dcpm)] fragments are highly reactive towards aldehyde C–H bond activation and hold promise for future hydroacylations with non-chelating aldehydes. Based on this work, we expect that other functional groups (e.g. amines, alcohols, carboxylic acids) can be used to generate anionic directing groups in situ and further expand the applications of hydroacylation.
2.6 Experimental

2.6.1 Substrate Preparation

**Method 2.1 Preparation of Vinyl Phenols from Salicylaldehydes**

![Chemical Reaction](image)

To a stirring suspension of PPh₃MeBr (2.1 equiv) in THF at 0°C was added n-BuLi (2.0 equiv) dropwise. The reaction became homogenous after approximately 15 min. Then, a solution of the salicylaldehyde (1 equiv) in THF was added to the reaction flask and the ice bath was removed. Once full conversion was achieved as judged by TLC, the reaction was quenched with saturated aqueous ammonium chloride solution and concentrated by rotary evaporation. Ethyl acetate was added and the organic layer was separated, dried with MgSO₄ and concentrated. The resulting residue was purified by column chromatography.

(Table 2.1, 2a)

**4-chloro-2-vinylphenol**

The title compound was synthesized according to Method 2.1 from 5-chlorosalicylaldehyde (1.000 g, 6.39 mmol) as a white solid (0.740 g, 75%). ¹H NMR data were consistent with those previously reported.³⁷ ¹H NMR (400 MHz, CDCl₃) δ 7.40 (s, 1H), 7.14 (d, J = 8.5 Hz, 1H), 6.91 (dd, J = 17.8, 11.2 Hz, 1H), 6.78 (d, J = 8.5 Hz, 1H), 5.79 (d, J = 17.8 Hz, 1H), 5.45 (d, J = 11.2 Hz, 1H), 5.08 (s, 1H).

(Table 2.2, 2b)

**4-nitro-2-vinylphenol**

The title compound was synthesized according to Method 2.1 from 5-nitrosalicylaldehyde (1.67 g, 10.0 mmol) as a yellow solid (0.815 g, 49%). ¹H NMR data were consistent with those previously reported.³⁸ ¹H NMR (400 MHz, CDCl₃) δ 8.32 (d, J = 2.7 Hz, 1H), 8.06 (dd, J = 8.9, 2.7 Hz, 1H), 6.92 (dd, J = 17.7, 11.2 Hz, 1H), 6.90 (d, J = 8.6 Hz, 1H), 6.17 (s, 1H, OH), 5.89 (d, J = 17.7 Hz, 1H), 5.53 (d, J = 11.2 Hz, 1H).
(Table 2.3, 2c)

6-methoxy-2-vinylphenol

The title compound was synthesized according to Method 2.1 from 3-methoxysalicylaldehyde (0.761 g, 5 mmol) as a colorless oil (0.356 g, 47%). $^1$H NMR data were consistent with those previously reported.$^{39}$ $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.07 (dd, $J = 7.7, 1.1$ Hz, 1H), 7.05 – 6.97 (m, 1H), 6.79 (dt, $J = 8.0, 7.3$ Hz, 2H), 5.88 (s, 1H), 5.80 (dd, $J = 17.8, 1.2$ Hz, 1H), 5.30 (dd, $J = 11.2, 1.2$ Hz, 1H), 3.89 (s, 3H).

(Table 2.3, 2d)

5-methoxy-2-vinylphenol

The title compound was synthesized according to Method 2.1 from 4-methoxysalicylaldehyde (1.141 g, 7.5 mmol) as a colorless oil (0.622 g, 55%). $^1$H NMR data were consistent with those previously reported.$^{40}$ $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.28 (d, $J = 8.6$ Hz, 1H), 6.84 (dd, $J = 17.7, 11.2$ Hz, 1H), 6.49 (dd, $J = 8.6, 2.4$ Hz, 1H), 6.36 (d, $J = 2.4$ Hz, 1H), 5.61 (dd, $J = 17.7, 1.2$ Hz, 1H), 5.25 (dd, $J = 11.2, 1.2$ Hz, 1H), 5.17 (s, 1H), 3.77 (s, 3H).

(Table 2.3, 2e)

4-methoxy-2-vinylphenol

The title compound was synthesized according to Method 2.1 from 4-methoxysalicylaldehyde (0.761 g, 5 mmol) as a colorless oil (0.420 g, 56%). $^1$H NMR data were consistent with those previously reported.$^{41}$ $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.98 – 6.86 (m, 2H), 6.75 – 6.69 (m, 2H), 5.73 (dd, $J = 17.7, 1.1$ Hz, 1H), 5.36 (dd, $J = 11.2, 1.1$ Hz, 1H), 4.64 (s, 1H), 3.78 (s, 3H).

Table 2.3, 2f

4-fluoro-2-vinylphenol
The title compound was synthesized according to Method 2.1 from 5-fluorosalicylaldehyde (1.051 g, 7.5 mmol) as a white solid (0.6680 g, 65%). \(^1\)H NMR data were consistent with those previously reported.\(^{12}\) \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.09 (dd, \(J = 9.4, 3.0\) Hz, 1H), 6.94 – 6.80 (m, 2H), 6.73 (dd, \(J = 8.8, 4.6\) Hz, 1H), 5.73 (d, \(J = 17.7\) Hz, 1H), 5.40 (d, \(J = 11.2\) Hz, 1H), 4.80 (s, 1H).

(Table 2.3, 2g)
6-methyl-2-vinylphenol

The title compound was synthesized according to Method 2.1 from 3-methylsalicylaldehyde (0.544 g, 4.00 mmol) as a colorless oil (0.440 g, 82%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.22 (d, \(J = 7.7\) Hz, 1H), 7.04 (d, \(J = 7.5\) Hz, 1H), 6.93 (dd, \(J = 17.7, 11.2\) Hz, 1H), 6.82 (t, \(J = 7.5\) Hz, 1H), 5.71 (d, \(J = 18.3\) Hz, 1H), 5.37 (d, \(J = 11.8\) Hz, 1H), 4.96 (s, 1H, OH), 2.26 (s, 3H). \(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 151.3, 132.0, 130.4, 125.3, 124.5, 123.8, 120.5, 116.3, 16.0. LRMS (EI) Calculated for [C\(_9\)H\(_{10}\)O]\(^+\) 134.1, found 134.0.

(Table 2.3, 2h)
3-methyl-2-vinylphenol

The title compound was synthesized according to Method 2.1 from 6-methylsalicylaldehyde (0.638 g, 4.69 mmol) as a colorless oil (0.281 g, 45%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.06 (t, \(J = 7.8\) Hz, 1H), 6.78 (d, \(J = 7.5\) Hz, 1H), 6.75 (d, \(J = 7.5\) Hz, 1H), 6.69 (dd, \(J = 18.2, 11.5\) Hz, 1H), 5.69 (dd, \(J = 11.5, 1.6\) Hz, 1H), 5.58 (dd, \(J = 18.2, 1.6\) Hz, 1H), 5.54 (d, \(J = 1.6\) Hz, 1H). \(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 152.7, 137.2, 132.3, 128.3, 123.9, 121.9, 120.5, 113.0, 20.1. LRMS (EI) Calcd for [C\(_9\)H\(_{10}\)O]\(^+\) 134.1, found 134.1.

(Table 2.3, 2i)
4,6-di-tert-butyl-2-vinylphenol

The title compound was synthesized according to Method 2.1 from 3,5-di-tert-butylsalicylaldehyde (0.702 g, 3.00 mmol) as a colorless oil (0.280 g, 40%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.25 (s, 1H), 7.14 (s, 1H), 6.85 (dd, \(J = 17.7, 11.2\) Hz, 1H), 5.73 (d, \(J = 17.7\) Hz, 1H), 5.40 (d, \(J = 11.2\) Hz, 1H), 4.80 (s, 1H).
Hz, 1H), 5.66 (d, J = 17.7 Hz, 1H), 5.46 (d, J = 11.2 Hz, 1H), 5.22 (s, 1H), 1.42 (s, 9H), 1.30 (s, 9H). $^{13}$C NMR (126 MHz, CDCl3) δ 149.4, 142.4, 135.7, 133.1, 124.8, 124.0, 122.6, 117.9, 35.0, 34.4, 31.7, 30.0. LRMS (EI) Calcd for [C$_{16}$H$_{24}$O]+ 232.2, found 232.1.

(Scheme 2.9)

d$_1$-2-naphthaldehyde

To a round bottom flask equipped with a stir bar was added sequentially N-(methoxy)methylammonium chloride (0.512 g, 5.25 mmol, 1 equiv), DMAP (0.064 g, 0.525 mmol, 0.1 equiv), dichloromethane (20 mL), triethylamine (1.536 mL, 11.02 mmol, 2.1 equiv), and 2-naphthoyl chloride (1.000 g, 5.25 mmol, 1 equiv). The solution was stirred for 10 minutes and then concentrated under reduced pressure. Ethyl acetate was added and the solution was washed twice with saturated NH$_4$Cl(aq) and then NaHCO$_3$(aq) solution. The organic layer was dried with MgSO$_4$ and then filtered and concentrated under reduced pressure to give the weinreb amide as a clear light yellow oil (0.920 g, 81 % yield) which was used without further purification. The Weinreb amide was added to a second round bottom flask equipped with a stir bar and septum, along with THF (25 mL). The flask was lowered into an ice bath, and then LiAlD$_4$ (0.197 g, 4.70 mmol, 1.1 equiv) was added slowly. After 10 minutes, the reaction was worked up using the Feiser method and purified by column chromatography to give the product as a white solid (0.636 g, 95%). $^1$H NMR data matched those previously reported.$^{43}$ $^1$H NMR (500 MHz, CDCl$_3$) δ 8.35 (s, 1H), 8.02 (d, J = 8.1 Hz, 1H), 8.00 – 7.87 (m, 3H), 7.66 (t, J = 7.4 Hz, 1H), 7.60 (t, J = 7.1 Hz, 1H).

(Scheme 2.9)

d$_1$-hydrocinnamaldehyde

The title compound was synthesized according to a literature procedure.$^{44}$ $^1$H NMR (400 MHz, CDCl$_3$) δ 7.39 – 7.10 (m, 5H), 2.96 (t, J = 7.6 Hz, 2H), 2.78 (t, J = 7.6 Hz, 2H).

2.6.2 Ketone Synthesis

Method 2.2 Hydroacylation of Vinyl Phenols with Aliphatic Aldehydes
To a 1 dram vial was added 2 mol % $[\text{Rh(COD)}\text{OMe}]_2$ and 4 mol % dcpm. The vinyl phenol (0.2 mmol, 1 equiv), aldehyde (1.5 equiv), and THF (200 μL) were added to the vial which was then sealed with a Teflon-lined screw cap. The reaction was heated to 60 °C for 24 hours and then cooled to room temperature. The branched to linear ratio was determined by integration of the methine proton (quartet) of the branched product versus the methylene protons of the linear product (triplets) in the crude $^1\text{H}$ NMR spectrum. The product was isolated by either column chromatography or preparatory TLC.

**Method 2.3 Hydroacylation of Vinyl Phenols with $\alpha,\beta$-Unsaturated Aldehydes or Aromatic Aldehydes**

To a 1 dram vial was added 4 mol % $[\text{Rh(COD)}\text{OMe}]_2$ and 8 mol % dcpm. The vinyl phenol (0.2 mmol, 1 equiv), aldehyde (1.5 equiv), and 1,4-dioxane (200 μL) were added to the vial which was then sealed with a Teflon-lined screw cap. The reaction was heated to 100 °C for 24 hours and then cooled to room temperature. The branched to linear ratio was determined by integration of the methine proton (quartet) of the branched product versus the methylene protons of the linear product (triplets) in the crude $^1\text{H}$ NMR spectrum. The product was isolated by either column chromatography or preparatory TLC.

The hydroxyketone products of this study can exist in equilibrium with two diastereomeric hemiketal forms in widely varying ratios and this is noted where appropriate in the characterization data. This phenomenon can give rise to very complicated NMR spectra because purified compounds can exist in three different isomeric forms. The small quantities of these
forms or the presence of overlapping peaks has precluded a full assignment in some cases. In these instances, only the key diagnostic peaks are listed.

(Table 2.1, 3a)

**4-(5-chloro-2-hydroxyphenyl)-1-phenylpentan-3-one**

The title compound was synthesized according to Method 2.2 from hydrocinnamaldehyde (40 μL, 0.30 mmol) and 4-chloro-2-vinylphenol (30.9 mg, 0.2 mmol) as a colorless oil (57.2 mg, 99%). **1H** NMR (400 MHz, CDCl3) δ 7.37 – 7.07 (m, 6H), 7.03 (d, J = 2.4 Hz, 1H), 6.78 (d, J = 8.6 Hz, 1H), 3.93 (q, J = 7.1 Hz, 1H), 2.88 (s, 4H), 1.43 (d, J = 7.2 Hz, 3H). **13C** NMR (126 MHz, CDCl3) δ 213.6, 153.1, 140.7, 129.0, 128.6, 128.5, 128.4, 127.7, 126.3, 125.6, 118.3, 48.6, 43.0, 29.8, 15.5. **LRMS** (ESI) Calcd for [C17H18ClO2]+ 289.1, found 289.2.

(Table 2.2, 3b)

**4-(2-hydroxy-5-nitrophenyl)-1-phenylpentan-3-one**

The title compound was synthesized according to Method 2.2 from hydrocinnamaldehyde (40 μL, 0.30 mmol) and 4-nitro-2-vinylphenol (33.0 mg, 0.2 mmol) as a colorless oil (57.2 mg, 96%). **1H** NMR (400 MHz, CDCl3) δ 8.08 (d, J = 8.9 Hz, 1H), 7.97 (s, 1H), 7.30 – 7.23 (m, 2H), 7.22 – 7.09 (m, 3H), 6.92 (d, J = 8.9 Hz, 1H), 3.92 (br s, 1H), 3.10 – 2.69 (m, 4H), 1.46 (d, J = 7.3 Hz, 3H). **13C** NMR (126 MHz, CDCl3) δ 214.0, 160.7, 141.3, 140.4, 128.6, 128.3, 126.8, 126.4, 125.5, 125.1, 117.1, 48.7, 43.2, 29.7, 15.7. **HRMS** (ESI): calcd for [C17H16NO4]− 298.1067, found 298.1079.

(Table 2.2, 3c)

**2-(2-hydroxy-5-nitrophenyl)octan-3-one**

The title compound was synthesized according to Method 2.2 from hexanal (38 μL, 0.30 mmol) and 4-nitro-2-vinylphenol (33.0 mg, 0.2 mmol) at 60 °C for 30 h as a colorless oil (52.7 mg, 99%). This compound exists as a 4.2:1 mixture of open and closed chain forms. **1H** NMR (400 MHz, CDCl3) δ 9.17 (s, 1H), 8.08 (dd, J = 9.0, 2.7 Hz, 1H), 8.03 (d, J = 2.7 Hz, 1H),
6.98 (d, J = 9.0 Hz, 1H), 4.01 (q, J = 7.3 Hz, 1H), 2.74 – 2.57 (m, 2H), 1.68 – 1.49 and 1.44 – 1.19 (m, 6H), 1.54 (d, J = 7.3 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 216.0, 161.0, 141.2, 127.0, 125.6, 125.1, 117.3, 48.8, 41.9, 31.2, 23.3, 22.5, 15.9, 14.0. HRMS (ESI): calcd for \([C_{14}H_{18}NO_4]^-\) 264.1236, found 264.1232.

(Table 2.2, 3d)

2-(2-hydroxy-5-nitrophenyl)-5-methylhexan-3-one

The title compound was synthesized according to Method 2.2 from isovaleraldehyde (32 \(\mu\)L, 0.3 mmol) and 4-nitro-2-vinylphenol (33.0 mg, 0.2 mmol) as a colorless oil (45.6 mg, 91%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.14 – 8.08 (m, 2H), 7.01 (d, J = 8.8 Hz, 1H), 4.07 (q, J = 7.2 Hz, 1H), 2.56 (d, J = 6.7 Hz, 2H), 2.28 – 2.15 (m, 1H), 1.56 (d, J = 7.2 Hz, 3H), 0.95 (d, J = 6.7 Hz, 6H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 215.8, 161.1, 141.2, 126.3, 125.7, 125.2, 117.8, 50.9, 49.8, 24.2, 22.4, 15.7. LRMS (ESI) Calcd for \([C_{13}H_{17}NO_4Na]^+\) 274.1, found 274.1.

(Table 2.2, 3e)

2-(2-hydroxy-5-nitrophenyl)-4-phenylbutan-3-one

The title compound was synthesized according to Method 2.2 from phenylacetaldehyde (35 \(\mu\)L, 0.3 mmol) and 4-nitro-2-vinylphenol (33.0 mg, 0.2 mmol) as a colorless oil (56.1 mg, 98%). The compound was isolated as a 0.8:1:0.2 mixture of an open chain form and two hemiketal diastereomers. \(^1\)H NMR (500 MHz, CDCl\(_3\)) Open chain form: \(\delta\) 8.68 (s, 1H), 8.06 (dd, J = 8.9, 2.5 Hz, 1H), 7.86 (d, J = 2.5 Hz, 1H), 7.49 – 7.27 (m, 3H), 7.16 (d, J = 7.2 Hz, 2H), 6.94 (d, J = 8.9 Hz, 1H), 4.13 (q, J = 7.2 Hz, 1H), 3.95 – 3.83 (m, 2H), 1.49 (d, J = 7.2 Hz, 3H). Major hemiketal isomer: \(\delta\) 8.15 – 8.11 (m, 1H), 8.01 (s, 1H), 7.48 – 7.27 (m, 5H), 6.85 (d, J = 8.8 Hz, 1H), 3.42 (q, J = 7.2 Hz, 1H), 3.35 (d, J = 13.9 Hz, 1H), 3.21 (d, J = 13.9 Hz, 1H), 3.02 (s, 1H), 1.38 (d, J = 7.2 Hz, 3H). Minor hemiketal isomer: \(\delta\) 8.18 – 8.11 (m, 2H), 7.50 – 7.28 (m, 5H), 6.86 (d, J = 8.6 Hz, 1H), 3.52 (q, J = 7.5 Hz, 1H), 3.30 (d, J = 13.9 Hz, 1H), 3.15 (s, 1H), 3.05 (d, J = 13.9 Hz, 1H), 1.41 (d, J = 7.5 Hz, 3H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 213.1, 162.4, 161.0, 142.4, 141.3, 133.8, 133.7, 133.0, 132.6, 131.1, 130.8, 129.6, 129.0, 128.9, 127.9, 127.8, 127.7, 126.1, 126.0, 125.8, 125.2, 120.7, 120.3, 118.1, 112.8, 110.0, 109.7, 77.3, 77.1, 76.8, 49.4,
The title compound was synthesized according to modified Method 2.2 from 3-((tert-butyldimethylsilyl)oxy)propanal (28 mg, 0.15 mmol) and 4-nitro-2-vinylphenol (16.5 mg, 0.1 mmol) with [Rh(COD)OMe]₂ (1.9 mg, 0.04 equiv) and dcpm (3.3 mg, 0.08 equiv) at 60 °C for 48 h as a colorless solid (24 mg, 68%). This compound was isolated as a 0.2:1:0.5 mixture of an open chain form and two hemiketal diastereomers. 

**1H NMR (500 MHz, CDCl₃)**

**Open chain form:** δ 8.78 (br s, 1H), 8.07 (dd, J = 8.8, 2.8 Hz, 1H), 8.04 (s, 1H), 6.96 (d, J = 8.8 Hz, 1H), 4.09 (q, J = 7.2 Hz, 1H), 4.00 – 3.85 (m, 2H), 2.86 – 2.71 (m, 2H), 1.52 (d, J = 7.3 Hz, 3H), 0.84 (s, 9H), 0.04 (s, 6H). 

**Hemiketal major isomer:** δ 8.12 (d, J = 8.8 Hz, 1H), 8.01 (s, 1H), 6.83 (d, J = 8.8 Hz, 1H), 6.45 (s, 1H), 4.46 – 4.33 (m, 1H), 4.02 – 3.89 (m, 1H), 3.21 (q, J = 7.2 Hz, 1H), 2.29 (ddd, J = 14.2, 11.5, 4.5 Hz, 1H), 1.97 (d, J = 14.4 Hz, 1H), 1.40 (d, J = 7.3 Hz, 3H), 0.94 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H). 

**Hemiketal minor isomer:** δ 8.12 (d, J = 8.8 Hz, 1H), 8.04 (s, 1H), 6.83 (d, J = 8.8 Hz, 1H), 6.75 (s, 1H), 4.46 – 4.33 (m, 1H), 4.02 – 3.89 (m, 1H), 3.37 (q, J = 7.2 Hz, 1H), 2.14 (ddd, J = 14.3, 12.1, 4.6 Hz, 1H), 1.85 (d, J = 14.4 Hz, 1H), 1.28 (d, J = 7.4 Hz, 3H), 0.94 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H). 

**13C NMR (126 MHz, CDCl₃)**

**Open chain form:** δ 213.9, 161.0, 141.4, 126.3, 125.2, 118.1, 58.8, 49.8, 44.8, 25.9, 18.4, 15.6, -5.4. 

**Major hemiketal isomer:** δ 162.7, 142.1, 133.5, 125.8, 120.4, 115.2, 109.6, 60.3, 45.1, 39.0, 25.9, 18.2, 12.8, -5.5. 

**Minor hemiketal isomer:** δ 162.4, 142.0, 133.7, 125.9, 120.6, 116.6, 109.8, 60.3, 46.1, 34.4, 25.9, 18.2, 15.3, -5.5. 

**LRMS (ESI)** Calcd for [C₁₇H₂₆NO₅Si]⁻ 352.2, found 352.3
The title compound was synthesized according to modified Method 2.2 from citronellal (54 μL, 0.30 mmol) and 4-nitro-2-vinylphenol (33.0 mg, 0.20 mmol) with [Rh(COD)OMe]$_2$ (3.9 mg, 0.04 equiv) and dpk (6.5 mg, 0.08 equiv) to give the title compounds as a colorless oil as a 1:1 mixture of diastereomers (64 mg, 99%). Signals for the diasteromers were either overlapping or closely spaced. $^1$H NMR (600 MHz, CDCl$_3$) δ 9.05 (br s, 1H), 8.10 – 8.03 (m, 2H), 6.96 (d, $J$ = 9.6 Hz, 1H), 5.04 (t, $J$ = 6.8 Hz, 1H), 4.11 – 4.01 (m, 1H), 2.66 – 2.56 (m, 1H), 2.49 – 2.38 (m, 1H), 2.07 – 2.00 (m, 1H), 2.00 – 1.86 (m, 2H), 1.66 (s, 3H), 1.57 (s, 3H), 1.51 (d, $J$ = 2.7 Hz, 3H), 1.50 (d, $J$ = 2.7 Hz, 3H), 1.32 – 1.25 (m, 1H), 1.22 – 1.13 (m, 1H), 0.88 (d, $J$ = 6.6 Hz, 3H), 0.86 (d, $J$ = 6.7 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 215.6 and 215.3, 161.0 and 161.0, 141.2, 131.8 and 131.8, 126.9, 125.6, 125.1, 124.1, 117.4 and 117.3, 49.3, 49.3 and 49.1, 36.8 and 36.8, 28.7, 25.8, 25.5 and 25.5, 19.7 and 19.7, 17.7, 15.9 and 15.8. HRMS (ESI): calcd for [C$_{18}$H$_{24}$NO$_4$]$^-$ 318.1705, found 318.1698.

The title compound was synthesized according to Method 2.2 from cyclopropanecarboxaldehyde (22 μL, 0.3 mmol) and 4-nitro-2-vinylphenol (33.0 mg, 0.2 mmol) as a colorless oil (44.0 mg, 94%). $^1$H NMR (500 MHz, CDCl$_3$) δ 9.35 (br s, 1H), 8.17 – 8.06 (m, 2H), 7.00 (d, $J$ = 8.5 Hz, 1H), 4.25 (q, $J$ = 7.3 Hz, 1H), 2.22 – 2.13 (m, 1H), 1.62 (d, $J$ = 7.3 Hz, 3H), 1.28 – 1.15 (m, 2H), 1.15 – 1.01 (m, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 215.0, 160.1, 140.0, 125.9, 124.7, 124.0, 116.4, 48.8, 19.3, 15.1, 12.1, 12.0. LRMS (ESI) Calcd for [C$_{13}$H$_{15}$NO$_4$Na]$^+$ 258.1, found 258.1.
The title compound was synthesized according to Method 2.2 from cyclohexanecarboxaldehyde (36 μL, 0.3 mmol) and 4-nitro-2-vinylphenol (33.0 mg, 0.2 mmol) as a colorless oil (50.4 mg, 91%). The compound was as a ca. 97:3 mixture of branched and linear isomers and the branched isomer existed as a 1:0.23:0.01 mixture of an open chain form and the two diastereomeric hemiketals.

**1H NMR** (500 MHz, CDCl₃) *Open chain form:* δ 9.71 (s, 1H), 8.07 (dd, J = 8.9, 2.7 Hz, 1H), 8.02 (d, J = 2.7 Hz, 1H), 6.97 (d, J = 8.9 Hz, 1H), 4.16 (q, J = 7.3 Hz, 1H), 2.69 – 2.56 (m, 1H), 2.07 – 1.10 (m, 10H), 1.51 (d, J = 7.3 Hz, 3H). *Major hemiketal isomer:* 1H NMR (500 MHz, CDCl₃) δ 8.12 (d, J = 8.6 Hz, 1H), 8.07 – 7.98 (m, 1H), 6.80 (d, J = 8.8 Hz, 1H), 3.47 (q, J = 6.8 Hz, 1H), 2.95 (s, 1H), 2.01 (d, J = 12.0 Hz, 1H), 1.96 – 1.04 (m, 13H). *Linear product:* 1H NMR (500 MHz, CDCl₃) δ 3.00 – 2.97 (m, 1H), 2.90 – 2.84 (m, 1H). **13C NMR** (126 MHz, CDCl₃) *Open chain form:* δ 219.9, 161.7, 141.0, 126.3, 125.9, 125.2, 118.7, 51.1, 49.3, 28.3, 28.2, 25.6, 25.4, 25.3, 16.6. **LRMS** (ESI) Calcd for [C₁₅H₁₉NO₄Na]⁺ 300.1, found 300.2.

The title compound was synthesized according to Method 2.3 from cinnamaldehyde (38 μL, 0.30 mmol) and 4-nitro-2-vinylphenol (33.0 mg, 0.2 mmol) as a slightly yellow oil (56 mg, 95%). **1H NMR** (400 MHz, CDCl₃) δ 9.57 (br s, 1H), 8.11 (d, J = 2.7 Hz, 1H), 8.07 (dd, J = 8.9, 2.7 Hz, 1H), 7.82 (d, J = 15.9 Hz, 1H), 7.62 – 7.56 (m, 2H), 7.48 – 7.38 (m, 3H), 6.99 (d, J = 8.9 Hz, 1H), 6.91 (d, J = 15.9 Hz, 1H), 4.35 (q, J = 7.2 Hz, 1H), 1.62 (d, J = 7.3 Hz, 3H). **13C NMR** (126 MHz, CDCl₃) δ 203.5, 161.4, 146.7, 141.2, 133.9, 131.6, 129.2, 129.0, 126.8, 126.0, 125.3, 123.6, 117.8, 47.9, 16.5. **HRMS** (ESI): calcd for [C₁₇H₁₄NO₄]⁻ 296.0923, found 296.0922.
(Table 2.2, 3k)

2-(2-hydroxy-5-nitrophenyl)-5-methylhex-4-en-3-one

The title compound was synthesized according to modified Method 2.3 from 3,3-dimethyl acrolein (30 μL, 0.32 mmol) and 4-nitro-2-vinylphenol (34.8 mg, 0.21 mmol) with a 48 h reaction time as a yellow oil (32.6 mg, 0.131 mmol, 62%). $^1$H NMR (400 MHz, CDCl$_3$) δ 9.97 (br s, 1H), 8.12 – 7.96 (m, 2H), 6.97 (d, $J = 8.8$ Hz, 1H), 6.29 (s, 1H), 3.97 (q, $J = 7.3$ Hz, 1H), 2.22 (s, 3H), 1.99 (s, 3H), 1.54 (d, $J = 7.3$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 204.5, 164.5, 162.0, 141.1, 126.7, 126.2, 125.2, 122.2, 118.5, 51.7, 28.6, 21.9, 16.4. HRMS (ESI): calcd for [C$_{13}$H$_{14}$NO$_4$]$^-$ 248.0923, found 248.0924.

(Table 2.2, 3l)

(E)-2-(2-hydroxy-5-nitrophenyl)-4-methylhex-4-en-3-one

The title compound was synthesized according to modified Method 2.3 from 2,3-dimethyl acrolein (15 μL, 0.32 mmol) and 4-nitro-2-vinylphenol (16.5 mg, 0.100 mmol) with a 60 h reaction time as a yellow oil (7.7 mg, 0.031 mmol, 31%). $^1$H NMR (500 MHz, CDCl$_3$) δ 10.27 (s, 1H), 8.05 (dd, $J = 8.9$, 2.8 Hz, 1H), 8.01 (d, $J = 2.7$ Hz, 1H), 7.17 (q, $J = 6.7$ Hz, 1H), 6.97 (d, $J = 8.9$ Hz, 1H), 4.67 (q, $J = 7.2$ Hz, 1H), 1.98 (d, $J = 6.9$ Hz, 3H), 1.84 (s, 3H), 1.53 (d, $J = 7.2$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 206.8, 162.4, 142.8, 141.0, 137.5, 126.8, 126.4, 125.3, 119.2, 45.0, 17.7, 15.8, 11.4. HRMS (ESI): calcd for [C$_{13}$H$_{14}$NO$_4$]$^-$ 248.0923, found 248.0927.

(Table 2.2, 4d)

N,N-dimethyl-4-(3-methyl-5-nitrobenzofuran-2-yl)aniline

The corresponding ketone was synthesized according to Method 2.3 from 4-dimethylaminobenzaldehyde (44.8 mg, 0.3 mmol) and 4-nitro-2-vinylphenol (33.0 mg, 0.2 mmol). The yield (77 %) and branched to linear ratio (ca. 97:3) were determined by analysis of the crude $^1$H NMR with an internal standard. The product could not be separated from a minor impurity, and so the crude mixture was subjected to 1:1 DCM:TFA for five minutes to form the benzofuran product in quantitative yield as judged from the crude NMR. The solvent was removed under reduced
pressure and the benzofuran was isolated preparatory TLC as a yellow solid. \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.45 (d, \(J = 2.2\) Hz, 1H), 8.22 (dd, \(J = 8.9, 2.2\) Hz, 1H), 7.76 (d, \(J = 8.8\) Hz, 2H), 7.54 (d, \(J = 8.9\) Hz, 1H), 6.87 (d, \(J = 8.8\) Hz, 2H), 3.11 (s, 6H), 2.54 (s, 3H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 156.5, 155.1, 150.5, 143.8, 132.3, 128.0, 119.2, 117.8, 115.1, 112.0, 110.7, 108.6, 40.2, 9.3. LRMS (ESI) Calcd for \([\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_3\text{Na}]^+\) 319.1, found 319.1.

(Table 2.2, 4c)

2-(4-methoxyphenyl)-3-methyl-5-nitrobenzofuran

The corresponding ketone was synthesized according to Method 2.3 from 4-methoxybenzaldehyde (36.5 \(\mu\)L, 0.3 mmol) and 4-nitro-2-vinylphenol (33.0 mg, 0.2 mmol). The yield (79 %) and branched to linear ratio (ca. 96:4) was determined by analysis of the crude \(^1^H\) NMR with an internal standard. The product could not be separated from a minor impurity, and so the crude mixture was subjected to 1:1 DCM:TFA for five minutes to form the benzofuran product in quantitative yield as judged from the crude NMR. The solvent was removed under reduced pressure and the benzofuran was isolated by preparatory TLC as a yellow solid. \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.43 (d, \(J = 2.2\) Hz, 1H), 8.20 (dd, \(J = 8.9, 2.3\) Hz, 1H), 7.76 (d, \(J = 8.8\) Hz, 2H), 7.52 (d, \(J = 8.9\) Hz, 1H), 7.05 (d, \(J = 8.8\) Hz, 2H), 3.89 (s, 3H), 2.49 (s, 3H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 160.0, 156.6, 154.2, 143.9, 131.9, 128.4, 122.7, 119.8, 115.8, 115.5, 114.3, 111.0, 110.2, 55.4, 9.3. LRMS (ESI) Calcd for \([\text{C}_{16}\text{H}_{13}\text{NO}_4\text{Na}]^+\) 306.1, found 306.1.

(Table 2.2, 3o)

2-(2-hydroxy-5-nitrophenyl)-1-phenylpropan-1-one

The title compound was synthesized according to Method 2.3 from benzaldehyde (31 \(\mu\)L, 0.3 mmol) and 4-nitro-2-vinylphenol (33.0 mg, 0.2 mmol) as a colorless oil (37.8 mg, 78 % yield). \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 9.28 (s, 1H), 8.16 – 8.03 (m, 4H), 7.65 (t, \(J = 7.4\) Hz, 1H), 7.52 (t, \(J = 7.8\) Hz, 2H), 6.98 (d, \(J = 8.9\) Hz, 1H), 5.00 (q, \(J = 7.2\) Hz, 1H), 1.65 (d, \(J = 7.2\) Hz, 3H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 204.7, 161.1, 141.2, 135.0, 134.6, 129.1, 129.0, 126.6, 126.3, 125.2, 118.2, 44.9, 17.2. LRMS (ESI) Calcd for \([\text{C}_{15}\text{H}_{14}\text{NO}_4]^+\) 272.1, found 272.0.
The title compound was synthesized according to Method 2.3 from methyl-4-formylbenzoate (44.2 μL, 0.3 mmol) and 4-nitro-2-vinylphenol (33.0 mg, 0.2 mmol) as a white solid (62.1 mg, 94% yield). The compound was isolated as a 12:1 b:l ratio and the branched isomer exists as a 1:0.07 mixture of an open chain form and a hemiketal. **\(^1\)H NMR** (500 MHz, CDCl\(_3\)) *Open chain form:* δ 8.45 (s, 1H), 8.19 – 8.03 (m, 6H), 6.98 (d, \(J = 8.9\) Hz, 1H), 5.01 (q, \(J = 7.1\) Hz, 1H), 3.97 (s, 3H) 1.65 (d, \(J = 7.1\) Hz, 1H). *Closed chain form:* δ 8.67 – 6.75 (m, 7H), 3.61 (q, \(J = 7.2\) Hz, 1H), 3.97 (s, 3H), 3.52 (s, 1H), 1.52 (d, \(J = 7.2\) Hz, 3H). Linear isomer: δ 8.67 – 6.64 (m, 8H), 3.96 (s, 3H), 3.50 (s, 2H), 3.36 (s, 2H).

**\(^{13}\)C NMR** (126 MHz, CDCl\(_3\)) *Open chain form:* δ 203.3, 166.0, 160.3, 141.5, 138.5, 134.8, 130.1, 128.8, 126.7, 126.1, 125.2, 117.9, 52.7, 44.5, 17.1. **LRMS** (ESI) Calcd for [C\(_{17}\)H\(_{15}\)NO\(_6\)Na]^+ 352.1, found 352.1.

**Table 2.2, 3q**

1-(4-hydroxy-3-methoxyphenyl)-2-(2-hydroxy-5-nitrophenyl)propan-1-one

The title compound was synthesized according to Method 2.3 from vanillin (18.3 mg, 0.12 mmol) and 4-nitro-2-vinylphenol (16.5 mg, 0.100 mmol) as a yellow oil (26 mg, 0.082 mmol, 82%). **\(^1\)H NMR** (400 MHz, Acetone-\(d_6\)) δ 8.05 (s, 1H), 8.01 (d, \(J = 8.9\) Hz, 1H), 7.66 (d, \(J = 9.5\) Hz, 1H), 7.63 (s, 1H), 7.10 (d, \(J = 8.9\) Hz, 1H), 6.86 (d, \(J = 8.3\) Hz, 1H), 5.23 (q, \(J = 6.9\) Hz, 1H), 3.88 (s, 3H), 1.48 (d, \(J = 6.9\) Hz, 3H). **\(^{13}\)C NMR** (126 MHz, Acetone-\(d_6\)) δ 198.9, 160.6, 152.4, 148.2, 141.8, 130.8, 129.2, 124.9, 124.8, 124.1, 116.4, 115.4, 112.1, 56.1, 39.8, 18.0. **HRMS** (ESI): calcd for [C\(_{16}\)H\(_{14}\)NO\(_6\)]^- 316.0821, found 316.0833.

**Table 2.2, 3r**

4-(2-hydroxy-3-methoxyphenyl)-1-phenylpenten-3-one

The title compound was synthesized according to Method 2.2 from hydrocinnamaldehyde (40.0 μL, 0.3 mmol) and 3-methoxy-2-hydroxystyrene (30.0 mg, 0.2 mmol) as a clear colorless liquid (48.2 mg, 85%). **\(^1\)H NMR** (500 MHz, CDCl\(_3\)) δ 7.34 – 7.26 (m, 2H), 7.22 (t, \(J = 7.3\) Hz, 1H), 7.17 (d,
J = 7.2 Hz, 2H), 6.90 – 6.82 (m, 2H), 6.73 (dd, J = 7.5, 1.4 Hz, 1H), 5.92 (s, 1H), 4.19 (q, J = 7.0 Hz, 3H), 3.95 (s, 3H), 2.99 – 2.84 (m, 2H), 2.81 – 2.74 (m, 2H), 1.43 (d, J = 7.0 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 210.6, 146.7, 143.3, 141.5, 128.5, 128.5, 126.6, 126.0, 120.5, 120.1, 109.4, 56.1, 46.0, 42.6, 30.1, 15.8. LRMS (ESI): calcd for [C$_{18}$H$_{20}$O$_3$Na]$^+$, 307.1, found 307.1.

(Table 2.2, 4b)

4-(2-hydroxy-4-methoxyphenyl)-1-phenylpenten-3-one

The corresponding ketone was synthesized according to Method 2.2 from hydrocinnamaldehyde (40.0 μL, 0.3 mmol) and 4-methoxy-2-hydroxystyrene (30.0 mg, 0.2 mmol). The yield (50 %) and branched to linear ratio (>20:1) was determined by analysis of the crude $^1$H NMR with an internal standard. The product could not be separated from a minor impurity, and so the crude mixture was subjected to 1:1 DCM:TFA for five minutes to form the benzofuran product in quantitative yield as judged from the crude NMR. The solvent was removed under reduced pressure and the benzofuran was isolated by preparatory TLC as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.32 – 7.11 (m, 6H), 6.98 (d, J = 2.1 Hz, 1H), 6.84 (dd, J = 8.4, 2.2 Hz, 1H), 3.86 (s, 3H), 3.05 – 2.90 (m, 4H), 1.96 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 157.4, 154.8, 152.1, 141.3, 128.5, 128.4, 126.1, 123.9, 118.9, 110.5, 110.0, 95.8, 55.8, 34.7, 28.6, 7.7. LRMS (ESI): calcd for [C$_{18}$H$_{18}$O$_2$Na]$^+$, 289.1, found 289.1.

(Table 2.2, 3t)

4-(2-hydroxy-5-methoxyphenyl)-1-phenylpentan-3-one

The title compound was synthesized according to Method 2.2 from hydrocinnamaldehyde (40.0 μL, 0.3 mmol) and 5-methoxy-2-hydroxystyrene (30.0 mg, 0.2 mmol) as a clear colorless liquid (31.4 mg, 55%). The compound exists as a 1:0.08 mixture of an open chain form and a hemiketal. $^1$H NMR (500 MHz, CDCl$_3$) Open chain form: δ 7.42 – 6.60 (m, 8H), 6.39 (s, 1H), 3.99 (q, J = 7.1 Hz, 1H), 3.79 (s, 3H), 2.98 – 2.84 (m, 4H), 1.50 (t, J = 7.1 Hz, 3H). Hemiketal: δ 3.43 (q, J = 7.1 Hz, 1H), 1.43 (d, J = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) Open chain form: δ 213.2, 153.8, 148.2, 140.8, 128.4, 128.3, 126.7, 126.1, 117.8, 114.7, 113.4, 55.7, 49.0, 42.8, 29.6, 15.4. LRMS (ESI): calcd for [C$_{18}$H$_{20}$O$_3$Na]$^+$, 307.1, found 307.0.
The title compound was synthesized according to Method 2.2 from hydrocinnamaldehyde (40.0 μL, 0.3 mmol) and 4-fluoro-2-vinylphenol (27.6 mg, 0.2 mmol) as a white solid (50.4 mg, 93%). The compound exists as a 1:0.07 mixture of an open chain form and a hemiketal.  

**1H NMR** (500 MHz, CDCl₃) **Open chain form:** δ 7.38 – 6.68 (m, 8H), 3.92 (q, J = 7.2 Hz, 1H), 2.94 – 2.79 (m, 4H), 1.44 (d, J = 7.2 Hz, 3H). **Hemiketal:** δ 3.37 (q, J = 7.2 Hz, 1H), 1.37 (d, J = 7.2 Hz, 3H).  

**13C NMR** (126 MHz, CDCl₃) **Open chain form:** δ 213.2, 140.6, 128.4 (d, J = 28.5 Hz), 127.0 (d, J = 6.7 Hz), 126.3, 118.2 (d, J = 8.1 Hz), 115.5 (d, J = 23.5 Hz), 115.0 (d, J = 22.8 Hz), 48.9, 42.9, 29.6, 15.4. (Some peaks are missing due to weak signals from ¹⁹F coupling).  

**LRMS (ESI):** calcd for [C₁₇H₁₇FO₂Na]⁺, 295.1, found 295.2.

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The title compound was synthesized according to modified Method 2.2 from hydrocinnamaldehyde (40.0 μL, 0.3 mmol) and 2-methyl-6-vinylphenol (27 mg, 0.2 mmol) in 1 mL THF at 60 °C for 60 h as a clear colorless oil (28 mg, 50%). The compound was isolated as a 1:0.39:0.15 mixture of an open chain form and two diasteromeric hemiketals.  

**1H NMR** (400 MHz, CDCl₃) **Open chain form:** δ 7.36 – 6.72 (m, 8H), 3.92 (q, J = 7.2 Hz, 1H), 3.06 – 2.68 (m), 2.85 (s, 4H), 2.23 (s, 3H), 1.44 (d, J = 7.2 Hz, 3H). **Major hemiketal isomer:** δ 3.37 (q, J = 7.2 Hz, 1H), 2.32 – 2.13 (m, 8H), 1.36 (d, J = 7.2 Hz, 3H). **Minor hemiketal isomer:** δ 2.7 (q, J = 7.3 Hz, 1H), 2.32 – 2.13 (m, 8H), 1.22 (d, J = 7.5 Hz, 3H).  

**13C NMR** (126 MHz, CDCl₃) **Open chain form:** δ 214.4, 153.1, 140.8, 130.3, 128.6, 128.4, 127.1, 126.2, 126.0, 125.0, 120.6, 49.8, 43.0, 29.7, 16.3, 15.5. **Major hemiketal isomer:** δ 155.3, 141.7, 130.4, 129.7, 128.6, 128.5, 126.1, 121.3, 121.0, 120.0, 44.3, 41.3, 30.0, 15.3, 13.0. **HRMS (ESI):** calcd for [C₁₈H₁₉O₂]⁻ 267.1385, found 267.1379.
The title compound was synthesized according to modified Method 2.2 from hydrocinnamaldehyde (40.0 μL, 0.3 mmol) and 3-methyl-2-vinylphenol (26.8 mg, 0.2 mmol) as a clear colorless oil (50.0 mg, 93%).

The compound was isolated as 1:2.8:3.1 mixture of an open chain form and diastereomeric hemiketals. **\( ^1 \)H NMR:** Open chain form: δ 7.45 – 6.66 (m, 8H), 6.49 (s, 1H), 4.01 (q, \( J = 7.0 \) Hz, 1H), 3.17 – 2.73 (m, 4H), 2.38 (s, 3H), 1.47 (d, \( J = 7.0 \) Hz, 3H). **Major hemiketal diastereomer:** δ 7.48 – 6.68 (m, 8H), 3.33 (q, \( J = 7.2 \) Hz, 1H), 3.08 (s, 1H), 2.38 (s, 3H), 2.35 – 2.28 (m, 2H), 2.28 – 2.23 (m, 2H), 1.25 (d, \( J = 7.2 \) Hz, 3H). **Minor hemiketal:** δ 7.45 – 6.67 (m, 8H), 3.41 (q, \( J = 7.2 \) Hz, 1H), 3.18 – 2.72 (m, 4H), 2.39 (s, 3H), 1.43 (d, \( J = 7.2 \) Hz, 3H). **\( ^{13} \)C NMR** (126 MHz, CDCl\(_3\)) δ 213.3, 156.4, 156.2, 154.5, 141.7, 141.6, 141.0, 137.3, 135.0, 134.8, 130.6, 129.1, 128.5, 128.4, 128.4, 128.3, 128.3, 128.1, 128.1, 128.0, 126.1, 126.0, 125.9, 125.3, 123.1, 122.8, 122.7, 115.1, 111.0, 110.9, 107.0, 107.2, 46.2, 45.3, 43.5, 43.1, 41.3, 36.9, 29.9, 29.8, 29.5, 20.4, 18.7, 18.1, 15.5, 13.9, 13.2. **LRMS** (ESI): calcd for [C\(_{18}\)H\(_{19}\)O\(_2\)]\(^-\) 267.1, found 267.2.

The title compound was synthesized according to modified Method 2.2 from hydrocinnamaldehyde (30 μL, 0.23 mmol) and 2,4-di-tert-butyl-6-vinylphenol (35 mg, 0.15 mmol) in 1.5 mL THF at 60 °C for 48 h as a clear colorless oil (36.6 mg, 67%). The compound was isolated as a 0.07:1:0.27 mixture of an open chain form and two diastereomeric hemiketals. **\( ^1 \)H NMR** (400 MHz, CDCl\(_3\)) **Major hemiketal:** δ 7.34 – 7.08 (m, 5H), 7.14 (s, 1H), 7.00 (s, 1H), 3.32 (q, \( J = 7.1 \) Hz, 1H), 2.95 (t, \( J = 8.4 \) Hz, 2H), 2.66 (s, 1H), 2.35 – 2.13 (m, 2H), 1.38 (s, 9H), 1.37 (d, \( J = 7.2 \) Hz, 3H), 1.31 (s, 9H). **Minor hemiketal:** δ 7.34 – 7.08 (m, 6H), 7.05 (s, 1H), 3.21 (q, \( J = 7.7 \) Hz, 1H), 3.08 – 2.86 (m, 2H), 2.84 (s, 1H), 2.35 – 2.13 (m, 2H), 1.39 (s, 9H), 1.31 (s, 9H). **\( ^{13} \)C NMR** (126 MHz, CDCl\(_3\)) **Major hemiketal:** δ 152.5, 143.8, 141.9, 132.2, 130.7, 128.6, 128.5, 126.1, 122.2, 118.5, 110.7, 43.9, 41.2, 34.7, 34.4, 32.0, 30.3, 29.6, 12.8. Minor hemiketal: δ 152.1,
143.8, 142.2, 132.3, 131.6, 128.7, 128.6, 126.2, 122.2, 118.9, 111.5, 47.1, 37.1, 34.7, 34.4, 32.0, 29.9, 29.7, 16.8. **HRMS** (ESI): calcd for [C$_{25}$H$_{34}$O$_2$Na]$^+$ 389.2456, found 389.2462.

(Table 2.2, 3y)

1-cyclohexyl-2-(2-hydroxy-5-methoxyphenyl)propan-1-one

The title compound was synthesized according to Method 2.2 from cyclohexane carboxaldehyde (36.3 μL, 0.3 mmol) and 3-methoxy-2-hydroxystyrene (30.0 mg, 0.2 mmol) as a clear colorless liquid (48.6 mg, 93%) as a single regioisomer without any formation of the hemiketal. **$^1$H NMR** (500 MHz, CDCl$_3$) $\delta$ 6.89 – 6.81 (m, 2H), 6.74 (dd, $J = 7.5$, 1.4 Hz, 1H), 6.03 (s, 1H), 4.39 (q, $J = 6.9$ Hz, 1H), 3.96 (s, 1H), 2.49 (tt, $J = 11.3$, 3.4 Hz, 1H), 2.00 – 1.06 (m, 10H), 1.39 (d, $J = 7.0$ Hz, 3H).

**$^{13}$C NMR** (126 MHz, CDCl$_3$) $\delta$ 214.8, 146.6, 143.2, 126.7, 120.6, 119.8, 109.2, 56.0, 49.3, 43.6, 29.6, 28.2, 26.0, 25.9, 25.4, 16.5. **LRMS** (ESI): calcd for [C$_{16}$H$_{22}$O$_3$Na]$^+$ 285.2, found 285.1.

(Table 2.2, 3z)

1-cyclohexyl-2-(2-hydroxy-5-methoxyphenyl)propan-1-one

The title compound was synthesized according to Method 2.2 from cyclohexane carboxaldehyde (36.3 μL, 0.3 mmol) and 5-methoxy-2-hydroxystyrene (30.0 mg, 0.2 mmol) as a clear colorless liquid (39.6 mg, 75%). The compound was isolated as a 91:9 mixture of branched and linear isomers, respectively. The branched product was a 1:0:05 mixture of open and closed chain form. **$^1$H NMR** (500 MHz, CDCl$_3$) Branched product: $\delta$ 6.81 (d, $J = 8.8$ Hz, 1H), 6.70 (dd, $J = 8.8$, 3.0 Hz, 1H), 6.61 (d, $J = 3.0$ Hz, 1H), 4.08 (q, $J = 7.2$ Hz, 1H), 3.74 (s, 3H), 2.54 (ddd, $J = 11.4$, 8.8, 2.9 Hz, 1H), 2.07 – 1.59 (m, 5H), 1.43 (d, $J = 7.2$ Hz, 3H), 1.39 – 1.11 (m, 5H). Hemiketal isomer: $\delta$ 3.42 (q, $J = 7.2$ Hz, 1H). Linear product: $\delta$ 2.92 – 2.86 (m, 2H), 2.83 – 2.75 (m, 2H).

**$^{13}$C NMR** (126 MHz, CDCl$_3$) $\delta$ 218.6, 153.6, 145.0, 126.8, 118.4, 115.5, 113.6, 55.9, 50.6, 48.4, 28.9, 28.4, 25.9, 25.8, 25.6, 16.5. **LRMS** (ESI): calcd for [C$_{16}$H$_{22}$O$_3$Na]$^+$ 285.2, found 285.2.
(Table 2.2, 3aa)

1-cyclohexyl-2-(2-hydroxy-3-methylphenyl)propan-1-one

The title compound was synthesized according to Method 2.2 from cyclohexanecarboxaldehyde (36 μL, 0.3 mmol) and 2-methyl-6-vinylphenol (27 mg, 0.2 mmol) as a clear colorless oil (45 mg, 91%). The compound was isolated as a single regioisomer by \(^1\)H NMR analysis, and exists as a 1:0.3 mixture of open to closed form. \(^1\)H NMR (500 MHz, CDCl\(_3\))  

**Open chain form**: \(\delta 8.15 (s, 1H), 7.03 (d, \(J = 7.6\) Hz, 1H), 6.88 (d, \(J = 7.6\) Hz, 1H), 6.74 (t, \(J = 7.5\) Hz, 1H), 4.06 (q, \(J = 7.2\) Hz, 1H), 2.25 (s, 3H), 1.96 – 1.60 and 1.42 – 1.11 (m, 10H), 1.46 (d, \(J = 7.3\) Hz, 3H).

**Closed chain form**: 6.94 (dt, \(J = 6.7\) Hz, 2H), 6.80 (t, \(J = 7.4\) Hz, 1H), 3.42 (q, \(J = 7.2\) Hz, 1H), 2.62 (s, 1H), 2.56 (t, \(J = 11.2\) Hz, 1H), 2.20 (s, 3H).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\))  

**Open chain form**: \(\delta 219.9, 153.8, 130.3, 128.0, 126.9, 124.8, 120.2, 112.4, 50.9, 49.5, 27.1, 26.9, 25.8, 25.7, 25.5, 16.4, 16.4.

**Closed chain form**: 155.3, 130.7, 129.4, 121.2, 120.7, 119.6, 47.6, 41.6, 26.5, 26.3, 26.3, 15.3, 14.1.  

HRMS (ESI): calcd for [C\(_{16}\)H\(_{21}\)O\(_2\)]\(^+\): \(m/z = 245.1542\); found \(m/z = 245.1549\).

(3ab)

1-cyclohexyl-2-(2-hydroxy-6-methylphenyl)propan-1-one

The title compound was synthesized according to modified Method 2.2 from hydrocinnamaldehyde (40.0 μL, 0.3 mmol) and 3-methyl-2-vinylphenol (26.8 mg, 0.2 mmol) with a two day reaction time as a clear colorless oil (48.9 mg, 95%). The compound was isolated as a 1:2.7:1 mixture of open chain and 2 diastereomeric hemiketals. \(^1\)H NMR (500 MHz, CDCl\(_3\))  

**Major hemiketal**: \(\delta 7.10 – 6.55 \) (m, 3H), 3.45 (q, \(J = 7.2\) Hz, 1H), 2.31 (s, 3H), 2.89 – 1.02 (m, 12H), 1.34 (d, \(J = 7.2\) Hz, H).  

**Minor hemiketal**: \(\delta 7.07 – 6.55 \) (m, 3H), 3.17 (q, \(J = 7.0\) Hz, 3H), 2.30 (s, 3H), 2.88 – 1.02 (m, 12H), 1.13 (d, \(J = 7.0\) Hz, 3H).  

**Open chain**: \(\delta 7.68 (s, 1H), 7.10 – 6.55 \) (m, 3H), 4.29 (q, \(J = 7.1\) Hz, 1H), 2.38 (s, 3H), 2.87 – 0.98 (m, 11H), 1.42 (d, \(J = 7.1\) Hz, 3H).  

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta 219.3, 156.8, 156.2, 155.8, 136.9, 134.9, 134.5, 131.6, 129.4, 128.2, 128.0, 127.9, 124.3, 122.9, 122.8, 122.5, 116.3, 110.8, 108.0, 106.9, 50.6, 47.5, 44.2, 44.1, 41.7, 40.9, 29.2, 28.7, 28.0, 26.7, 26.5, 26.4, 26.4, 26.2, 26.1, 26.0, 26.0, 25.9, 25.8, 25.3, 20.9, 18.9, 18.0, 15.5, 14.8, 13.8.  

LRMS (ESI): calcd for [C\(_{16}\)H\(_{22}\)O\(_2\)Na\(^+\)] \(269.2\), found 269.1.
(Table 2.2, 3ac)

(E)-4-(2-hydroxy-3-methoxyphenyl)-1-phenylpent-1-en-3-one

The title compound was synthesized according to Method 2.3 from cinnamaldehyde (38 μL, 0.3 mmol) and 3-methoxy-2-hydroxystyrene (30.0 mg, 0.2 mmol) as a white solid (51.7 mg, 92%). \(^1\)H NMR: (500 MHz, CDCl\(_3\)) \(\delta\) 7.66 (d, \(J = 16.0\) Hz, 1H), 7.49 – 7.43 (m, 2H), 7.35 – 7.30 (m, 3H), 6.85 – 6.78 (m, 1H), 6.78 – 6.71 (m, 3H), 6.03 (s, 1H), 4.50 (q, \(J = 6.9\) Hz, 1H), 3.88 (s, 3H), 1.45 (d, \(J = 6.9\) Hz, 3H).

\(^{13}\)C NMR: (126 MHz, CDCl\(_3\)) \(\delta\) 200.3, 146.7, 143.2, 142.5, 134.9, 130.3, 128.9, 128.5, 126.6, 125.3, 120.6, 120.2, 109.4, 56.1, 44.2, 16.4. LRMS (ESI): calcd for [C\(_{18}\)H\(_{18}\)O\(_3\)Na]\(^+\) 305.1, found 305.1.

(Table 2.2, 3ad)

(E)-4-(2-hydroxy-5-methoxyphenyl)-1-phenylpent-1-en-3-one

The title compound was synthesized according to Method 2.3 from cinnamaldehyde (38 μL, 0.3 mmol) and 5-methoxy-2-hydroxystyrene (30.0 mg, 0.2 mmol) as a white solid (29.0 mg, 51%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.72 (d, \(J = 15.9\) Hz, 1H), 7.52 – 7.49 (m, 2H), 7.41 – 7.35 (m, 3H), 7.01 (s, 1H), 6.86 – 6.80 (m, 2H), 6.73 – 6.67 (m, 2H), 4.29 (q, \(J = 7.1\) Hz, 1H), 3.74 (s, 3H), 1.54 (d, \(J = 7.1\) Hz, 3H).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 202.7, 153.9, 148.6, 144.8, 134.5, 131.0, 129.1, 128.8, 127.1, 124.5, 118.1, 115.2, 113.7, 55.9, 47.7, 16.3. LRMS (ESI): calcd for [C\(_{18}\)H\(_{18}\)O\(_3\)Na]\(^+\) 305.1, found 305.1.

(Table 2.2, 3ae)

(E)-4-(2-hydroxy-3-methylphenyl)-1-phenylpent-1-en-3-one

The title compound was synthesized according to Method 2.3 from cinnamaldehyde (38 μL, 0.3 mmol) and 2-methyl-6-vinylphenol (27 mg, 0.2 mmol) at 100 °C for 18 h as a yellow oil (32.8 mg, 62%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.74 (d, \(J = 15.9\) Hz, 1H), 7.61 (s, 1H), 7.56 – 7.51 (m, 2H), 7.41 – 7.35 (m, 3H), 7.05 (d, \(J = 7.3\) Hz, 1H), 6.99 (d, \(J = 7.6\) Hz, 1H), 6.85 (d, \(J = 15.9\) Hz, 1H), 6.79 (t, \(J = 7.5\) Hz, 1H), 4.26 (q, \(J = 7.2\) Hz, 1H), 2.26 (s, 3H), 1.57 (d, \(J = 7.2\) Hz, 3H).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 203.6, 153.6, 145.3, 134.3, 131.1, 130.4, 129.1 (2 × CH), 128.8.
(Table 2.2, 3af)

(E)-4-(2-hydroxy-6-methylphenyl)-1-phenylpent-1-en-3-one

The title compound was synthesized according to Method 2.3 from cinnamaldehyde (38 μL, 0.3 mmol) and 3-methyl-2-hydroxy styrene (26.8 mg, 0.2 mmol) as a white solid (51.2 mg, 96%). The compound was isolated as a single regioisomer by \(^1\)H NMR analysis, and exists as a 1:0.13:0.05 mixture of open to closed forms (two diastereomers). \(^1\)H NMR (500 MHz, CDCl\(_3\)) Open chain form: δ 7.67 (d, \(J = 15.9\) Hz, 1H), 7.47 – 7.38 (m, 3H), 7.37 – 7.27 (m, 3H), 7.02 (t, \(J = 7.8\) Hz, 1H), 6.79 – 6.69 (m, 2H), 6.73 (d, \(J = 15.9\) Hz, 1H), 4.32 (q, \(J = 7.0\) Hz, 1H), 2.40 (s, 3H), 1.50 (d, \(J = 7.0\) Hz, 3H). Major hemiketal isomer: δ 3.35 (q, \(J = 7.3\) Hz, 1H), 2.30 (s, 3H), 1.12 (d, \(J = 7.3\) Hz, 3H). Minor hemiketal isomer: δ 3.47 (q, \(J = 6.9\) Hz, 1H), 2.30 (s, 3H), 1.42 (d, \(J = 7.2\) Hz, 4H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) δ 203.3, 155.4, 144.0, 137.4, 134.4, 130.8, 129.0, 129.7, 128.3, 125.2, 124.5, 123.1, 115.6, 45.4, 20.7, 14.4. LRMS (ESI): calcd for [C\(_{18}\)H\(_{18}\)O\(_2\)Na]\(^+\) 289.1, found 289.2.

(Table 2.2, 3ag)

2-(2-hydroxy-3-methoxyphenyl)-1-phenylpropan-1-one

The title compound was synthesized according to Method 2.3 from benzaldehyde (31 μL, 0.3 mmol) and 3-methoxy-2-hydroxystyrene (30.0 mg, 0.2 mmol) as a white solid (43.0 mg, 84%). The compound was isolated as a 95:5 mixture of branched and linear isomers, respectively, without any hemiketal isomers. \(^1\)H NMR (500 MHz, CDCl\(_3\)) Branched product: δ 8.03 (d, \(J = 7.5\) Hz, 2H), 7.44 (t, \(J = 7.5\) Hz, 1H), 7.35 (t, \(J = 7.5\) Hz, 2H), 6.76 – 6.67 (m, 3H), 6.05 (s, 1H), 5.11 (q, \(J = 6.9\) Hz, 1H), 3.85 (s, 3H), 1.48 (d, \(J = 6.9\) Hz, 3H). Linear product: δ 7.98 (d, \(J = 7.4\) Hz, 2H), 7.53 (t, \(J = 7.4\) Hz, 1H), 7.45 – 7.40 (m, 2H), 6.84 – 6.66 (m, 3H), 3.86 (s, 3H), 3.33 (t, \(J = 7.6\) Hz, 2H), 3.07 (t, \(J = 7.6\) Hz, 2H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) Branched product: δ 201.1, 146.7, 142.4, 136.5, 132.8, 128.8, 128.5, 127.5, 120.3, 120.2, 109.2, 56.1, 40.3, 17.7. Linear product: δ 200.3, 146.8,
The title compound was synthesized according to Method 2.3 from benzaldehyde (31 μL, 0.3 mmol) and 5-methoxy-2-hydroxystyrene (30.0 mg, 0.2 mmol) as a white solid (31.4 mg, 55%). The compound was isolated as a 90:10 mixture of branched and linear isomers, which equilibrated with its closed-chain form. 

1H NMR (500 MHz, CDCl3) Branched product: δ 8.05 (d, J = 7.5 Hz, 2H), 7.53 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.7 Hz, 2H), 6.84 (s, 1H), 6.80 (d, J = 8.6 Hz, 1H), 6.70 – 6.63 (m, 2H), 4.93 (q, J = 7.0 Hz, 1H), 3.70 (s, 3H), 1.56 (d, J = 7.0 Hz, 3H). Hemiketal isomer: 1H NMR (500 MHz, CDCl3) δ 1.36 (d, J = 6.8 Hz, 3H). Linear product: 1H NMR (500 MHz, CDCl3) δ 7.97 (d, J = 7.5 Hz, 2H), 7.60 – 7.55 (m, 1H), 7.48 – 7.39 (m, 2H), 6.90 – 6.60 (m, 3H), 3.74 (s, 3H), 3.46 – 3.42 (m, 2H), 3.02 – 2.99 (m, 2H). 

13C NMR (126 MHz, CDCl3) Branched product: δ 203.6, 153.8, 148.0, 136.1, 133.7, 129.0, 128.8, 127.7, 118.0, 115.2, 113.6, 55.9, 43.8, 17.4. Linear product: δ 202.0. LRMS (ESI): calcd for [C16H16O3Na]+ 279.1, found 279.1.

(Table 2.2, 3ai)  
2-(2-hydroxy-3-methylphenyl)-1-phenylpropan-1-one

The title compound was synthesized according to Method 2.3 from benzaldehyde (31 μL, 0.3 mmol) and 2-methyl-6-vinylphenol (27 mg, 0.2 mmol) as a colorless oil (39 mg, 81%). The compound was isolated as a >98:2 mixture of branched and linear products, respectively. The branched product exists as a 1:0.06:0.04 mixture of open to closed forms (two diastereomers). 1H NMR (400 MHz, CDCl3) Open form: δ 8.06 (d, J = 7.2 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.50 (s, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.01 (t, J = 8.0 Hz, 2H), 6.75 (t, J = 7.5 Hz, 1H), 4.90 (q, J = 7.1 Hz, 1H), 2.26 (s, 3H), 1.60 (d, J = 7.1 Hz, 3). Major hemiketal isomer: δ 3.54 – 3.42 (m, 1H), 2.30 (s, 3H), 1.42 (d, J = 7.1 Hz, 3). Minor hemiketal isomer: δ 3.54 – 3.42 (m, 1H), 2.33 (s, 3), 0.75 (d, J = 7.4 Hz, 3). 13C NMR (126 MHz, CDCl3) δ 204.6, 153.1, 136.0, 133.8, 130.2, 129.0, 128.8, 127.8, 126.1.
125.6, 120.5, 44.9, 17.1, 16.3. **HRMS** (ESI): calcd for $[\text{C}_{16}\text{H}_{16}\text{O}_2\text{H}]^-$: $m/z = 239.1072$; found $m/z = 239.1065$.

**(Table 2.2, 3aj)**

**2-(2-hydroxy-6-methylphenyl)-1-phenylpropan-1-one**

The title compound was synthesized according to Method 2.3 from benzaldehyde (31.0 μL, 0.3 mmol) and 6-methyl-2-hydroxystyrene (26.8 mg, 0.2 mmol) as a white solid (37.0 mg, 77%). The branched product existed as 1:1.4:0.5 mixture of open to closed forms (two diastereomers). **$^1$H NMR** (500 MHz, CDCl$_3$) *Branched product*: δ 7.92 (d, $J = 7.7$ Hz, 2H), 7.54 – 7.32 (m, 3H), 6.98 (t, $J = 7.7$ Hz, 1H), 6.72 (d, $J = 7.7$ Hz, 1H), 6.66 (d, $J = 7.7$ Hz, 1H), 4.91 (q, $J = 7.0$ Hz, 1H), 2.41 (s, 3H), 1.57 (d, $J = 7.0$ Hz, 3H). *Major hemiketal isomer*: δ 7.66 – 7.63 (m, 2H), 7.46 – 7.32 (m, 3H), 7.11 (t, $J = 7.8$ Hz, 1H), 6.81 (d, $J = 7.9$ Hz, 1H), 6.77 (d, $J = 7.5$ Hz, 1H), 3.44 (q, $J = 7.3$ Hz, 1H), 2.31 (s, 3H), 0.71 (d, $J = 7.3$ Hz, 3H). *Minor hemiketal isomer*: δ 7.60 (d, $J = 7.0$ Hz, 2H), 7.54 – 7.32 (m, 3H), 7.08 (t, $J = 7.8$ Hz, 1H), 6.78 – 6.73 (m, 1H), 6.73 – 6.68 (m, 1H), 3.53 (q, $J = 6.8$ Hz, 1H), 2.28 (s, 3H), 1.47 (d, $J = 6.8$ Hz, 1H). **$^{13}$C NMR** (126 MHz, CDCl$_3$) δ 205.2, 156.6, 155.2, 139.8, 136.9, 136.7, 135.3, 134.9, 134.0, 133.5, 131.0, 128.8, 128.7, 128.6, 128.3, 128.2, 128.2, 126.8, 125.9, 125.4, 123.5, 123.3, 123.2, 115.9, 115.4, 111.9, 110.1, 108.1, 107.5, 67.1, 48.2, 46.8, 41.8, 20.7, 19.0, 18.3, 17.5, 15.5, 12.5. **LRMS** (ESI): calcd for $[\text{C}_{16}\text{H}_{16}\text{O}_2\text{Na}]^+$ 263.1, found 263.0.

**(Table 2.2, 3ak)**

**2-(2-hydroxy-3,5-di-tert-butylphenyl)-1-phenylpropan-1-one**

The title compound was synthesized according to modified Method 2.3 from benzaldehyde (23 μL, 0.23 mmol) and 2,4-di-tert-butyl-6-vinylphenol (35 mg, 0.15 mmol) as a colorless oil (42.8 mg, 84%). The compound was isolated as a single regioisomer by $^1$H NMR analysis, and exists as a 1:0.77:0.24 mixture of closed (two diastereomers) to open forms. **$^1$H NMR** (500 MHz, CDCl$_3$) *Major hemiketal*: δ 7.69 (d, $J = 6.8$ Hz, 2H), 7.44 – 7.33 (m, 3H), 7.20 (s, 1H), 7.01 (s, 1H), 3.45 – 3.36 (q, 1H), 2.98 (s, 1H), 1.43 (s, 9H), 1.44 – 1.41 (d, 3H), 1.33 (s, 9H). *Minor hemiketal* δ 7.63 (d, $J = 6.9$ Hz, 2H), 7.47 (t, $J = 7.7$ Hz, 1H), 7.44 – 7.33 (m, 2H), 7.20 (s,
1H), 7.09 (s, 1H), 3.45 – 3.36 (q, 1H), 3.14 (s, 1H), 1.45 (s, 9H), 1.32 (s, 9H), 0.75 (d, J = 7.4 Hz, 3H). Open form: δ 8.30 (s, 1H), 8.09 (d, J = 8.8 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.44 – 7.33 (m, 2H), 7.23 (s, 1H), 7.00 (s, 1H), 4.84 (q, J = 7.2 Hz, 1H), 1.66 (d, J = 7.2 Hz, 3H), 1.47 – 1.40 (s, 9H), 1.28 (s, 9H). 13C NMR (126 MHz, CDCl3) Major hemiketal δ 152.7, 144.2, 143.2, 132.5, 130.6, 128.6, 128.5, 125.6, 122.3, 118.1, 110.2, 48.1, 34.8, 34.43, 32.0, 29.7, 11.0. Minor hemiketal: δ 152.3, 144.2, 140.5, 132.5, 131.9, 128.7, 128.3, 126.8, 122.2, 119.2, 111.8, 47.8, 34.8, 34.5, 32.0, 29.8, 19.7. Open form: δ 206.0, 152.6, 142.1, 138.0, 136.0, 134.0, 129.2, 128.9, 125.5, 125.2, 123.8, 47.2, 35.3, 34.4, 31.8, 30.1, 16.9. HRMS (ESI): calcd for [C23H29O2]⁻ 337.2168, found 337.2184.

(Scheme 2.10, 3al)

1-cyclopropyl-2-(2-hydroxy-5-nitrophenyl)propan-1-one

The title compound was synthesized according to Method 2.2 from cyclopropanecarboxaldehyde (181 μL, 2.43 mmol) and 4-chloro-2-vinylphenol (250 mg, 1.62 mmol) as a colourless oil with a 93:7 b:l ratio (291 mg, 80 % yield). 1H NMR (500 MHz, CDCl3) Branched isomer: δ 7.79 (s, 1H), 7.14 – 7.06 (m, 2H), 6.82 (d, J = 8.5 Hz, 1H), 4.10 (q, J = 7.2 Hz, 1H), 2.11 – 1.98 (m, 1H), 1.50 (d, J = 7.2 Hz, 3H), 1.19 – 1.04 (m, 2H), 1.03 – 0.87 (m, 2H). Linear isomer: δ 3.11 – 3.04 (m, 2H), 2.84 – 2.75 (m, 2H). 13C NMR (126 MHz, CDCl3) Branched isomer: δ 215.3, 153.4, 129.1, 128.4, 127.7, 125.2, 118.5, 49.6, 20.1, 15.9, 12.5, 12.5. LRMS (ESI): calcd for [C12H13ClO2Na]+ 247.1, found 247.0.

(Table 2.7)

4-(2-hydroxy-5-nitrophenyl)-1-phenylpentan-3-one-5-d

To a 1 dram vial was added 4 mol % [Rh(COD)OMe]2 and 8 mol % dcpm. The vinyl phenol (0.2 mmol, 1 equiv), aldehyde (1.5 equiv), and THF (200 μL) were added to the vial which was then sealed with a Teflon-lined screw cap. The reaction was heated to 60 °C for 24 hours and then cooled to room temperature. The branched to linear ratio was determined by integration of the methine proton (quartet) of the branched product versus the methylene protons of the linear product (triplets) in the crude 1H NMR spectrum. The product was isolated by preparatory TLC as a
colorless oil (54.0 mg, 90%). This compound has very concentration dependent $^1$H NMR spectrum and sharp peaks can only be obtained under very dilute conditions. The additional peaks in the $^1$H NMR correspond to hemiketal isomers of the product. Only the peaks corresponding to the open-chain form are tabulated here. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.08 (d, $J = 8.9$ Hz, 1H), 7.97 (s, 1H), 7.30 – 7.23 (m, 2H), 7.22 – 7.09 (m, 3H), 6.92 (d, $J = 8.9$ Hz, 1H), 3.92 (br s, 1H), 3.10 – 2.69 (m, 4H), 1.46 (d, $J = 7.3$ Hz, 2H). $^2$H NMR (77 MHz, CDCl$_3$) $\delta$ 1.47. $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 213.96, 160.51, 141.14, 140.21, 128.50, 128.18, 126.59, 126.24, 125.38, 124.98, 117.03, 48.51, 43.06, 29.52, 15.20. LRMS (ESI): calcd for [C$_{17}$H$_{15}$DNO$_4$]$^-$ 299.11 (100%), 300.12 (18.4%), 301.12 (1.6%), found 298.0 (2.0%), 299.3 (100%), 300.31 (17.0%), 301.35 (2.0%).

(2.7)
4-(2-hydroxy-5-nitrophenyl)-1-phenylpentan-3-one-5-d

To a 1 dram vial was added 4 mol % [Rh(COD)OMe]$_2$ and 8 mol % dcpm. The vinyl phenol (0.2 mmol, 1 equiv), aldehyde (1.5 equiv), and 1,4-dioxane (200 μL) were added to the vial which was then sealed with a Teflon-lined screw cap. The reaction was heated to 100 °C for 24 hours and then cooled to room temperature. The branched to linear ratio was determined by integration of the methine proton of the branched product versus the methylene protons of the linear product in the crude $^1$H NMR spectrum. The product was isolated by preparatory TLC as a white solid (50.3 mg, 78%). The compound was isolated with a 92:8 branched:linear ratio. $^1$H NMR (500 MHz, CDCl$_3$) Linear isomer: $\delta$ 9.36 (s, 1H), 8.71 (s, 1H), 8.25 (d, $J = 1.8$ Hz, 1H), 8.18 – 7.87 (m, 4H), 7.67 (t, $J = 7.4$ Hz, 1H), 7.61 (t, $J = 7.4$ Hz, 1H), 7.03 (d, $J = 8.9$ Hz, 1H), 5.28 (t, $J = 6.9$ Hz, 1H), 1.72 (d, $J = 6.9$ Hz, 1H). Branched isomer: $\delta$ 3.69 (d, $J = 6.0$ Hz, 1H), 3.17 (t, $J = 6.0$ Hz, 1H). $^2$H NMR (77 MHz, CDCl$_3$) $\delta$ 1.70. $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 204.55, 161.05, 141.25, 136.17, 132.46, 132.43, 131.36, 129.97, 129.43, 129.07, 127.88, 127.25, 126.23, 125.18, 124.14, 117.91, 44.23, 17.21 (t, $J = 20.2$ Hz).
2.6.3 Ketone Derivatization

(Scheme 2.10)

**4-chloro-2-(1-cyclopropyl-1-oxopropan-2-yl)phenyltrifluoromethanesulfonate**

To a flame dried round bottom flask equipped with a septum and magnetic stir bar was added 1-cyclopropyl-2-(2-hydroxy-5-nitrophenyl)propan-1-one (260 mg, 1.16 mmol, 1 equiv.), pyridine (186 μL, 2.31 mmol, 2 equiv.) and dichloromethane (5 mL). The flask was lowered into an ice bath and then triflic anhydride (292 μL, 1.74 mmol, 1.5 equiv.) was added dropwise to the stirring solution. After two hours, the solution was diluted with dichloromethane, washed twice with 1 M HCl and finally washed once with saturated NaHCO₃(aq) solution. The solvent was removed under reduced pressure and the residue was purified by column chromatography (0 to 10% EtOAc in Hx). The product was isolated as a colourless oil (315 mg, 76% yield) contaminated with about 7% of the triflate of the linear isomer. **¹H NMR** (500 MHz, CDCl₃) δ 7.44 – 7.28 (m, 3H), 4.34 (q, J = 7.1 Hz, 1H), 2.01 – 1.87 (m, 1H), 1.51 (d, J = 7.1 Hz, 3H), 1.19 – 1.12 (m, 1H), 1.12 – 1.03 (m, 1H), 1.03 – 0.95 (m, 1H), 0.95 – 0.85 (m, 1H). **¹³C NMR** (126 MHz, CDCl₃) δ 208.6, 145.6, 135.6, 134.6, 129.9, 128.9, 122.8, 46.2, 20.2, 17.0, 12.0, 11.9. **LRMS** (EI): calcd for [C₁₃H₁₂ClF₃O₄S]⁺ 356.0, found 356.0

(Scheme 2.10, 5a)

**2-(4-chloro-4′-methoxy-[1,1′-biphenyl]-2-yl)-1-cyclopropylpropan-1-one**

To a 1 dram vial was added p-methoxyboronic acid (12.8 mg, 0.0841 mmol, 1.5 equiv), Pd(OAc)₂ (1.4 mg, 0.0056 mmol, 10 mol %), triphenylphosphine (2.9 mg, 0.012 mmol, 20 mol %), K₃PO₄ (17.8 mg, 0.0841 mmol, 1.5 equiv.), and 4-chloro-2-(1-cyclopropyl-1-oxopropan-2-yl)phenyltrifluoromethanesulfonate (20.0 mg, 0.056 mmol, 1 equiv). The vial was equipped with a stir bar and septum and then purged with N₂. A 5:1 mixture of degassed THF:water (0.5 mL was added). The solution was stirred rapidly for 4 hours. The reaction was then diluted with EtOAc and filtered through a plug of silica and concentrated under reduced pressure. The product was isolated by preparatory TLC as a white solid (16.0 mg, 91% yield). **¹H NMR** (500 MHz, CDCl₃) δ 7.38 – 7.15 (m, 5H), 7.05 (d, J = 8.7 Hz, 2H), 4.11 (q, J = 6.9 Hz,
1H), 3.93 (s, 3H), 1.67 – 1.58 (m, 1H), 1.41 (d, J = 6.9 Hz, 3H), 1.10 – 0.91 (m, 2H), 0.89 – 0.67 (m, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 210.4, 159.0, 140.7, 140.2, 133.6, 132.5, 131.7, 130.2, 127.5, 126.9, 113.9, 55.3, 49.3, 20.1, 17.9, 11.5, 11.4. LRMS (ESI): calcd for [C$_{19}$H$_{20}$ClO$_2$]$^+$ 315.1, found 315.1.

(Scheme 2.10, 4a)

5-chloro-3-methyl-2-phenethylbenzofuran

To a 1 dram vial was added 4-(5-chloro-2-hydroxyphenyl)-1-phenylpentan-3-one (21.3 mg, 0.0948 mmol, 93:7 mixture of regioisomers) and 1:1 DCM:TFA (200 μL). The solvent was then removed under reduced pressure and the residue was purified by preparatory TLC to give the product as colourless oil (18.1 mg, quantitative yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.34 (d, J = 2.0 Hz, 1H), 7.21 (d, J = 8.6 Hz, 1H), 7.12 (dd, J = 8.6, 2.1 Hz, 1H), 2.20 (s, 3H), 2.05 – 1.93 (m, 1H), 1.10 – 1.03 (m, 2H), 1.02 – 0.95 (m, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 155.8, 151.5, 132.3, 127.6, 122.8, 117.9, 111.2, 109.2, 7.7, 7.6, 6.7. LRMS (ESI): calcd for [C$_{12}$H$_{11}$ClONa]$^+$ 229.0, found 229.0.

2.6.4 Neolignan Synthesis
6-formyleugenol

To a 100 mL round bottom flask was added hexamine (6 g, 42.8 mmol, 4.75 equiv), eugenol (1.5 mL, 9.7 mmol, 1 equiv), and acetic acid (12 mL). The reaction was heated at 125 °C for 3 hours. The reaction was cooled to approximately 100 °C and then 15 mL of 33 v/v % aq. H₂SO₄ (which was used immediately after its preparation) was added. The reaction was heated at 100 °C for 5 more minutes and then allowed to cool to room temperature. The reaction was diluted with Et₂O and washed once with water. The aqueous layer was back-extracted three times with Et₂O and the organic fractions were combined. To the organic layer was added water and then saturated NaHCO₃ (aq) was added until the pH of the aqueous layer was 7. The organic layer was separated and dried with MgSO₄ and concentrated under vacuum. The product was isolated via column chromatography (gradient 0 to 30% EtOAc in Hx) as a light yellow solid (564 mg, 30%). ¹H NMR (500 MHz, CDCl₃) δ 10.98 (s, 1H), 9.88 (s, 1H), 6.99 (s, 1H), 6.95 (ddt, J = 16.8, 10.2, 6.6 Hz, 1H), 5.19 – 5.07 (m, 2H), 3.92 (s, 3H), 3.38 (d, J = 6.6 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 196.6, 150.0, 148.2, 136.7, 131.4, 123.7, 120.4, 118.6, 116.5, 56.3, 39.4. LRMS (EI) Calcd for [C₁₁H₁₂O₃]⁺ 192.1, found 192.0.

6-vinyleugenol

The title compound was prepared according to Method 2.1 from 6-formyleugenol (680 mg, 3.53 mmol) and isolated as a clear colorless oil (550 mg, 81%). ¹H NMR (500 MHz, CDCl₃) δ 6.98 (dd, J = 17.8, 11.2 Hz, 1H), 6.88 (s, 1H), 6.60 (d, J = 1.2 Hz, 1H), 5.95 (ddt, J = 16.8, 10.0, 6.7 Hz, 1H), 5.79 (dd, J = 17.8, 1.1 Hz, 1H), 5.75 (s, 1H), 5.29 (dd, J = 11.2, 1.1 Hz, 1H), 5.12 – 5.03 (m, 2H), 3.88 (s, 3H), 3.32 (d, J = 6.7 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 146.6, 141.6, 137.7, 131.1, 131.0, 123.5, 118.5, 115.6, 114.7, 110.1, 56.1, 40.0. LRMS calcd for [C₁₂H₁₄O₂Na]⁺ 213.1, found 213.2.
6-formyl-isoeugenol

To a 20 mL vial was added 6-formyleugenol (552 mg, 2.87 mmol), cat. A (depicted in the synthesis scheme above, 9 mg, 0.01435 mmol, 0.005 equiv) and acetone (1.25 mL). After 1.5 hours, the reaction was diluted with EtOAc and filtered through a pad of silica. The product was isolated via column chromatography (Hx to 20% EtOAc in Hx) as a yellow solid (540 mg, 98 % yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 11.02 (s, 1H), 9.89 (s, 1H), 7.12 (d, $J = 1.7$ Hz, 1H), 7.08 (d, $J = 1.7$ Hz, 1H), 6.35 (dd, $J = 15.7$, 1.6 Hz, 1H), 6.16 (dq, $J = 15.7$, 6.6 Hz, 1H), 3.94 (s, 3H), 1.90 (dd, $J = 6.6$, 1.6 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 196.7, 150.6, 148.3, 130.1, 129.4, 125.2, 121.79, 120.4, 114.8, 56.2, 18.3. LRMS calcd for [C$_{11}$H$_{12}$O$_3$Na]$^+$ 215.1, found 215.1.

6-vinyl-isoeugenol

The title compound was prepared according to Method 2.1 from 6-formyl-isoeugenol (520 mg, 2.71 mmol) and isolated as a light yellow oil (403 mg, 78 % yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.04 – 6.89 (m, 2H), 6.79 (s, 1H), 6.33 (d, $J = 15.7$ Hz, 1H), 6.17 – 6.01 (m, 1H), 5.88 – 5.74 (m, 2H), 5.30 (dd, $J = 11.2$, 1.2 Hz, 1H), 3.90 (s, 3H), 1.86 (dd, $J = 6.6$, 1.2 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 146.7, 142.4, 131.1, 130.7, 129.7, 123.6, 123.5, 116.8, 114.9, 106.7, 106.7, 56.0, 18.3. LRMS calcd for [C$_{12}$H$_{14}$O$_2$Na]$^+$ 213.1, found 213.0.

(Table 2.4)

(E)-1-(3,4-dimethoxyphenyl)-2-(2-hydroxy-3-methoxy-5-(prop-1-en-1-yl)phenyl)propan-1-one

The title compound was synthesized according to modified Method 2.3 from 3,4-dimethoxy benzaldehyde (20 mg, 0.12 mmol) and (E)-2-methoxy-4-(prop-1-en-1-yl)-6-vinylphenol (19 mg, 0.1 mmol) at 80 °C for 24 h to give the title compound after purification (PTLC Hex:EtOAc 2:1) as a colorless oil (28.6 mg, 80%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.71 (dd, $J = 8.4$, 2.0 Hz, 1H), 7.61 (d, $J = 2.0$ Hz, 1H), 6.80 (d, $J = 8.5$ Hz, 1H), 6.72 (d, $J = 1.8$ Hz, 1H), 6.67 (d, $J = 1.8$ Hz, 1H), 6.22 (dq, $J = 15.7$, 1.6 Hz, 1H), 6.05 – 5.96 (m, 2H and OH), 5.05 (q, $J = 6.8$ Hz, 1H), 3.88 (s, 6H), 3.88 (s, 3H), 3.88 (s, 3H),
1.80 (dd, J = 6.6, 1.6 Hz, 3H), 1.46 (d, J = 6.8 Hz, 3H). $^{13}\text{C NMR}$ (126 MHz, CDCl$_3$) δ 199.6, 153.0, 148.7, 146.8, 141.2, 130.7, 130.5, 129.5, 127.6, 123.9, 123.3, 118.2, 111.0, 110.2, 106.2, 56.0, 56.0, 39.7, 18.4, 17.9. HRMS (ESI): calcd for [C$_{21}$H$_{23}$O$_5$]$^-$ 355.1545, found 355.1540.

(Table 2.4, 4e, eupomatenoid 12)

**(E)**-2-(3,4-dimethoxyphenyl)-7-methoxy-3-methyl-5-(prop-1-en-1-yl)benzofuran

(€)-1-(3,4-dimethoxyphenyl)-2-(2-hydroxy-3-methoxy-5-(prop-1-en-1-yl)phenyl)propan-1-one (28.6 mg, 0.080 mmol) was dissolved in CDCl$_3$ (0.5 mL) and trifluoroacetic acid (2 μL in 0.2 mL CDCl$_3$) was added. The mixture was kept at rt or 40 °C until complete conversion to the title compound was observed by $^1$H NMR. Purification from the linear isomer was achieved by PTLC to give the title compound (24.0 mg, 0.071 mmol, 89%). H NMR matched those previously reported (Engler, T. A.; Chai, W.; LaTessa, K. O. J. Org. Chem. 1996, 61, 9297). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.36 – 7.31 (m, 2H), 7.05 (s, 1H), 6.95 (d, J = 8.9 Hz, 1H), 6.83 (s, 1H), 6.50 (d, J = 16.4 Hz, 1H), 6.22 (dq, J = 16.0, 7.0 Hz, 1H), 4.04 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H), 2.42 (s, 3H), 1.91 (d, J = 6.6 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 151.5, 149.07 (2 × C$q$), 145.0, 142.3, 133.8, 133.2, 131.6, 124.5, 124.3, 120.0, 111.2, 110.6, 110.1, 109.3, 104.5, 56.2 (OCH$_3$), 56.1 (OCH$_3$), 56.0 (OCH$_3$), 18.6, 9.8.

(Table 2.4, 4f, eupomatenoid 16)

**(E)**-2-(4-methoxyphenyl)-7-methoxy-3-methyl-5-(prop-1-en-1-yl)benzofuran

The title compound was prepared according to modified Method 2.3 from 6-vinyl-isoeugenol (19.0 mg, 0.1 mmol). The reaction was carried out at 70 °C. After 24 hours, the solvent was removed in vacuo and replaced with 1.100 mL of 10:1 DCM:TFA. After stirring at room temperature for 4 hours, the solvent was removed in vacuo and the product was purified by preparatory TLC to obtain the product (24.6 mg, 80 % yield over 2 steps). $^1$H NMR matched those previously reported (Carroll, A. R.; Taylor, W. C. Aust. J. Chem., 1991, 44, 1627-1633) $^1$H NMR (500 MHz, CDCl$_3$) δ 7.74 (d, J = 8.9 Hz, 1H), 7.03 (s, 1H), 6.98 (d, J = 8.9 Hz, 1H), 6.82 (s, 1H), 6.49 (dd, J = 15.7, 1.3 Hz, 1H), 6.21 (dq, J = 15.7, 6.6, 1H), 4.04 (s, 1H), 3.85 (s, 1H), 2.40 (s, J = 5.9 Hz, 1H), 1.91 (dd, J = 6.6, 1.3 Hz, 1H).
(Table 2.4, 4g, eupomatenoid 17)

5-allyl-7-methoxy-2-(4-methoxyphenyl)-3-methylbenzofuran

The title compound was prepared according to modified Method 2.3 from 6-vinyleugenol (19.0 mg, 0.1 mmol). The reaction was carried out at 70 °C. After 24 hours, the solvent was removed in vacuo and replaced with 0.700 mL of 20:1 CHCl₃:TFA. After stirring at room temperature for 3 hours, the solvent was removed in vacuo and the product was purified by preparatory TLC to obtain the product (24.0 mg, 78 % yield over 2 steps). ¹H NMR matched those previously reported ([Carroll, A. R.; Taylor, W. C. Aust. J. Chem., 1991, 44, 1627-1633] ¹H NMR (500 MHz, CDCl₃) δ 7.81 (d, J = 8.9 Hz, 2H), 7.06 (d, J = 8.9 Hz, 2H), 7.00 (s, 1H), 6.70 (s, 1H), 6.11 (ddt, J = 16.8, 10.0, 6.7 Hz, 1H), 5.26 – 5.09 (m, 2H), 4.09 (s, 3H), 3.92 (s, 3H), 3.55 (d, J = 6.7 Hz, 2H).

(Table 2.4, 4h, eupomatenoid 17)

5-allyl-7-methoxy-2-(3,4-dimethoxyphenyl)-3-methylbenzofuran

The title compound was prepared according to modified Method 2.3 from 6-vinyleugenol (19.0 mg, 0.1 mmol). The reaction was carried out at 70 °C. After 24 hours, the solvent was removed in vacuo and replaced with 0.700 mL of 20:1 CHCl₃:TFA. After stirring at room temperature for 15 minutes, the solvent was removed in vacuo and the product was purified by preparatory TLC to obtain the product (27.8 mg, 82 % yield over 2 steps). ¹H NMR matched those previously reported (Anthony R. Carroll and Walter C. Taylor, Aust. J. Chem., 1991, 44, 1627-1633) ¹H NMR (500 MHz, CDCl₃) δ 13.88 – 13.83 (m, 1H), 7.36 (s, 1H), 7.35 (d, J = 9.0 Hz, 1H), 6.96 (d, J = 9.0 Hz, 1H), 6.95 (s, 1H), 6.65 (s, 1H), 6.06 (ddt, J = 17.1, 10.1, 6.7 Hz, 1H), 5.15 (d, J = 17.1 Hz, 1H), 5.11 (d, J = 10.1 Hz, 1H), 4.04 (s, 3H), 3.99 (s, 3H), 3.94 (s, 3H), 3.50 (d, J = 6.7 Hz, 2H), 2.43 (s, 3H).
2.6.5 Organometallic Synthesis

[Rh(dcpm)]$_2$Cl

To a 1 dram vial was added [Rh(COD)Cl]$_2$ (20 mg, 0.041 mmol, 1 equiv) and dcpm (66 mg, 0.162 mmol, 4 equiv). Chloroform (0.5 mL) was added and a homogenous solution was obtained. Precipitate began to form after approximately 30 seconds. Hexanes was added and the product was collected by decantation. The powder was triturated with hexanes and decanted twice. The product was obtained as an orange powder (33.6 mg, 86 % yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.08 – 3.00 (m, 4H), 2.28 – 1.05 (m, 88H). $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ -16.9 (d, $J = 110.8$ Hz). LRMS (ESI) calcd for [C$_{50}$H$_{92}$P$_4$Rh]+ 919.5, found 919.5.

[Rh(4-nitro-2-vinyl-phenolate)$_2$][(18-crown-6)K]

To a 1 dram vial was added [Rh(COD)OMe]$_2$ (10 mg, 0.0207 mmol, 1 equiv), 4-nitro-2-vinylphenol (13.6 mg, 0.0826 mmol, 4 equiv), $^4$BuOK (4.6 mg, 0.0414 mmol, 2 equiv), and 18-crown-6 (10.9 mg, 0.0414 mmol, 2 equiv). THF (0.650 mL) was added and the solution was shaken for 5 minutes. Hexanes was added to afford a yellow solid which was decanted, triturated with hexanes, decanted again, and finally dried under vacuum. The product was obtained as a yellow solid (21 mg, 67% yield). X-ray quality crystals were obtained after two rounds of crystallization from saturated THF/Hexanes solutions. $^1$H NMR (600 MHz, $d_8$-THF) $\delta$ 7.78 (dd, $J = 9.0$, 2.8 Hz, 2H), 7.67 (d, $J = 2.8$ Hz, 2H), 6.19 (d, $J = 9.0$ Hz, 2H), 3.65 (dd, $J = 12.1$, 8.0 Hz, 2H), 3.61 (s, 24H), 3.50 (dd, $J = 12.1$, 2.6 Hz, 2H), 2.08 (d, $J = 8.0$ Hz, 2H). $^{13}$C NMR (126 MHz, $d_8$-THF) $\delta$ 180.10, 136.31, 135.73, 126.11, 123.06, 116.42, 75.34 (d, $J = 12.0$ Hz), 71.27, 58.06 (d, $J = 15.4$ Hz). LRMS (ESI) calcd for [C$_{16}$H$_{12}$N$_2$O$_6$Rh]$^-$ 431.0, found 431.0.

[Rh(dcpm)]$_2$[Rh(4-nitro-2-vinyl-phenolate)$_2$]

To a 1 dram vial was added [Rh(COD)OMe]$_2$ (10 mg, 0.0207 mmol, 1 equiv), dcpm (16.9 mg, 0.0413 mmol, 2 equiv), and 4-nitro-2-vinylphenol (6.8 mg, 0.0413 mmol, 2 equiv). THF (0.400 mL) was added
and the solution was heated to 60 °C until the reaction became homogeneous. The solution was cooled to room temperature and filtered into a separate vial. Hexanes (2 mL) was added to the solution and then the vial was sealed and placed in a -30 °C freezer for 24 hours. The precipitate was decanted, triturated with hexanes, decanted again, and finally dried under reduced pressure. The product was obtained as an orange powder (35.0 mg, 75 % yield) contaminated with approximately 10% of [Rh(dcpm)\(\text{Cl}\)]\(\text{+}\)(4-nitro-2-vinylphenolate). Spectroscopic data were very similar to [Rh(dcpm)]\(\text{Cl}\) and [Rh(4-nitro-2-vinyl-phenolate)\(\text{2}\)]\([(18\text{-crown-6})\text{K}]\).

\[\text{1H NMR (600 MHz, } d_8\text{-THF)} \delta 7.77 (dd, \text{ } J = 9.1, 2.8 \text{ Hz, } 2H), 7.66 (d, \text{ } J = 2.8 \text{ Hz, } 2H), 6.13 (d, \text{ } J = 9.1 \text{ Hz, } 2H), 3.64 \sim 3.56 (m, 2H), 3.49 (dd, \text{ } J = 12.1, 2.2 \text{ Hz, } 1H), 3.26 \sim 3.20 (m, 4H), 2.19 (d, \text{ } J = 11.8 \text{ Hz, } 8H), 2.05 (d, \text{ } J = 7.9 \text{ Hz, } 2H), 1.97 \sim 1.20 (m, 80H).\]

\[\text{13C NMR (126 MHz, } d_8\text{-THF)} \delta 181.30, 136.69, 136.47, 126.91, 123.72, 116.88, 75.92 (d, \text{ } J = 11.9 \text{ Hz), } 58.52 (d, \text{ } J = 15.2 \text{ Hz), } 38.41 (d, \text{ } J = 5.1 \text{ Hz), } 31.46, 30.10, 29.23 \sim 28.97 (m), 28.76 \sim 28.63 (m), 27.76 (s).\]

\[\text{31P NMR (162 MHz, } d_8\text{-THF)} \delta -17.2 (d, \text{ } J = 110.7 \text{ Hz).} \]

\[\text{LRMS (ESI) calcd for } [C_{50}H_{92}P_{4}Rh]^{\text{+}} 919.5, \text{ found } 919.5; \text{ calcd for } [C_{16}H_{12}N_{2}O_{6}Rh]^{-} 431.0, \text{ found } 431.0.\]

\[\text{[Rh(dcpm)(COD)]BF}_4\]

A solution of dcpm (20 mg, 0.0493 mmol, 1 equiv) in DCM (1.5 mL) was added dropwise to a solution of [Rh(COD)\(\text{2}\)]\(\text{BF}_4\) (20 mg, 0.0493 mmol, 1 equiv) in DCM (1.5 mL) in a 20 mL vial. The resulting solution was filtered and the solvent was removed under reduced pressure. The solid was triturated with hexanes and decanted. The solid was dissolved in chloroform and THF and then precipitated with hexanes. The product was isolated as an orange powder (25 mg, 69 % yield). \[\text{1H NMR (400 MHz, CDCI}_3) \delta 5.37 (s, 4H), 3.28 (t, \text{ } J = 9.9 \text{ Hz, } 2H), 2.33 (s, 8H), 2.18 \sim 1.13 (m, 44H).\]

\[\text{31P NMR (162 MHz, CCl}_3) \delta -27.1 (d, \text{ } J = 125.0 \text{ Hz).} \]

\[\text{LRMS (ESI) calcd for } [C_{33}H_{58}P_{2}Rh]^{\text{+}} 619.3, \text{ found } 619.2.\]

\[\text{[Rh(dcpm)(4-nitro-2-vinylphenolate)]}\]

To a 1 dram vial was added [Rh(dcpm)(COD)]\(\text{BF}_4\) (6.4 mg, 0.0089 mmol, 1 equiv.), 4-nitro-2-vinylphenol (1.5 mg, 0.0089 mmol, 1 equiv.) and \(\text{^tBuOK (1.0 mg, 0.0089 mmol). } d_8\text{-THF (0.65 mL) was added and a white precipitate formed (KBF}_4). The solution was transferred to an NMR tube and
sealed with a septum and parafilm. The product was formed in ca. 98% NMR yield. Repeating this experiment on larger scale lead to NMR yields that varied from 90-99%. Attempts to crystallize this compound were unsuccessful. The coupling of the carbons of the olefin and both Rh and P in the $^{13}$C NMR are characteristic of the title compound.  

$^{1}$H NMR (400 MHz, $d_8$-THF) δ 7.69 (d, $J = 9.2$ Hz, 1H), 7.61 (s, 1H), 6.08 (d, $J = 9.2$ Hz, 1H), 5.49 – 5.40 (m, 1H), 4.63 (d, $J = 14.8$ Hz, 1H), 4.51 – 4.42 (m, 1H), 3.02 – 2.72 (m, $J = 27.5$ Hz, 2H), 2.44 – 0.71 (m, 44H).  

$^{13}$C NMR δ 135.44, 132.83, 130.08, 127.17, 124.62, 118.03, 94.94 – 94.64 (m), 78.49 – 78.10 (m), 32.60, 31.7 – 31.3 (m), 29.72, 28.92 (d, $J = 12.0$ Hz), 27.84.  

$^{31}$P NMR (162 MHz, CDCl$_3$) δ 0.41 (dd, $J = 125$, 92.3 Hz), -27.15 (dd, $J = 147.9$, 92.3 Hz).

[Rh(dcpm)(4-nitro-2-vinylphenolate)(hydrocinnamaldehyde)]

To the NMR sample from the synthesis of [Rh(dcpm)(4-nitro-2-vinylphenolate)] (above) was added 5 μL of hydrocinnamaldehyde. The title compound could be observed in small quantities (ca. 10 %) transiently before being converted to the hydroacylation product below. Larger quantities could be formed if excess 4-nitro-2vinylphenol and aldehyde were added to establish a steady state concentration of the title compound. However, due to the high concentration of reagents required to form this complex, we could only characterize it by $^{31}$P NMR. We assign the structure as the title compound by comparison of the chemical shift and coupling constants to [Rh(dcpm)(4-nitro-2-vinylphenolate)]. Both the title compound and [Rh(dcpm)(4-nitro-2-vinylphenolate)] display a $^{31}$P peak at about 1 ppm with a coupling constant to Rh of ca. 125 Hz. We assign this peak as the phosphine trans to the phenoxide. A new peak at -9.9 ppm is present in the title compound which we assign as the phosphine trans to the aldehyde. $^{31}$P NMR (162 MHz, CDCl$_3$) δ 1.7 (dd, $J = 126$, 69 Hz), -9.9 (dd, $J = 117$, 69 Hz).

[Rh(dcpm)(COD)][4-nitro-2-(3-oxo-5-phenylpentan-2-yl)phenolate]

The title compound was synthesized according to the same procedure for [Rh(dcpm)(4-nitro-2-vinylphenolate)(hydrocinnamaldehyde)] except that a large excess of hydrocinnamaldehyde (100 μL) was
added which resulted in immediate hydroacylation at room temperature (ca. 80% yield). $^{31}$P analysis showed a doublet at -27.1 ppm indicative of the [Rh(dcpm)(COD)]$^{+}$ fragment based on analogy to [Rh(dcpm)(COD)]BF$_4$. Analysis of the reaction mixture by ESI MS confirmed formation of [Rh(dcpm)(COD)]$^{+}$ and the anion of the hydroacylation product. As well, a dimer of the hydroacylation product and its phenolate was observed by ESI MS when both excess aldehyde and olefin were added. $^{31}$P NMR (162 MHz, CDCl$_3$) δ -26.95 (d, $J = 125.7$ Hz).

LRMS (ESI) calcd for [C$_{33}$H$_{58}$P$_2$Rh]$^+$ 619.3, found 619.2. Calcd for [C$_{17}$H$_{16}$NO$_4$]- 298.1, found 298.3. Calcd for [C$_{34}$H$_{33}$N$_2$O$_8$]- 597.2, found 597.4.

2.7 References


15. Coordinatively saturated acyl-RhIII-hydrides must dissociate a ligand to undergo decarbonylation, and this dissociation is often rate limiting. For example, see ref 15a.
21. Benzofurans have been previously synthesized by TFA mediated cyclocondensation of α-(2-hydroxyaryl)ketones, see refs 7 and 23a.


25. We expected catalyst 11 to exhibit a faster rate than the optimized reaction because none of the Rh would be sequestered as the double salt of 4 and 9. The fact that 11 provides only a slightly higher initial TOF than the optimized reaction is likely a result of the low solubility of the t-BuOK/vinylphenol mixture and the lack of stirring during NMR analysis.


29. To our knowledge, there are only two examples of olefin hydroacylation where reductive elimination has been ruled out as the rate limiting step, see: a) Coulter, M. C.; Dornan, P. K.; Dong, V. M. J. Am. Chem. Soc. 2009, 131, 6932; b) ref 2k.

30. An intermolecular KIE experiment is appropriate for this system given that C-H bond cleavage is the first step in the catalytic cycle and our observed catalyst resting states ([Rh(dcpm)(vinylphenolate)]) and [Rh(dcpm)(vinylphenolate)(aldehyde)]) directly precede aldehyde activation. For a discussion on KIE’s in metal catalysis, see: a) Simmons, E. M.;


33. For use of a Hammett plot to study the mechanism of Rh(dppp)+ catalyzed aldehyde decarbonylation, see ref. 18.


36. Branched-selective migratory insertion is generally fast and reversible for olefin hydroacylation whereas linear-selective insertion has a higher barrier, see: a) ref. 16b; b) ref. 2d; c) ref. 15g; For a related example of the hydroformylation reaction, see: d) Casey, C. P.; Petrovich, L. M. *J. Am. Chem. Soc.* **1995**, *117*, 6007.


3 Ruthenium-Catalyzed Ketone Hydroacylation*

3.1 Introduction

The γ-butyrolactone core occurs in more than fourteen thousand natural products\(^1\) and it is a useful building block in organic synthesis.\(^2\) To prepare enantioenriched lactones, our laboratory has been developing rhodium-catalyzed hydroacylation of ketones using substrates such as 1 and 2.\(^3\) These rhodium catalysts, however, fail to cyclize 1,4-ketoaldehydes such as 3 to generate the corresponding γ-butyrolactones (Figure 3.1).\(^4\),\(^5\) Instead, significant decarbonylation occurs, presumably due to the conformational flexibility of these substrates. Poor reactivity and chemoselectivity has limited the use of other catalysts in this transformation, including N-heterocyclic carbenes,\(^6\),\(^6b\) ruthenium hydrides such as RuHCl(CO)(PPh\(_3\))\(_3\), \(^6c\) and iridium hydrides.\(^6d\) Enantioselectivity is difficult to achieve, and only one moderately enantioselective (43-84\% ee) Tishchenko-type cyclization of related 1,5-ketoaldehydes has been reported which uses stoichiometric SmI\(_2\) and a chiral auxiliary.\(^6c\) These results highlight a need for hydroacylation catalysts that operate by alternative mechanisms. To address these challenges, I considered that a bifunctional ruthenium-hydride catalyst could be applied to achieve a novel chemo- and enantio-selective hydroacylation of 1,4-dioxygenated substrates.\(^7\)

![Figure 3.1 Scope and limitations of cationic Rh catalysts for ketone hydroacylation.](image)

By applying an asymmetric transfer hydrogenation (ATH) catalyst,\(^8\) the 1,4-ketoaldehyde substrate, which is sensitive to decomposition via aldol type pathways, can be replaced with a

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stable 1,4-ketoalcohol that undergoes in situ oxidation to the requisite aldehyde (Figure 3.2). Krische and coworkers have demonstrated diene and alkyne hydroacylation from the alcohol oxidation state by applying transfer hydrogenation conditions. Hydroacylation of 1,4-ketoalcohol 4 could occur by initial asymmetric reduction of the ketone to afford diol 5. Oxidation of the primary alcohol would generate a 1,4-hydroxylaldehyde 6 which could cyclize to hemiacetal 7. Finally, irreversible oxidation of 7 would yield the desired γ-butyrolactone 8. In contrast to rhodium-catalyzed hydroacylations, this mechanistic scenario circumvents activation of the aldehyde C–H bond and therefore avoids competing aldehyde decarbonylation.

Figure 3.2 Hydroacylation of a 1,4-ketoalcohol using a bifunctional Ru-hydride catalyst.

3.2 Intramolecular Ketone Hydroacylation

With this mechanism in mind, Noyori’s ATH catalyst was applied in this ketone hydroacylation. To test this hypothesis, 4-hydroxybutyrophenone 4a was combined with 5% I and 1.2 equivalents of a hydrogen acceptor (acetone) (Figure 3.2). A number of solvents were evaluated and the use of ethyl acetate (EtOAc) led to the formation of γ-phenyl-γ-butyrolactone 8a to in 92% yield and 91% ee in favor of the R stereoisomer. In contrast to reports of RuHCl(CO)(PPh₃)₆ and iridium hydrides in ketone hydroacylation, this transformation proceeds at 22 °C and no aldehyde dimerization or over-oxidation products are observed.
This transformation was monitored by \(^1\)H NMR spectroscopy and sigmoidal reaction profile was observed (Figure 3.3).\(^{17}\) When the reaction was initiated with three equivalents of the co-product, iso-propanol (\(^i\)PrOH), the reaction rate increased and the induction period was nearly eliminated. To explain this autocatalytic behavior,\(^{18}\) the \(^i\)PrOH, which is generated via reduction of acetone during hydroacylation, likely promotes formation of the ruthenium-hydride catalyst and accelerates the ATH step. A larger excess of \(^i\)PrOH results in formation of a reductive cyclization product (2-phenyl-tetrahydrofuran) while excess acetone inhibits the reaction.

**Figure 3.3** Time course data for hydroacylation of 4-hydroxybutyrophenone with 5% I and different amounts of \(^i\)PrOH and acetone in C\(_6\)D\(_6\).

The active catalyst can also be prepared *in situ* by dehydrochlorination of the commercially available ruthenium salt \([(R,R)-TsDPEN](mesitylene)RuCl\) (II). Although the aldehyde intermediate 6 is likely sensitive to base-induced decomposition *via* aldol pathways, *in situ* NMR monitoring of the reaction (*vide supra*) with I indicated that this aldehyde accounts for less than 1% of the substrate distribution during catalysis. Thus, a mixture of II and sodium tert-butoxide (\(^t\)BuONa) produced the desired \(\gamma\)-butyrolactone 8a in 90% yield with 93% ee (Table 3.1, entry 1). Increasing the reaction scale to 3 mmols (0.5 grams) gave similar results.
With this convenient protocol, a range of 4-hydroxybutyrophenone derivatives\textsuperscript{19a} were oxidized to the corresponding chiral lactones (Table 3.1). Substitution at the 3- and 4-positions of the phenyl group with electron donating or withdrawing groups (entries 2-6) resulted in yields and ee’s ranging from 70-91% and 87-92%, respectively. Substrates with low oxidation potentials, such as 4-methoxyacetophenone, are known to undergo ATH in moderate enantioselectivity when \textsuperscript{t}PrOH is used as a hydrogen donor due to partial racemization of the product via reversible dehydrogenation.\textsuperscript{8,19a} In contrast, 4-methoxy-substituted hydroxyketone (entry 6) underwent hydroacylation with relatively high enantioselectivity (92% ee). This result suggests that either the lactol formation or lactonization enforces greater kinetic control on the stereodetermining hydrogenation than in conventional ATH.\textsuperscript{20} Other substituents that are capable of forming $\pi$-interactions with the catalyst,\textsuperscript{21} such as 2-naphthyl, 2-furyl, and alkynyl\textsuperscript{19b} (entries 7-10), gave good results as well (65-79% yield and 87-91% ee). In general, performing the reaction at 0°C led to higher enantioselectivity and II furnished products in similar yields but 2-16% higher ee than I.\textsuperscript{22}

\begin{table}[h]
\centering
\caption{Enantioselective hydroacylation of 1,4-ketoalcohols.} \label{table:hydroacylation}
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Entry & \# & R & Isolated Yield (\%)\textsuperscript{a} & ee (\%) & \# \\
\hline
1 & 4a & Ph & 90 (92\textsuperscript{b}) & 93 (93\textsuperscript{b}) & 8a \\
2 & 4b & 3-Cl-Ph & 83 & 90 & 8b \\
3 & 4c & 3-OMe-Ph & 82 & 91 & 8c \\
4\textsuperscript{c} & 4d & 4-Br-Ph & 91 & 87 & 8d \\
5 & 4e & 4-F-Ph & 84 & 87 & 8e \\
6\textsuperscript{c,d} & 4f & 4-OMe-Ph & 70 & 92 & 8f \\
7\textsuperscript{d} & 4g & 2-naphthyl & 78 & 90 & 8g \\
8\textsuperscript{e} & 4h & 2-furyl & 77 & 87 & 8h \\
9\textsuperscript{c,d,e} & 4i & Ph-C\equiv-C & 65 & 91 & 8i \\
10\textsuperscript{c,d,e} & 4j & nBu-C\equiv-C & 79 & 90 & 8j \\
\hline
\end{tabular}
\begin{flushleft}
\textsuperscript{a}0.3 mmol scale unless otherwise noted; \textsuperscript{b}3 mmol scale (0.5 g); \textsuperscript{c}0 °C; \textsuperscript{d}3 d; \textsuperscript{e}10\% II/BuONa
\end{flushleft}
\end{table}
This method can be applied to cyclize 1,5-hydroxyketones to δ-valerolactones (Table 3.2), despite the greater ring strain in six-membered lactones compared to five-membered lactones (approx. 2.4 kcal/mol\(^2\)). Substrates with aryl substituents performed similarly to the 5-membered ring analogues and gave excellent results (entries 1-4). Yields ranged from 65-81% and high levels of enantioselectivity were obtained for both electron rich and electron deficient substrates (entries 2 and 3, 96% and 95% ee, respectively). While a benzofuryl substituted ketone was cyclized in good yield (entry 5), furyl and alkynyl substrates (entries 6-8) were transformed with poor efficiency.\(^2\) However, introducing a gem-dimethyl group on the backbone (entries 9-11) promoted cyclization of these otherwise challenging substrates in yields up to 98% and ee’s of 90%.

Table 3.2 Enantioselective hydroacylation of 1,5-ketoalcohols.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R(_1)</th>
<th>R(_2)</th>
<th>Isolated Yield (%)(^a)</th>
<th>ee (%)</th>
<th>#</th>
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<tbody>
<tr>
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<td>81</td>
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<td>96</td>
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<tr>
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<td>3-OMe-Ph</td>
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<td>95</td>
<td>8m</td>
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<tr>
<td>4(^b)</td>
<td>4n</td>
<td>4-Me-Ph</td>
<td>73</td>
<td>91</td>
<td>8n</td>
</tr>
<tr>
<td>5</td>
<td>4o</td>
<td>2-benzofuryl</td>
<td>65</td>
<td>90</td>
<td>8o</td>
</tr>
<tr>
<td>6(^e)</td>
<td>4p</td>
<td>2-furyl</td>
<td>&lt;10</td>
<td>n.d.</td>
<td>8p</td>
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<tr>
<td>7(^d,e)</td>
<td>4q</td>
<td>&quot;Bu-C(\equiv)C</td>
<td>42</td>
<td>86</td>
<td>8q</td>
</tr>
<tr>
<td>8(^e)</td>
<td>4r</td>
<td>Ph-C(\equiv)C</td>
<td>32</td>
<td>86</td>
<td>8r</td>
</tr>
<tr>
<td>9</td>
<td>4s</td>
<td>2-furyl</td>
<td>Me</td>
<td>98</td>
<td>8s</td>
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<td>4t</td>
<td>&quot;Hex-C(\equiv)C</td>
<td>Me</td>
<td>55</td>
<td>8t</td>
</tr>
<tr>
<td>11</td>
<td>4u</td>
<td>Ph-C(\equiv)C</td>
<td>Me</td>
<td>87</td>
<td>90</td>
</tr>
</tbody>
</table>

\(^a\)0.3 mmol scale unless otherwise noted; \(^b\)0 °C; \(^c\)3 d; \(^d\)10% [Ru-B] and 'BuONa; \(^e\)NMR yield

Finally, the ruthenium catalysts were compared to the cationic rhodium catalysts previously used to cyclize 7-membered ring precursors 1 and 2-ketobenzaldehydes 2.\(^3\)\(^a\), \(^3\)c For
In this study, I was chosen as the catalyst to avoid base-induced aldol reactions and acetone was not added because 1 and 2 are already at the aldehyde oxidation state. While derivatives of 1 and other 7 or 8-membered ring precursors were resistant to hydroacylation, a 2-ketobenzaaldehyde derivative 2a (Scheme 3.2) underwent efficient hydroacylation to generate the corresponding phthalide 9a in 85% yield and 90% ee. Thus, the rhodium and ruthenium catalysts provide complementary scope and mechanistic pathways for asymmetric ketone hydroacylation.

![Scheme 3.2 Hydroacylation of a 2-ketobenzaldehyde](image)

### 3.3 Conclusions

A novel strategy for asymmetric hydroacylation of 1,4- and 1,5-ketoalcohols was developed. Using a bifunctional ATH catalyst is crucial for obtaining reactivity at room temperature, chemoselectivity for ketone hydroacylation over aldehyde dimerization, and high enantioselectivity. Although this transformation is oxidative overall, the reaction is autocatalytic in a reductant (iPrOH) and inhibited by excess oxidant (acetone). γ-Butyrolactones, δ-valerolactones, and phthalides are accessible by this method.
3.4 Supporting Information

3.4.1 Substrate Preparation

Method 3.1 MnO₂ oxidation of diols

\[
\text{OH} \quad \text{OH} \quad \text{MnO}_2, \text{rt} \quad \text{OH} \quad \text{OH}
\]

To a stirring solution of diol (1 equiv) in acetone at room temperature was added activated MnO₂ (2 equiv). Additional activated MnO₂ (4 equiv) was added every hour for 4 hours, and then the solution was stirred for a total of 24 hours. The solids were removed via filtration and the organic solution was concentrated \textit{in vacuo}. The crude residue was purified \textit{via} flash chromatography.

Method 3.2 Acylation of γ-butyrolactone and decarboxylation

\[
\begin{align*}
\text{R}^+\text{Cl} + \text{LDA} & \overset{i) \text{LDA}}{\longrightarrow} \text{R}^+\text{O} \quad \text{LDA} \\
& \overset{\text{ii) HCl}}{\longrightarrow} \text{R}^+\text{O} \quad \text{HCl}
\end{align*}
\]

Acylation of γ-butyrolactone was carried out according to a modified literature procedure.²⁶ To a flame-dried round-bottom flask equipped with a stir bar and rubber septum was added THF and LDA (2.0 M in heptane, 2.1 equiv), and the flask was immersed in a -78 °C dry ice/acetone bath. Lactone (1 equiv) was added dropwise \textit{via} syringe, and the solution was stirred for 1 hour. A solution of the benzoylchloride (1 equiv) in THF was added \textit{via} syringe and the solution was stirred for 30 minutes and then quenched at with 1 M HCl\textit{(aq)}. Ethyl acetate was added and the solution was washed with water and then brine. The organic layer was separated, dried with MgSO₄, and concentrated \textit{in vacuo} to give the β-ketoester that was used without further purification.

The crude β-ketoester was transferred to a small round bottom flask equipped with a stir bar and condenser. 1:1:1 THF:MeOH:H₂O was added followed by a few drops of conc. HCl, and the solution was refluxed until full conversion of the β-ketoester was observed by TLC. The solution was cooled to room temperature, diluted with ethyl acetate and washed with water then
brine. The organic layer was separated, dried with MgSO₄, and concentrated *in vacuo*. The crude residue was purified *via* flash chromatography.

**Method 3.3** Addition of furyl-lithium derivatives to lactones

According to a modified literature procedure: to a flame-dried round-bottom flask equipped with a stir bar and rubber septum was added THF and the furan and the flask was immersed in an ice bath. nBuLi was added dropwise and the reaction was stirred for 0.5 h. The ice bath was replaced with a dry ice/acetone bath, and then the lactone was added dropwise. The reaction was stirred for 1 h and then warmed to room temperature and quenched with brine. The organic layer was separated, dried with MgSO₄, and concentrated *in vacuo*. The crude residue was purified *via* flash chromatography.

(Note: Some of the hydroxyketones cyclise to appreciable amounts of the hemiketal isomer after a few hours.)

*(Table 3.1, 4a)*

**4-Oxo-4-phenyl-1-butanol**

The title compound was synthesized according to Method 3.1 from 4-phenylbutan-1,4-diol (2.000 g, 12.07 mmol, synthesized according to ref. 28) to give the title compound as a clear colourless oil (1.050 g, 53%) after column chromatography (gradient of 9:1 → 7:3 hexanes:ethyl acetate eluent). ¹H NMR data were consistent with those previously reported (ref. 29). ¹H NMR (400 MHz, CDCl₃) δ 8.02 – 7.93 (m, 2H), 7.60 – 7.53 (m, 1H), 7.50 – 7.42 (m, 2H), 3.74 (t, *J* = 5.9 Hz, 2H), 3.13 (t, *J* = 7.0 Hz, 2H), 2.20 (s, *J* = 15.2 Hz, 1H), 2.06 – 1.97 (m, 2H).
(Table 3.1, 4b)

4-Oxo-4-(3-chlorophenyl)-1-butanol

The title compound was synthesized according to Method 3.2 from γ-butyrolactone (0.767 mL, 10 mmol) and 3-chlorobenzoylchloride (1.28 mL, 10 mmol) to give the title compound as a light yellow oil (0.521 g, 26% over 2 steps) after column chromatography (gradient 9:1 → 3:2 hexanes:ethyl acetate eluent). $^{1}$H NMR (300 MHz, CDCl$_3$) δ 7.97 – 7.92 (m, 1H), 7.89 – 7.82 (m, 1H), 7.57 – 7.50 (m, 1H), 7.45 – 7.37 (m, 1H), 3.75 (t, $J$ = 6.1 Hz, 2H), 3.11 (t, $J$ = 7.0 Hz, 2H), 2.07 – 1.97 (m, 2H), 1.75 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 199.06, 138.37, 134.93, 133.00, 129.92, 128.20, 126.13, 62.11, 35.30, 26.71; HRMS (ESI) Calcd. for [C$_{10}$H$_{12}$Cl$_{1}$O$_{2}$]$^+$ 199.05258, found 199.05295.

(Table 3.1, 4c)

4-Oxo-4-(3-methoxyphenyl)-1-butanol

The title compound was synthesized according to Method 3.2 from γ-butyrolactone (0.54 mL, 7.12 mmol) and 3-methoxybenzoylchloride (1.00 mL, 7.12 mmol) to give the title compound as a light yellow oil (0.363 g, 29% over 2 steps) after column chromatography (gradient 9:1 → 3:2 hexanes:ethyl acetate eluent). $^{1}$H NMR (400 MHz, CDCl$_3$) δ 7.58 – 7.51 (m, 1H), 7.51 – 7.46 (m, 1H), 7.35 (t, $J$ = 7.9 Hz, 1H), 7.09 (ddd, $J$ = 8.2, 2.7, 0.9 Hz, 1H), 3.84 (s, 3H), 3.78 – 3.68 (m, 2H), 3.10 (t, $J$ = 6.9 Hz, 2H), 2.09 – 1.91 (m, 2H), 1.81 – 1.72 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 200.27, 159.80, 138.19, 129.55, 120.71, 119.57, 112.29, 62.30, 55.41, 35.38, 26.94; HRMS (ESI) Calcd. for [C$_{11}$H$_{15}$O$_{3}$]$^+$ 195.10212, found 195.10249.

(Table 3.1, 4d)

4-Oxo-4-(4-bromophenyl)-1-butanol

The title compound was synthesized according to Method 3.2 from γ-butyrolactone (0.75 mL, 9.83 mmol) and 4-bromobenzoylchloride (1.962 g, 8.94 mmol) to give the title compound as a white solid (0.589 g, 28% over 2 steps) after column chromatography (3:2 hexanes:ethyl acetate eluent). $^{1}$H NMR (400 MHz, CDCl$_3$) δ 7.87 – 7.77 (m, 2H), 7.64 – 7.54 (m, 2H), 3.72 (t, $J$ = 6.0 Hz, 2H), 3.07 (t, $J$...
= 7.0 Hz, 2H), 2.05 – 1.93 (m, 2H), 1.76 (s, 1H); \(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta\) 199.35, 135.52, 131.88, 129.58, 128.25, 62.13, 35.15, 26.75; \(\text{HRMS}\) (ESI) Calcd. for [C\(_{10}\)H\(_{12}\)Br\(_2\)O\(_2\)]\(^+\) 243.00207, found 243.00196.

(Table 3.1, 4e)

4-Oxo-4-(4-fluorophenyl)-1-butanol

The title compound was synthesized according to Method 3.2 with the exception that methyl-4-fluorobenzoate was used instead of 4-fluorobenzylochloride, only 1.1 equivalents of LDA was used, and the reaction was stirred for 1 hour at -78°C instead of 30 minutes. The compound was prepared from \(\gamma\)-butyrolactone (1.00 mL, 13.11 mmol) and methyl-4-fluorobenzoate (1.695 mL, 13.11 mmol) to give the title compound as a clear colourless oil (0.6972 g, 29% over 2 steps) after column chromatography (3:2 hexanes:ethyl acetate eluent). \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 8.10 – 7.92 (m, 2H), 7.21 – 7.02 (m, 2H), 3.73 (t, \(J = 6.1\) Hz, 2H), 3.10 (t, \(J = 7.0\) Hz, 2H), 2.66 (s, 1H), 2.08 – 1.92 (m, 2H); \(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta\) 198.97, 165.68 (d, \(J = 254.7\) Hz), 133.20 (d, \(J = 3.0\) Hz), 130.67 (d, \(J = 9.3\) Hz), 115.61 (d, \(J = 21.9\) Hz), 61.93, 35.06, 26.85; \(\text{HRMS}\) (ESI) Calcd. for [C\(_{10}\)H\(_{12}\)F\(_1\)O\(_2\)]\(^+\) 183.08213, found 183.08278.

(Table 3.1, 4f)

4-Oxo-4-(4-methoxyphenyl)-1-butanol

The title compound was synthesized according to Method 3.2 from \(\gamma\)-butyrolactone (0.769 mL, 10.00 mmol) and 4-methoxybenzylochloride (1.354 mL, 10.00 mmol) to give the title compound as a yellow solid (0.553 g, 29% over 2 steps) after column chromatography (gradient 3:2 → 2:3 hexanes:ethyl acetate eluent). \(^1\text{H NMR}\) data were consistent with those previously reported (ref. 29). \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 8.07 – 7.85 (m, 2H), 7.02 – 6.85 (m, 2H), 3.87 (s, 3H), 3.78 – 3.67 (m, 2H), 3.11 – 3.06 (m, 2H), 2.08 (s, 1H), 2.05 – 1.96 (m, 2H).
4-Oxo-4-(2-naphthyl)-1-butanol

The title compound was synthesized according to Method 3.2 from γ-butyrolactone (0.538 mL, 7.00 mmol) and 2-naphthoylchloride (1.334 g, 7.00 mmol) to give the title compound as a white solid (0.610 g, 41% over 2 steps) after column chromatography (3:2 → 2:3 hexanes:ethyl acetate eluent). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.51 (s, 1H), 8.10 – 8.02 (m, 1H), 7.96 (dd, $J$ = 8.0, 0.7 Hz, 1H), 7.89 (t, $J$ = 8.1 Hz, 2H), 7.65 – 7.50 (m, 2H), 3.85 – 3.73 (m, 2H), 3.28 (t, $J$ = 6.9 Hz, 2H), 2.16 – 2.01 (m, 2H), 1.84 (t, $J$ = 4.8 Hz, 1H); $^{13}$C NMR (101 MHz, cdcl$_3$) δ 200.44, 135.62, 134.18, 132.52, 129.80, 129.57, 128.47, 128.46, 127.77, 126.78, 123.84, 62.40, 35.38, 27.06; HRMS (ESI) Calcd. for [C$_{14}$H$_{15}$O$_2$]$^+$ 215.10720, found 215.10646.

4-Oxo-4-(2-furyl)-1-butanol

The title compound was synthesized according ref. 30. $^1$H NMR data were consistent with those previously reported (ref. 30). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.62 – 7.55 (m, 1H), 7.25 – 7.19 (m, 1H), 6.56 – 6.50 (m, 1H), 3.72 (t, $J$ = 5.8 Hz, 2H), 2.98 (t, $J$ = 7.1 Hz, 2H), 2.23 (d, $J$ = 24.2 Hz, 1H), 2.06 – 1.94 (m, 2H).

4-Oxo-4-(2-phenylethynyl)-1-butanol

The title compound was synthesized according ref. 31. $^1$H NMR data were consistent with those previously reported (ref. 31). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.61 – 7.53 (m, 2H), 7.49 – 7.34 (m, 3H), 3.72 (t, $J$ = 6.2 Hz, 2H), 2.82 (t, $J$ = 7.1 Hz, 2H), 2.08 – 1.94 (m, 3H).

4-Oxo-4-(2-butylethynyl)-1-butanol

The title compound was synthesized according ref. 31. $^1$H NMR data were consistent with those previously reported (ref. 31). $^1$H NMR (400 MHz, CDCl$_3$) δ 3.72 – 3.61 (m, 2H), 2.68 (t, $J$ = 7.1
Hz, 2H), 2.37 (t, \(J = 7.1\) Hz, 2H), 1.99 – 1.80 (m, 3H), 1.64 – 1.52 (m, 2H), 1.52 – 1.36 (m, 2H), 0.94 (t, \(J = 7.3\) Hz, 3H).

(Table 3.2, 4k)

**5-Oxo-5-phenyl-1-pentanol**

The title compound was synthesized according to Method 3.1 from 5-Phenyl-1,5-pentanediol (1.802 g, 10.00 mmol, synthesized according to ref. 28) to give the title compound as a colourless oil (1.286 g, 71%) after column chromatography (gradient of 7:3 → 1:1 hexanes:ethyl acetate eluent). ¹H NMR data were consistent with those previously reported (ref. 8).

¹H NMR (200 MHz, CDCl₃) δ 8.04 – 7.90 (m, 2H), 7.64 – 7.31 (m, 3H), 3.68 (t, \(J = 5.9\) Hz, 2H), 3.04 (t, \(J = 7.0\) Hz, 2H), 1.96 – 1.49 (m, 5H).

(Table 3.2, 4l)

**5-Oxo-5-(4-chlorophenyl)-1-pentanol**

The title compound was synthesized according to Method 3.2 from δ-valerolactone (0.742 mL, 8.00 mmol) and 4-chlorobenzoyl chloride (1.026 mL, 8.00 mmol) to give the title compound as a yellow solid (0.978 g, 57% over 2 steps) after column chromatography (3:2 → 2:3 hexanes:ethyl acetate eluent). ¹H NMR data were consistent with those previously reported (ref. 29).

¹H NMR (500 MHz, CDCl₃) δ 7.91 (d, \(J = 8.7\) Hz, 2H), 7.44 (d, \(J = 8.7\) Hz, 2H), 3.68 (s, 2H), 3.00 (t, \(J = 7.1\) Hz, 2H), 1.88 – 1.80 (m, 2H), 1.71 – 1.62 (m, 2H), 1.55 (s, 1H).

(Table 3.2, 4m)

**5-Oxo-5-(3-methoxyphenyl)-1-pentanol**

The title compound was synthesized according to Method 3.2 from δ-valerolactone (0.742 mL, 8.00 mmol) and 3-methoxybenzoyl chloride (1.120 mL, 8.00 mmol) to give the title compound as a colourless oil (0.758 g, 45% over 2 steps) after column chromatography (3:2 → 2:3 hexanes:ethyl acetate eluent). ¹H NMR data were consistent with those previously reported (ref. 29).

¹H NMR (500 MHz, CDCl₃) δ 7.91 (d, \(J = 8.7\) Hz, 2H), 7.44 (d, \(J = 8.7\) Hz, 2H), 3.68 (s, 2H), 3.00 (t, \(J = 7.1\) Hz, 2H), 1.88 – 1.80 (m, 2H), 1.71 – 1.62 (m, 2H), 1.55 (s, 1H).
hexanes:ethyl acetate eluent). $^1$H NMR data were consistent with those previously reported (ref. 32). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.65 – 7.48 (m, 2H), 7.48 – 7.33 (m, 1H), 7.26 – 7.01 (m, 1H), 3.94 – 3.90 (m, 3H), 3.74 (t, $J$ = 12.4 Hz, 2H), 3.12 – 2.95 (m, 2H), 1.97 – 1.58 (m, 5H).

(Table 3.2, 4n)

5-Oxo-5-(3-methylphenyl)-1-pentanol

The title compound was synthesized according to Method 3.2 from δ-valerolactone (0.742mL, 8.00 mmol) and 3-methylbenzoyl chloride (1.054 mL, 8.00 mmol) to give the title compound as a colourless oil (0.6596 g, 45% over 2 steps) after column chromatography (3:2 → 2:3 hexanes:ethyl acetate eluent). $^1$H NMR data were consistent with those previously reported (ref. 32). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.83 – 7.70 (m, 2H), 7.43 – 7.30 (m, 2H), 3.71 – 3.63 (m, 2H), 3.02 (t, $J$ = 7.1 Hz, 2H), 2.41 (s, 3H), 1.92 – 1.76 (m, 3H), 1.72 – 1.56 (m, 2H).

(Table 3.2, 4o)

5-Oxo-5-(2-benzofuryl)-1-pentanol

The title compound was synthesized according to Method 3.3 from δ-valerolactone (0.63 mL, 6.8 mmol) and benzofuran (0.75 mL, 6.8 mmol) to give the title compound as a white powder (0.5610 g, 38%) after column chromatography. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.76 (d, $J$ = 7.9 Hz, 1H), 7.64 (d, $J$ = 8.4 Hz, 1H), 7.58 (s, 1H), 7.56 – 7.51 (m, 1H), 7.37 (t, $J$ = 7.3 Hz, 1H), 3.76 (t, $J$ = 6.4 Hz, 2H), 3.08 (t, $J$ = 7.2 Hz, 2H), 1.98 – 1.91 (m, 2H), 1.81 – 1.69 (m, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 191.54, 155.64, 152.59, 152.59, 128.29, 127.08, 123.96, 123.34, 112.80, 112.51, 62.41, 38.50, 32.18, 20.24. HRMS (ESI) Calcd. for [NaC$_{13}$H$_{14}$O$_3$]+ 241.0841, found 241.0843.

(Table 3.2, 4p)

5-Oxo-5-(2-furyl)-1-pentanol

The title compound was synthesized according to Method 3.3 from δ-valerolactone (0.89 mL, 9.6 mmol) and furan (1.40 mL, 19.3 mmol) to give the title compound as a light yellow liquid (0.505 g, 31%) after column chromatography. $^1$H NMR (600 MHz, CDCl$_3$) δ 7.61 – 7.54 (m, 1H), 7.20 (d, $J$ = 3.5
Hz, 1H), 6.53 (dt, \( J = 8.1, 4.0 \) Hz, 1H), 3.67 (t, \( J = 6.4 \) Hz, 2H), 2.88 (t, \( J = 7.2 \) Hz, 2H), 1.86 – 1.80 (m, 2H), 1.70 – 1.60 (m, 3H, overlapping with H_2O). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 189.66, 146.37, 117.08, 112.25, 62.35, 37.99, 32.21, 20.19. HRMS (ESI) Calcd. for [NaC\(_9\)H\(_{12}\)O\(_3\)]+ 191.0684, found 191.0684.

(Table 3.2, 4q)
5-Oxo-5-(2-butylenyl)-1-pentanol

The title compound was synthesized according ref. 31. \(^1\)H NMR data were consistent with those previously reported (ref. 31). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 3.65 (t, \( J = 6.4 \) Hz, 2H), 2.59 (t, \( J = 7.2 \) Hz, 2H), 2.40 – 2.34 (m, 2H), 1.79 – 1.71 (m, 2H), 1.65 – 1.53 (m, 4H), 1.50 – 1.39 (m, 2H), 0.93 (t, \( J = 7.3 \) Hz, 3H).

(Table 3.2, 4r)
5-Oxo-5-(2-phenylethynyl)-1-pentanol

The title compound was synthesized according ref. 31. \(^1\)H NMR data were consistent with those previously reported (ref. 31). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.58 (d, \( J = 8.1 \) Hz, 2H), 7.46 (t, \( J = 7.4 \) Hz, 1H), 7.39 (t, \( J = 7.6 \) Hz, 2H), 3.69 (t, \( J = 6.3 \) Hz, 2H), 2.73 (t, \( J = 7.2 \) Hz, 2H), 1.84 (dt, \( J = 13.1, 6.4 \) Hz, 2H), 1.65 (dt, \( J = 13.1, 6.4 \) Hz, 2H), 1.54 (br s, 1H).

(Table 3.2, 4s)
3,3-dimethyl-5-Oxo-5-(2-furyl)-1-pentanol

The title compound was synthesized according to Method 3.3 from \( \beta \)-dimethyl-\( \delta \)-valerolactone (1.44 g, 11.2 mmol) and furan (1.16 mL, 16 mmol) to give the title compound as a colourless oil (0.578 g, 26%) after column chromatography. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.63 (s, 1H), 7.23 (d, \( J = 3.5 \) Hz, 1H), 6.60 – 6.54 (m, 1H), 3.81 (t, \( J = 6.8 \) Hz, 2H), 2.85 (s, 2H), 1.73 (t, \( J = 6.8 \) Hz, 2H), 1.09 (s, 6H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 189.97, 153.76, 146.69, 117.75, 112.45, 59.55, 48.33, 43.93, 33.76, 28.48. HRMS (ESI) Calcd. for [NaC\(_{11}\)H\(_{16}\)O\(_3\)]+ 219.0997, found 219.0999.
3,3-dimethyl-5-Oxo-5-(2-hexylethynyl)-1-pentanol

The title compound was synthesized according to ref. 31 from β-dimethyl-δ-valerolactone (0.30 g, 2.34 mmol) and phenylacetylene (0.287 mL, 2.6 mmol) to give the title compound as a colourless oil (0.203 g, 14%) after column chromatography. This compound was observed by $^1$H NMR as a 66:34 mixture of open and closed chain forms. Due to the complexity of the $^1$H spectrum, only well-resolved peaks are listed. In the proton spectrum, an asterisk denotes the closed chain form. All 29 peaks are listed for the 13C spectrum. $^1$H NMR (500 MHz, CDCl$_3$) δ 4.00 (ddd, $J = 12.0, 9.2, 3.1$ Hz, 0.5H)*, 3.82 – 3.77 (m, 0.5H), 3.76 (t, $J = 7.1$ Hz, 2H), 2.57 (s, 2H), 2.38 (t, $J = 7.2$ Hz, 2H), 2.22 (t, $J = 7.2$ Hz, 1H)*, 1.74 (s, 1H)*, 1.68 (t, $J = 7.1$ Hz, 2H). 13C NMR (126 MHz, CDCl$_3$) δ 188.21, 94.70, 91.10, 83.55, 82.80, 81.61, 59.48, 59.43, 56.19, 48.16, 44.01, 37.65, 33.57, 31.31, 31.21, 30.77, 28.93, 28.76, 28.60, 28.57, 28.30, 28.06, 27.64, 22.53, 22.49, 18.99, 18.49, 14.06, 14.03. HRMS (ESI) Calcd. for [NaC$_{15}$H$_{26}$O$_2$]+ 261.1830, found 261.1820.

3,3-dimethyl-5-Oxo-5-(2-phenylethynyl)-1-pentanol

The title compound was synthesized according to ref. 31 from β-dimethyl-δ-valerolactone (0.30 g, 2.34 mmol) and phenylacetylene (0.287 mL, 2.6 mmol) to give the title compound as a colourless oil (0.130 g, 24%) after column chromatography. This compound was observed by $^1$H NMR as a 54:46 mixture of open and closed chain forms. Due to the complexity of the $^1$H spectrum, only well-resolved peaks are listed. In the proton spectrum, an asterisk denotes the closed chain form. All 25 peaks are listed for the 13C spectrum. $^1$H NMR (500 MHz, CDCl$_3$) δ 4.10 – 3.82 (m, 1.7 H)*, 3.79 (t, $J = 7.0$ Hz, 2H), 2.68 (s, 2H), 1.91 – 1.79 (m, 1.7 H)*, 1.72 (t, $J = 7.0$ Hz, 1H), 1.54 – 1.37 (m, 1.7 H)*, 1.13 (s, overlapping with closed chain form), 1.08 (s, 2.6 H)*. 13C NMR (126 MHz, CDCl$_3$) δ 187.93, 133.08, 131.82, 130.84, 128.80, 128.71, 128.34, 121.93, 120.02, 91.61, 90.84, 89.90, 89.62, 82.65, 59.83, 59.62, 56.31, 48.00, 44.05, 37.62, 33.85, 30.60, 29.07, 28.99, 28.20. HRMS (ESI) Calcd. for [NaC$_{15}$H$_{18}$O$_2$]+ 253.1205, found 253.1213.
3.4.2 Reaction Optimization

**Method 3.4 Hydroacylation of 1,4-ketoalcohols with base**

In a nitrogen-filled glove box, \((R,R)\)-II (0.015 mmol, 5 mol %) and \(\text{tBuONa}\) (0.015 mmol, 5 mol %) were weighed into a vial. A stir bar was added and then 0.6 mL of EtOAc, acetone (0.36 mmol, 1.2 equiv.), iso-propanol (0.9 mmol, 3 equiv) and finally the substrate (0.3 mmol, 1 equiv.). The vial was sealed with a Teflon-lined polypropylene screw cap and removed from the glove box, and the solution was stirred at either 22 °C or 0 °C for the indicated period of time. The product was isolated by preparative thin layer chromatography. When solid substrates were used, the substrate was added to the reaction vial prior to addition of solvent.

**Method 3.5 Hydroacylation of 1,4-ketoalcohols without base**

In a nitrogen-filled glove box, \((S,S)\)-I or \((R,R)\)-I (0.015 mmol, 5 mol %) was weighed into a vial. A stir bar was added and then 0.6 mL of EtOAc, acetone (0.36 mmol, 1.2 equiv.), iso-propanol (0.9 mmol, 3 equiv) and finally the substrate (0.3 mmol, 1 equiv.). The vial was sealed with a Teflon-lined polypropylene screw cap and removed from the glove box, and the solution was stirred at either 22°C or 0 °C for the indicated period of time. The product was isolated by preparative thin layer chromatography. When solid substrates were used, the substrate was added to the reaction vial prior to addition of solvent.
<table>
<thead>
<tr>
<th>Solvent</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>benzene</td>
<td>85</td>
</tr>
<tr>
<td>toluene</td>
<td>88</td>
</tr>
<tr>
<td>DCM</td>
<td>n.d.</td>
</tr>
<tr>
<td>1,2-DCE</td>
<td>89</td>
</tr>
<tr>
<td>THF</td>
<td>n.d.</td>
</tr>
<tr>
<td>dioxane</td>
<td>n.d.</td>
</tr>
<tr>
<td>acetonitrile</td>
<td>91</td>
</tr>
<tr>
<td>acetone</td>
<td>n.d.</td>
</tr>
<tr>
<td>EtOAc</td>
<td>91</td>
</tr>
</tbody>
</table>
5 mol% (S,S)-I
or
5 mol% (R,R)-II and
5 mol% tBuONa
1.2 equiv acetone
3 equiv iPrOH
EtOAc, 22 °C, 24 h

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>(S,S)-I (22 °C)</th>
<th>(R,R)-II (22 °C)</th>
<th>(R,R)-II (0 °C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yield (%) ee (%)</td>
<td>Yield (%) ee (%)</td>
<td>Yield (%) ee (%)</td>
</tr>
<tr>
<td>1</td>
<td>C₆H₅-</td>
<td>92 91</td>
<td>90 93</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>3-Cl-C₆H₄-</td>
<td>96 80</td>
<td>83 90</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>3-OMe-C₆H₄-</td>
<td>87 85</td>
<td>82 91</td>
<td>-</td>
</tr>
<tr>
<td>4ᵃ</td>
<td>4-Br-C₆H₄-</td>
<td>94 80</td>
<td>95 84</td>
<td>91 87</td>
</tr>
<tr>
<td>5ᵃ</td>
<td>4-F-C₆H₄-</td>
<td>78 73</td>
<td>80 80</td>
<td>84 87</td>
</tr>
<tr>
<td>6ᵃ,b</td>
<td>4-OMe-C₆H₄-</td>
<td>72 84</td>
<td>78 87</td>
<td>70ᵃ 92ᵃ</td>
</tr>
<tr>
<td>7ᵇ</td>
<td>2-naphthyl</td>
<td>68 83</td>
<td>78 90</td>
<td>-</td>
</tr>
<tr>
<td>8ᵃ</td>
<td>2-furyl</td>
<td>84 67</td>
<td>81 83</td>
<td>77 87</td>
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<tr>
<td>9ᵃ,b</td>
<td>Ph-C≡C-</td>
<td>84 80</td>
<td>73 87</td>
<td>65ᵃ 91ᵃ</td>
</tr>
<tr>
<td>10ᵃ,b</td>
<td>C₄H₉-C≡C-</td>
<td>86 81</td>
<td>60 90</td>
<td>79ᵃ 90ᵃ</td>
</tr>
</tbody>
</table>

ᵃ3 d;ᵇ10% catalyst
### 3.4.3 Lactone Synthesis

The absolute configuration of (+)-(R)-γ-Phenyl-γ-butyrolactone, \(^3\text{3}\) (+(R)-γ-(3-Methoxyphenyl)-γ-butyrolactone, \(^3\text{4}\) (+)-(R)-γ-(4-Bromophenyl)-γ-butyrolactone, \(^3\text{5}\) (+)-(R)-γ-(4-methoxyphenyl)-γ-butyrolactone, \(^3\text{3}\) (+)-(R)-γ-(2-Naphthyl)-γ-butyrolactone, \(^3\text{6}\) (+)-(R)-δ-(phenyl)-δ-valerolactone \(^3\text{3}\) and (+)-(R)-3,5-dimethylisobenzofuran-1(3H)-one \(^3\text{7}\) were all assigned the R configuration based on correlation of the optical rotation data with literature values. The remaining substrates were assigned based on analogy.
(Table 3.1, 8a)

(+)-(R)-γ-Phenyl-γ-butyrolactone

The title compound was synthesized according to Method 3.4 (22°C, 24h) from 4-oxo-4-phenyl-1-butanol (49.3 mg, 0.3 mmol) to give the title compound as a clear colourless oil (44.2 mg, 90% yield) after preparative TLC (1:1 hexanes:ethyl acetate eluent). \(^1\)H NMR data were in agreement with those previously reported (ref. 38). \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.43 – 7.29 (m, 5H), 5.54 – 5.45 (m, 1H), 2.71 – 2.59 (m, 3H), 2.26 – 2.11 (m, 1H). GC: 93% ee (CYCLODEX B, inlet temp 220°C, flow rate 5.3781 mL/min, initial temp 80°C, hold 2 min, ramp 10°C/min up to 180°C, hold 3 min, ramp 40°C/min up to 230°C, hold 1 min, \(t_{R1}\) 14.68 min, \(t_{R2} = 14.76\) min); \([\alpha]_D^{25}\) +17.1 (1.0, CH\(_2\)Cl\(_2\)).

(Table 3.1, 8b)

(+)-(R)-γ-(3-Chlorophenyl)-γ-butyrolactone

The title compound was synthesized according to Method 3.4 (22°C, 24h) from 4-oxo-4-(3-chlorophenyl)-1-butanol (59.0 mg, 0.3 mmol) to give the title compound as a clear colourless oil (49.0 mg, 83% yield) after preparative TLC (3:2 hexanes:ethyl acetate eluent). \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.36 – 7.29 (m, 3H), 7.25 – 7.19 (m, 1H), 5.51 – 5.45 (m, 1H), 2.73 – 2.61 (m, 3H), 2.24 – 2.09 (m, 1H). \(^13\)C NMR (100 MHz, CDCl\(_3\)) δ 176.39, 141.47, 134.77, 130.11, 128.56, 125.41, 123.29, 80.17, 30.85, 28.71; HRMS (ESI) Calcd. for [C\(_{10}\)H\(_9\)ClO\(_2\) + NH\(_4\)]\(^+\) 214.06348, found 214.06378; HPLC: 90% ee (CHIRALPAK ADH, 5:95 MeOH:CO\(_2\), 1.8 mL/min, 44°C, 210 nm, \(t_{R1} = 3.8\) min, \(t_{R2} = 4.2\) min); \([\alpha]_D^{25}\) +14.3 (1.0, CH\(_2\)Cl\(_2\)).
(Table 3.1, 8c)

**(+)-(R)-\(\gamma\)-(3-Methoxyphenyl)-\(\gamma\)-butyrolactone**

The title compound was synthesized according to Method 3.4 (22°C, 24h) from 4-oxo-4-(3-methoxyphenyl)-1-butanol (58.3 mg, 0.3 mmol) to give the title compound as a clear colourless oil (47.2 mg, 82% yield) after preparative TLC (7:3 hexanes:ethyl acetate eluent, 2 elutions). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.34 – 7.27 (m, 1H), 6.94 – 6.84 (m, 3H), 5.56 – 5.41 (m, 1H), 3.82 (s, 3H), 2.73 – 2.59 (m, 3H), 2.27 – 2.10 (m, 1H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 176.87, 159.97, 141.08, 129.91, 117.39, 113.90, 110.80, 81.03, 55.35, 30.96, 28.90; HRMS (ESI) Calcd. for [C\(_{11}\)H\(_{12}\)O\(_3\) + NH\(_4\)]\(^+\) 210.11302, found 210.11338; HPLC: 91% ee (CHIRALPAK ADH, 6:94 MeOH:CO\(_2\), 2.0 mL/min, 44°C, 210 nm, \(t_{R1}\) = 3.3 min, \(t_{R2}\) = 4.1 min); \([\alpha]_D^{25}\) + 12.0 (0.79, EtOH).

(Table 3.1, 8d)

**(+)-(R)-\(\gamma\)-(4-Bromophenyl)-\(\gamma\)-butyrolactone**

The title compound was synthesized according to Method 3.4 (0°C, 24h) from 4-oxo-4-(4-bromophenyl)-1-butanol (72.9 mg, 0.3 mmol) to give the title compound as a white solid (66.0 mg, 91% yield) after preparative TLC (3:2 hexanes:ethyl acetate eluent). \(^1\)H NMR data were in agreement with those previously reported (ref. 38). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.56 – 7.49 (m, 2H), 7.24 – 7.19 (m, 2H), 5.51 – 5.42 (m, 1H), 2.75 – 2.58 (m, 3H), 2.24 – 2.06 (m, 1H). HPLC: 87% ee (CHIRALPAK ADH, 15:85 MeOH:CO\(_2\), 2.5 mL/min, 44°C, 210 nm, \(t_{R1}\) = 2.0 min, \(t_{R2}\) = 2.3 min); \([\alpha]_D^{25}\) + 16.5 (1.0, CH\(_2\)Cl\(_2\)).

(Table 3.1, 8e)

**(+)-(R)-\(\gamma\)-(4-Fluorophenyl)-\(\gamma\)-butyrolactone**

The title compound was synthesized according to Method 3.4 (0°C, 24h) from 4-oxo-4-(4-fluorophenyl)-1-butanol (54.7 mg, 0.3 mmol) to give the title compound as a white solid (45.7 mg, 84% yield) after preparative TLC (3:2 hexanes:ethyl acetate eluent). \(^1\)H NMR data were in agreement with those
previously reported (ref. 38). \textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) δ 7.34 – 7.25 (m, 2H), 7.13 – 6.99 (m, 2H), 5.46 (dd, \( J = 8.4, 5.9 \) Hz, 1H), 2.69 – 2.57 (m, 3H), 2.21 – 2.06 (m, 1H). \textbf{HPLC:} 87\% ee (CHIRALPAK ADH, 15:85 MeOH:CO\textsubscript{2}, 2.5 mL/min, 44°C, 210 nm, \( t\textsubscript{R1} = 1.0 \) min, \( t\textsubscript{R2} = 1.1 \) min); [\( \alpha \)]\textsubscript{D}\textsuperscript{25} + 13.8 (1.0, CH\textsubscript{2}Cl\textsubscript{2}).

\begin{table}[h]
\centering
\begin{tabular}{|c|}
\hline
(+)-(\( R \))-\( \gamma \)-(4-methoxyphenyl)-\( \gamma \)-butyrolactone \\
\hline
\end{tabular}
\end{table}

The title compound was synthesized according to Method 3.4 (0°C, 3d) from 4-oxo-4-(4-methoxyphenyl)-1-butanol (58.3 mg, 0.3 mmol) to give the title compound as a light yellow oil (40.8 mg, 70\% yield) after preparative TLC (1:1 hexanes:ethyl acetate eluent). \textbf{\textsuperscript{1}H NMR} data were in agreement with those previously reported (ref. 38). \textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) δ 7.29 – 7.20 (m, 2H), 6.95 – 6.84 (m, 2H), 5.49 – 5.39 (m, 1H), 3.80 (s, 3H), 2.69 – 2.53 (m, 3H), 2.27 – 2.10 (m, 1H). \textbf{HPLC:} 92\% ee (CHIRALPAK ADH, 15:85 MeOH:CO\textsubscript{2}, 2.0 mL/min, 44°C, 210 nm, \( t\textsubscript{R1} = 2.0 \) min, \( t\textsubscript{R2} = 2.2 \) min); [\( \alpha \)]\textsubscript{D}\textsuperscript{25} + 3.1 (1.0, CH\textsubscript{2}Cl\textsubscript{2}).

\begin{table}[h]
\centering
\begin{tabular}{|c|}
\hline
(+)-(\( R \))-\( \gamma \)-(2-Naphthyl)-\( \gamma \)-butyrolactone \\
\hline
\end{tabular}
\end{table}

The title compound was synthesized according to Method 3.4 (22°C, 3d) from 4-oxo-4-(2-naphthyl)-1-butanol (63.7 mg, 0.3 mmol) to give the title compound as an off-white solid (49.5 mg, 78\% yield) after preparative TLC (3:2 hexanes:ethyl acetate eluent). \textbf{\textsuperscript{1}H NMR} data were in agreement with those previously reported (ref. 38). \textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) δ 7.94 – 7.77 (m, 4H), 7.58 – 7.46 (m, 2H), 7.41 (dd, \( J = 8.5, 1.8 \) Hz, 1H), 5.76 – 5.62 (m, 1H), 2.82 – 2.63 (m, 3H), 2.37 – 2.18 (m, 1H). \textbf{HPLC:} 90\% ee (CHIRALPAK ADH, 15:85 MeOH:CO\textsubscript{2}, 2.5 mL/min, 44°C, 210 nm, \( t\textsubscript{R1} = 2.5 \) min, \( t\textsubscript{R2} = 2.8 \) min); [\( \alpha \)]\textsubscript{D}\textsuperscript{25} + 14.9 (0.67, CHCl\textsubscript{3}).
(Table 3.1, 8h)

(-)-(R)-γ-(2-Furyl)-γ-butyrolactone

The title compound was synthesized according to Method 3.4 (22°C, 3d) from 4-oxo-4-(2-furyl)-1-butanol (46.2 mg, 0.3 mmol) to give the title compound as an colourless liquid (37.6 mg, 81% yield) after preparative TLC (5.5:4.5 hexanes:ethyl acetate eluent). ¹H NMR (400 MHz, CDCl₃) δ 7.42 (dd, J = 1.8, 0.8 Hz, 1H), 6.46 – 6.31 (m, 2H), 5.48 (t, J = 6.9 Hz, 1H), 2.80 – 2.68 (m, 1H), 2.66 – 2.58 (m, 1H), 2.57 – 2.47 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 176.39, 150.96, 143.48, 110.50, 109.30, 74.37, 28.55, 26.58; HRMS (ESI) Calcd. for [C₈H₉O₃]⁺ 153.05517, found 153.05514; HPLC: 87% ee (CHIRALCEL OJH, 5:95 MeOH:CO₂, 1.7 mL/min, 44°C, 210 nm, tᵣ₁ = 1.7 min, tᵣ₂ = 1.9 min); [α]²⁵D - 49.4 (0.57, CH₂Cl₂).

(Table 3.1, 8i)

(-)-(R)-γ-(2-Phenylethynyl)-γ-butyrolactone

The title compound was synthesized according to Method 3.4 (0°C, 3d) from 4-oxo-4-(2-phenylethynyl)-1-butanol (56.5 mg, 0.3 mmol) to give the title compound as an colourless liquid (37.0 mg, 65% yield) after preparative TLC (5.5:4.5 hexanes:ethyl acetate eluent). ¹H NMR data were in agreement with those previously reported (ref. 38). ¹H NMR (400 MHz, CDCl₃) δ 7.47 – 7.38 (m, 2H), 7.37 – 7.28 (m, 3H), 5.41 – 5.29 (m, 1H), 2.78 – 2.67 (m, 1H), 2.65 – 2.49 (m, 2H), 2.45 – 2.35 (m, 1H). HPLC: 91% ee (CHIRALPAK ADH, 15:85 MeOH:CO₂, 2.5 mL/min, 44°C, 210 nm, tᵣ₁ = 1.6 min, tᵣ₂ = 2.4 min); [α]²⁵D - 17.5 (1.0, CH₂Cl₂).

(Table 3.1, 8j)

(-)-(R)-γ-(2-Butylethynyl)-γ-butyrolactone

The title compound was synthesized according to Method 3.4 (0°C, 3d) from 4-oxo-4-(2-butylethynyl)-1-butanol (50.5 mg, 0.3 mmol) to give the title compound as an colourless liquid (39.8 mg, 79% yield) after preparative TLC (6.5:3.5 hexanes:ethyl acetate eluent). ¹H NMR data were in agreement with
those previously reported (ref. 39). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.13 – 5.06 (m, 1H), 2.70 – 2.56 (m, 1H), 2.54 – 2.40 (m, 2H), 2.28 – 2.14 (m, 3H), 1.52 – 1.31 (m, 4H), 0.88 (t, \(J = 7.3\) Hz, 3H). GC: 90% ee (CYCLODEX B, inlet temp 220°C, flow rate 5.3781 mL/min, initial temp 80°C, hold 2 min, ramp 3°C/min up to 145°C, hold 3 min, ramp 3°C/min up to 170°C, hold 3 min, ramp 40°C/min up to 230°C, hold 3 min \(t_R 1 = 29.38\) min, \(t_R 2 = 29.54\) min); \([\alpha]^{25}_D\) – 10.7 (1.0, CH\(_2\)Cl\(_2\)).

(Table 3.2, 8k)

\(\text{(+)-(R)-}\delta-(\text{phenyl})-\delta-\text{valerolactone}\)

The title compound was synthesized according to Method 3.4 (0°C, 3d) from 5-oxo-5-phenyl-1-pentanol (53.5 mg, 0.3 mmol) to give the title compound as a colourless liquid (43.2 mg, 81% yield) after preparative TLC (3:2 hexanes:ethyl acetate eluent). \(^1\)H NMR data were in agreement with those previously reported (ref. 29). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.43 – 7.28 (m, 5H), 5.36 (dd, \(J = 10.4, 3.4\) Hz, 1H), 2.77 – 2.65 (m, 1H), 2.63 – 2.52 (m, 1H), 2.23 – 2.12 (m, 1H), 2.05 – 1.93 (m, 2H), 1.93 – 1.80 (m, 1H). HPLC: 90% ee (CHIRALPAK ADH, 15:85 MeOH:CO\(_2\), 2.5 mL/min, 44°C, 210 nm, \(t_{R1} = 1.5\) min, \(t_{R2} = 1.7\) min); \([\alpha]^{25}_D\) + 39.2 (1.0, CHCl\(_3\)).

(Table 3.2, 8l)

\(\text{(+)-(R)-}\delta-(4\text{-chlorophenyl})-\delta-\text{valerolactone}\)

The title compound was synthesized according to Method 3.4 (22°C, 24h) from 5-oxo-5-(4-chlorophenyl)-1-pentanol (63.8 mg, 0.3 mmol) to give the title compound as a white solid (41.0 mg, 65% yield) after preparative TLC (3:2 hexanes:ethyl acetate eluent). \(^1\)H NMR data were in agreement with those previously reported (ref. 40) \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.36 (d, \(J = 8.5\) Hz, 2H), 7.29 (d, \(J = 8.4\) Hz, 2H), 5.33 (dd, \(J = 10.7, 3.2\) Hz, 1H), 2.76 – 2.66 (m, 1H), 2.64 – 2.52 (m, 1H), 2.20 – 2.12 (m, 1H), 2.04 – 1.95 (m, 2H), 1.88 – 1.76 (m, 1H). HPLC: 96% ee (CHIRALPAK ADH, 15:85 MeOH:CO\(_2\), 2.5 mL/min, 44°C, 210 nm, \(t_{R1} = 3.3\) min, \(t_{R2} = 3.5\) min); \([\alpha]^{25}_D\) + 28.0 (0.5, CH\(_2\)Cl\(_2\)).
The title compound was synthesized according to Method 3.4 (0°C, 3d) from 5-oxo-5-(3-methoxyphenyl)-1-pentanol (62.5 mg, 0.3 mmol) to give the title compound as a colourless liquid (43.5 mg, 70% yield) after preparative TLC (3:2 hexanes:ethyl acetate eluent). $^1$H NMR data were in agreement with those previously reported (ref. 41). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.38 – 7.28 (m, 1H), 7.00 – 6.87 (m, 3H), 5.37 (dd, $J$ = 10.5, 3.3 Hz, 1H), 3.85 (s, 3H), 2.80 – 2.68 (m, 1H), 2.68 – 2.54 (m, 1H), 2.27 – 2.14 (m, 1H), 2.08 – 1.96 (m, 2H), 1.96 – 1.84 (m, 1H). HPLC: 95% ee (CHIRALPAK ADH, 15:85 MeOH:CO$_2$, 2.5 mL/min, 44°C, 210 nm, $t_R1$ = 5.8 min, $t_R2$ = 6.5 min); $[\alpha]_D^{25}$ + 26.2 (1.0, CH$_2$Cl$_2$).

The title compound was synthesized according to Method 3.4 (22°C, 24h) from 5-oxo-5-(3-methylphenyl)-1-pentanol (57.8 mg, 0.3 mmol) to give the title compound as a colourless liquid (42.0 mg, 73% yield) after preparative TLC (3:2 hexanes:ethyl acetate eluent). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.32 (t, $J$ = 7.6 Hz, 1H), 7.26 – 7.15 (m, 3H), 5.38 (dd, $J$ = 10.5, 3.3 Hz, 1H), 2.82 – 2.72 (m, 1H), 2.69 – 2.58 (m, 1H), 2.42 (s, 3H), 2.26 – 2.18 (m, 1H), 2.09 – 2.00 (m, 2H), 1.98 – 1.87 (m, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 171.52, 139.73, 138.40, 129.03, 128.51, 126.41, 122.79, 81.76, 30.59, 29.57, 21.49, 18.66. HRMS (ESI) Calcd. for [NaC$_{11}$H$_{14}$O$_3$]+ 213.0892, found 213.0885; HPLC: 91% ee (CHIRALPAK ADH, 15:85 MeOH:CO$_2$, 2.5 mL/min, 44°C, 210 nm, $t_R1$ = 3.3 min, $t_R2$ = 3.5 min); $[\alpha]_D^{25}$ + 29.2 (1.0, CHCl$_3$).
(Table 3.2, 8o)

(+)-(R)-δ-(2-benzofuryl)-δ-valerolactone

The title compound was synthesized according to Method 3.4 (22°C, 24h) from 5-oxo-5-(2-benzofuryl)-1-pentanol (65.5 mg, 0.3 mmol) to give the title compound as a white powder (36.0 mg, 55% yield) after preparative TLC (3:2 hexanes:ethyl acetate eluent. $^{1}H$ NMR (500 MHz, CDCl$_3$) δ 7.57 (d, $J$ = 7.6 Hz, 1H), 7.47 (d, $J$ = 8.2 Hz, 1H), 7.34 – 7.28 (m, 1H), 7.24 (t, $J$ = 7.5 Hz, 1H), 6.76 (s, 1H), 5.56 (dd, $J$ = 8.9, 4.2 Hz, 1H), 2.76 – 2.58 (m, 2H), 2.34 – 2.18 (m, 2H), 2.12 – 1.91 (m, 2H). $^{13}C$ NMR (126 MHz, CDCl$_3$) δ 170.24, 154.96, 154.18, 127.70, 124.83, 123.09, 121.40, 111.42, 104.71, 75.44, 29.75, 26.52, 18.27. HRMS (ESI) Calcd. for [NaC$_{13}$H$_{12}$O$_3$]+ 239.0684, found 239.0676; HPLC: 90% ee (CHIRALPAK ADH, 10:90 MeOH:CO$_2$, 3 mL/min, 44°C, 254 nm, t$_R1$ = 3.0 min, t$_R2$ = 3.5 min); $[\alpha]_D^{25}$ + 13.3 (1.0, CH$_2$Cl$_2$).

(Table 3.2, 8q)

(+)-(R)-δ-(2-butylethynyl)-δ-valerolactone

The title compound was synthesized according to Method 3.4 (22°C, 24h) from 5-Oxo-5-(2-butylethynyl)-1-pentanol (60.7 mg, 0.3 mmol) to give the title compound as a colourless liquid (35.5 mg, 65% yield) after preparative TLC. The product was found to decompose on silica and was not isolated in pure form. $^1$H NMR data were in agreement with those previously reported (ref. 41) although some additional peaks were present, presumably due to decomposition products. The reaction was repeated and an NMR yield was obtained via integration of the propargylic proton versus an internal standard (42% NMR yield). Because the product is not UV active, it was derivatized with excess PhMgBr to the corresponding tertiary alcohol and then the ee was determined by chiral HPLC. HPLC: 86% ee (CHIRALPAK ADH, 10:90 MeOH:CO$_2$, 3 mL/min, 44°C, 210 nm, t$_R1$ = 4.1 min, t$_R2$ = 4.7 min).
(+)-(R)-δ-(2-phenylethynyl)-δ-valerolactone

The title compound was synthesized according to Method 3.4 (22°C, 24h) from 5-Oxo-5-(2-phenylethynyl)-1-pentanol (60.7 mg, 0.3 mmol) to give the title compound as a colourless liquid (40.0 mg, 66% yield) after preparative TLC. The product was found to decompose on silica and was not isolated in pure form. 1H NMR data were in agreement with those previously reported (ref. 41) although some additional peaks were present, presumably due to decomposition products. The reaction was repeated and an NMR yield was obtained via integration of the propargylic proton versus an internal standard (32% NMR yield). **HPLC**: 86% ee (CHIRALPAK ODH, 4:96 MeOH:CO\(_2\), 3 mL/min, 44°C, 210 nm, t\(_R1\) = 2.9 min, t\(_R2\) = 4.2 min).

(R)-β,β-dimethyl-δ-(2-furyl)-δ-valerolactone

The title compound was synthesized according to Method 3.4 (22°C, 24h) from 3,3-dimethyl-5-oxo-5-(2-furyl)-1-pentanol (58.9 mg, 0.3 mmol) to give the title compound as a colourless liquid (57.5 mg, 98% yield) after preparative TLC. 1H NMR (500 MHz, CDCl\(_3\)) δ 7.44 – 7.40 (m, J = 0.9 Hz, 1H), 6.42 – 6.38 (m, J = 3.2 Hz, 1H), 6.38 – 6.34 (m, 1H), 2.49 – 2.43 (m, 1H), 2.33 (d, J = 16.8 Hz, 1H), 2.12 – 2.05 (m, 1H), 1.94 – 1.87 (m, 1H), 1.17 (s, 3H), 1.14 (s, 3H). 13C NMR (126 MHz, CDCl\(_3\)) δ 170.85, 151.46, 143.05, 110.46, 108.63, 72.26, 43.87, 39.87, 30.90, 29.98, 26.93. HRMS (ESI) Calcd. for [NaC\(_{11}\)H\(_{14}\)O\(_3\)]+ 217.0841, found 217.0840. **HPLC**: 90% ee (CHIRALPAK ADH, 4:96 MeOH:CO\(_2\), 3 mL/min, 44°C, 210 nm, t\(_R1\) = 2.6 min, t\(_R2\) = 3.4 min).
(Table 3.2, 8t)

(R)-β,β-dimethyl-δ-(phenylethynyl)-δ-valerolactone

The title compound was synthesized according to Method 3A (22°C, 24h) from 3,3-dimethyl-5-oxo-5-(2-phenylethynyl)-1-pentanol (69.1 mg, 0.3 mmol) to give the title compound as a colourless liquid (59.8 mg, 87% yield) after preparative TLC. ¹H NMR (500 MHz, CDCl₃) δ 7.47 – 7.41 (m, 2H), 7.39 – 7.29 (m, 3H), 5.33 (dd, J = 9.8, 4.8 Hz, 1H), 2.48 – 2.35 (m, 2H), 2.06 – 1.92 (m, 2H), 1.16 (s, 3H), 1.12 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 170.46, 131.80, 129.00, 128.43, 121.85, 86.83, 85.35, 67.83, 43.72, 42.64, 30.78, 30.20, 27.86. HRMS (ESI) Calcd. for [NaC₁₅H₁₆O₂]⁺ 251.1048, found 251.1054. HPLC: 90% ee (CHIRALPAK ODH, 4:96 MeOH:CO₂, 3 mL/min, 44°C, 254 nm, t₁ = 1.8 min, t₂ = 2.3 min).

(Table 3.2, 8u)

(R)-β,β-dimethyl-δ-(2-hexylethynyl)-δ-valerolactone

The title compound was synthesized according to Method 3.4 (22°C, 24h) from 3,3-dimethyl-5-oxo-5-(2-hexylethynyl)-1-pentanol (71.5 mg, 0.3 mmol) to give the title compound as a colourless liquid (39.3 mg, 55% yield) after preparative TLC. ¹H NMR (500 MHz, CDCl₃) δ 5.17 – 5.11 (m, 1H), 2.47 – 2.36 (m, 2H), 2.33 – 2.21 (m, 2H), 2.00 – 1.83 (m, 2H), 1.60 – 1.51 (m, 2H), 1.48 – 1.27 (m, 6H), 1.17 (s, 3H), 1.13 (s, 3H), 0.95 (t, J = 7.0 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 170.73, 88.16, 76.73, 67.76, 43.65, 43.04, 31.33, 30.82, 30.06, 28.55, 28.32, 27.91, 22.56, 18.71, 14.10. HRMS (ESI) Calcd. for [NaC₁₅H₂₄O₂]⁺ 259.1674, found 259.1681. HPLC: 90% ee (CHIRALPAK ADH, 8:92 MeOH:CO₂, 3 mL/min, 44°C, 220 nm, t₁ = 1.3 min, t₂ = 1.8 min).
The title compound was synthesized according to Method 3.5 (22°C, 24h) (except that acetone was not added) from 2-acetyl-4-methylbenzaldehyde 2a (48.7 mg, 0.3 mmol) to give the title compound as a white solid (41.4 mg, 85% yield) after preparative TLC (7:3 hexanes:ethyl acetate eluent). \(^1\)H NMR data were in agreement with those previously reported (ref. 37). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.77 (d, \(J = 7.8\) Hz, 2H), 7.38 – 7.28 (m, 1H), 7.25 – 7.19 (m, 1H), 5.51 (q, \(J = 6.7\) Hz, 1H), 2.50 (s, 3H), 1.62 (d, \(J = 6.7\) Hz, 3H). **HPLC**: 90% ee (CHIRALPAK ADH, 15:85 MeOH:CO\(_2\), 2.5 mL/min, 44°C, 210 nm, \(t_R1 = 0.9\) min, \(t_R2 = 1.4\) min); \([\alpha]^{25}_D + 45.2\) (0.59, CHCl\(_3\)).

### 3.4.4 Mechanistic Studies

**Method 3.6** Procedure for monitoring hydroacylation of 1,4-ketoalcohols by \(^1\)H NMR

In a nitrogen-filled glove box, \([(R,R)-I]\) (0.015 mmol, 5 mol %) was weighed into a vial. To a separate vial was added 5-oxo-5-phenyl-1-butanol (4a, 57.5 mg, 0.35 mmol) and the indicated amount of acetone and iso-propanol followed by C\(_6\)D\(_6\) to make the final concentration of 5-oxo-5-phenyl-1-butanol 0.45 M. The solution was transferred to the vial containing \([(R,R)-I]\) and the time was noted. The mixture was then transferred to a J. Young tube and \(^1\)H NMR spectra were recorded at various time intervals. As no by-products or intermediates are observable, the conversions were calculated based on product-to-starting material ratios. The product-to-starting material ratios were calculated based on integration of the aryl protons of 5-oxo-5-phenyl-1-butanol 4a at 7.8 ppm (2H) and integration of the benzylic proton of \(\gamma\)-phenyl-\(\gamma\)-butyrolactone 8a at 4.8 ppm (1H).
Reaction of 5-oxo-5-phenyl-1-butanol with [(R,R)-I] and 1.2 equiv acetone (Method 3.6).
Reaction of 5-oxo-5-phenyl-1-butanol with [(R,R)-I] and 1.2 equiv acetone and 3 equiv isopropanol (Method 3.6).
Reaction of 5-oxo-5-phenyl-1-butanol 4a with [(R,R)-I] and 3 equiv acetone (Method 3.6).

### 3.5 References

4. Applying [Rh((S,S,R,R)-Duanphos)NO₃] (catalyst in ref. 3c) for hydroacylation of 4-oxo-
butyrophenone yielded only the decarbonylation product (Unpublished result).
5. Hydroacylation of 4-oxobutyrophenone with [Rh(dppe)(acetone)₂][ClO₄] gives 60% yield of
the ketone hydroacylation product along with 35% of the decarbonylation product: Bergens,
S. H.; Fairlie, D. P.; Bosnich, B. Organometallics 1990, 9, 566-571.
6. (a) For the use of an NHC to cyclize 2-ketobenzaldehydes, see: Chan, A.; Scheidt, K. A. J.
Am. Chem. Soc. 2006, 128, 4558-4559. (b) The NHC catalyst from ref. 2b was not applicable
to cyclization of 4-oxo-butyrophenone: Chan, A. Ph.D Thesis, Northwestern University,
2008. (c) Hydroacylation of 4-oxo-1-pentanal with RuHCl(CO)(PPh₃)₃ gives 32% yield of
the ketone hydroacylation product along with 55% yield of the aldehyde dimerization
6743. (d) For use of iridium hydrides in hydroacylation of 2-(2-oxo-propyl)benzaldehydes,
7. A DKR reduction/lactonization sequence has been developed to cyclize 1,4-ketoesters using
2012, 134, 7329-7332.
2010, 110, 681-703.
10. For in situ oxidation of alcohols to aldehydes in diene and alkyne hydroacylation protocols
under transfer hydrogenation conditions, see: (a) Shibahara, F.; Bower, J. F.; Krische, M. J. J.
Krische, M. J. Tetrahedron 2009, 65, 5024-5029. For a review on this topic and other C-C
bond forming reactions under transfer hydrogenation conditions, see: (c) Moran, J.; Krische,
11. An alternative mechanism where oxidation of the primary alcohol precedes ketone reduction
is possible.


15. EtOAc gave the highest enantioselectivity among the various solvents that were examined. Benzene, toluene, 1,2-DCE, and acetonitrile gave good reactivity but slightly lower enantioselectivity. Tetrahydrofuran, 1,4-dioxane and DCM showed lower reactivity. See SI for details.

16. The absolute configuration of the lactone were determined by correlation of the optical rotation with literature data and are the same configuration as would be expected for ATH of the same ketone. See the SI for details.

17. See experimental section for plots of reaction rate versus time.


20. Deuterium labeling studies indicate that lactonization of 1,4-diols, where one alcohol is primary and the other is secondary, is faster than oxidation of the secondary alcohol. See ref. 9a. This data supports a mechanism in which ATH of the ketone is rate limiting.


22. See the SI for a comparison of ee’s obtained using I versus II.


24. The δ-valerolactone products with alkynyl substituents and no substitution on the backbone (Table 2, entries 5 and 7) decompose on silica and could not be isolated in pure form. The reaction was repeated for these substrates several times and isolated yields varied from 20-66%. Due to these difficulties in product isolation, NMR yields are reported in Table 2, entries 6-8. In these instances, the ee values were determined by derivitization of the products with excess phenyl lithium to form a diol, followed by purification and chiral HPLC analysis.

25. Substrates that were tested include: 6-oxo-6-phenyl-hexan-1-ol, 7-oxo-7-phenyl-heptan-1-ol, 1a (X = O, R = Ph).


Rh-Catalyzed C-C Bond Cleavage by Transfer Hydroformylation*

4.1 Introduction

The cytochrome P450 enzymes have captured the imagination of chemists who seek to emulate their reactivity. For example, monooxygenases motivated the design of catalysts that epoxidize olefins and oxidize C–H bonds.1–4 This enzyme superfamily also includes various demethylases that break C–C bonds.5 In particular, lanosterol demethylase converts aldehydes to olefins by dehydroformylation during the biosynthesis of sterols in bacteria, algae, fungi, plants, and animals (Scheme 4.1).6 Inspired by this step in biosynthesis, we sought a transition-metal catalyst for dehydroformylations in organic synthesis.

Scheme 4.1 Dehydroformylation during sterol biosynthesis.

To this end, we aimed to trigger C–C bond cleavage7–11 by chemoselective activation of aldehyde C–H bonds using Rh-catalysis (Scheme 4.2). Over the past 50 years, activating aldehyde C–H bonds with Rh has been thoroughly investigated;12 however, the resulting acyl–RhIII–hydrides have been trapped mainly by hydroacylation13 or decarbonylation.14,15 This common intermediate is also implicated in hydroformylation, which is practiced on industrial scale using synthesis gas.16 Thus, we needed a strategy for diverting the acyl–RhIII–hydride toward dehydroformylation. To date, olefins generated by dehydroformylation have been observed in low-quantities during decarbonylations.15,17,18 One report describes the use of stoichiometric Ru for dehydroformylation of butyraldehyde19, while another uses heterogeneous Rh or Pd catalysts for transforming steroidal aldehydes at 160–300°C.20 In contrast, an Fe-

* From Murphy, S. K.; Park, J.-W.; Cruz, F. A.; Dong, V. M. Rh-catalyzed C-C bond cleavage by transfer hydroformylation. Science 2015, 2, 56. Reprinted with permission from AAAS.
peroxo complex cleaves aldehyde C–C bonds at room temperature, but this complex must be used in stoichiometric amounts and can lead to olefin epoxidation.\textsuperscript{21,22}

\[ \text{Scheme 4.2 Reactivity of acyl-Rh}^{\text{III}}\text{-hydrides.} \]

Given this challenge, we designed a strategy in which dehydroformylation of an aldehyde substrate is driven by the concomitant hydroformylation of a strained olefin acceptor (Scheme 4.3).\textsuperscript{23,24} This transfer hydroformylation avoids the accumulation of CO gas, which acts as a catalyst poison in related aldehyde dehomologations. Thus, formyl group transfer should proceed under mild conditions. Brookhart’s study on the linear-to-branched isomerization of aldehydes with Rh-catalysis supports the feasibility of this approach.\textsuperscript{25} Moreover, Morimoto developed hydroformylations of mono-substituted olefins using formaldehyde as a source of CO and H\textsubscript{2}.\textsuperscript{26} Here, we report a Rh-catalyst for transfer hydroformylation that operates in the 22\textdegree{} to 80\textdegree{}C temperature range, with loadings as low as 0.3 mol\%. This mild protocol for dehydroformylation can be applied to a wide range of aldehydes, including those derived from alkaloid, terpene, steroid, and macrolide natural products.

\[ \text{Scheme 4.3 Proposed transfer hydroformylation.} \]

### 4.2 Aldehyde Dehydroformylation

During initial studies, we obtained promising results by investigating non-traditional counterions for Rh(Xantphos) complexes (Scheme 4.4). The Xantphos ligand was chosen given its success in related hydroacylations, hydroformylations, and decarbonylations.\textsuperscript{13,16} Using citronellal (1a) and norbornadiene (5a) as the model substrate and acceptor, respectively, we observed that typical counterions such as BF\textsubscript{4}⁻ and Cl⁻ yielded trace amounts of decarbonylation
products, whereas a softer counterion, \( \Gamma \), led to mixed dehydroformylation and decarbonylation reactivity. An increase in reactivity and selectivity was obtained by switching to organic counterions such as phenolates and sulfonamidates. The use of a benzoate counterion provided a breakthrough in efficiency. Against expectations, further tuning of the counterion revealed few trends related to acidity, Hammett parameters, or coordinating ability. This observation suggests that the counterion plays a critical role in the mechanism \( (\text{vide infra}) \). 3-Methoxybenzoate provided a five-fold increase in initial rate compared to benzoate. We also identified 5-norbornene-2-carboxaldehyde (6a) as a stoichiometric product in each of these reactions indicating that a transfer hydroformylation mechanism operates.

![Scheme 4.4 Effects of counterion structure and ring strain. Data for counterion screen obtained by Colin Rathbun. Yields were determined by GC-FID analysis of the reaction mixtures using durene as an internal standard.](image)

The choice of olefin acceptor influences both catalyst loading and reaction temperature (Scheme 4.4). Because norbornadiene (5a) gave selectivity greater than 99:1 \( 2a:3a \), the catalyst loading could be lowered to 0.3 mol\% at 80 °C or 1 mol\% at 60 °C using this acceptor. The reaction temperature could be further reduced by using olefin acceptors that cannot chelate to Rh. For instance, norbornene (5b) displayed excellent reactivity at 40 °C, while a slightly more strained acceptor, benzonorbornadiene (5c), provided reactivity at ambient temperature. To
examine the scope of this strategy, we chose norbornadiene (5a) as the acceptor because it afforded the highest chemoselectivity with the lowest catalyst loadings.

This transfer hydroformylation protocol enables access to olefins from a wide range of aldehyde precursors (Scheme 4.5). The Diels-Alder cycloaddition was used to generate cyclohexene-4-carboxaldehyde substrates 1b through 1d. The trans adduct 1b underwent dehydroformylation to yield the conjugated 1,3-diene, whereas 1c gave a mixture of 1,3- and 1,4-dienes. The cis Diels-Alder adduct 1d yielded the 1,3-diene exclusively, most likely as a result of a syn-selective β-hydride elimination. We reason that the observed regioselectivities are controlled by kinetics because 4-phenylbutanal (1e) yields the terminal olefin (2e) without any isomerization to the styrene derivative. In general, Lewis basic functionality, such as ethers, esters, amines, phthalimides, and indoles, were tolerated (1f-1i, 1l). A vinylindole was derived by dehydroformylation of 1g, which was ultimately prepared from commercial indole and acrolein. Although 4-pentenals are prototypical substrates for intramolecular olefin hydroacylation, the α-allylated aldehyde 1h underwent chemoselective dehydroformylation to yield the conjugated diene. Disubstituted olefins enriched in the E-stereoisomer (>20:1 E/Z) were accessed from the corresponding α-arylated aldehydes (1i). Substrates that do not form conjugated products upon dehydroformylation were transformed with modest regioselectivities (1j and 1k); however, steric congestion favored terminal olefins over tri-substituted products (1l). Nonetheless, tri-substituted olefins were generated from substrates containing a single syn-β-hydrogen such as 1m.
Yields are of isolated materials and mixtures of regioisomers where indicated; \(rr\) = regioisomeric ratio; \(rr\) values were determined by \(^1\)H NMR analysis of the reaction mixtures; the yields of 2e and 2k were determined by \(^1\)H NMR analysis of the reaction mixtures using durene as an internal standard; see the supplementary materials for details. \(^3\) Reaction and analysis performed by Jung-Woo Park. \(^1\) Reaction and analysis performed by Faben Cruz.

Next, we applied this protocol to generate structurally complex olefins from natural products (Scheme 4.6). By dehydroformylation of a (+)-sclareolide derivative, we accessed a carbon-based scaffold 2n containing an exocyclic diene adjacent to a quaternary center. This product is a key intermediate in the synthesis of several terpenes. Furthermore, (+)-sclareolide is an inexpensive and readily available precursor, whereas typical precursors such as (+)-manool and (-)-polygodial have either been discontinued by commercial suppliers or are available only in milligram quantities.\(^{27}\) To study the chemoselectivity of dehydroformylation, we examined steroid and macrolide substrates (Scheme 4.6). Deoxycholic acid derivative 2o was prepared without protection of the hydroxyl groups, despite the potential for alcohol oxidation under Rh-
catalysis.\textsuperscript{28,29} Thus, activation of the aldehyde C–H bond occurred with high chemoselectivity to initiate C–C bond cleavage. Smooth dehydroformylation of the antibiotic spiramycin I to generate macrolide 2p highlights the tolerance of this method to many functional groups, including dienes, amines, ethers, esters, and acetals. In this case, dehydroformylation introduced an exocyclic olefin that dramatically altered the topology of the macrolide.

![Scheme 4.6 Dehydroformylation of natural product derivatives.](image)

\textsuperscript{§} Reaction and analysis performed by Jung-Woo Park. \textsuperscript{†} Reaction and analysis performed by Faben Cruz.

The yohimbinoid family of indole alkaloids has often served as a testing ground for methodology.\textsuperscript{30} Padwa reported the \textit{de novo} synthesis of racemic yohimbenone in 11 steps from methyl 3-indolylacetate.\textsuperscript{31} By using dehydroformylation as a key step, we prepared (+)-yohimbenone in 3 steps from commercially available and inexpensive (+)-yohimbine (Scheme 4.7). Conversion of ester 7a to β-hydroxy aldehyde 7b was achieved in 87\% yield by LiAlH\textsubscript{4} reduction followed by Parikh-Doering oxidation, and the resulting aldehyde was purified by a simple workup with sodium bisulfite. This aldehyde contains both a \\textit{syn}- and an \\textit{anti}-β-hydrogen. Syn-selective dehydroformylation established the trisubstituted olefin at the ring-junction. To our surprise, however, the resulting allylic alcohol underwent transfer dehydrogenation in the same pot to yield (+)-yohimbenone in 65\% yield. Because dehydroformylation is faster that the allylic alcohol oxidation, either the allylic alcohol or enone product could be selectively formed by controlling the reaction temperature and stoichiometry of the strained olefin acceptor.\textsuperscript{32}
Through experiments designed to probe the mechanism, we obtained insight into why the counterion and strained acceptor are critical in diverting the acyl-Rh\textsuperscript{III}-hydride intermediate along the dehydroformylation pathway (Scheme 4.8). Isotopic labeling studies revealed that the deuterium label of aldehyde \textit{d-1q} is incorporated into the formyl group of the product \textit{d-6c}. However, statistical scrambling occurred when protio-\textit{1q} was subjected to transfer hydroformylation in the presence of deuterated methanol. Together, these results suggest that the aldehyde proton is transferred to the product through the intermediacy of 3-methoxybenzoic acid, which can undergo proton-exchange with methanol. Experiments using stoichiometric Rh support this mechanistic scenario (Scheme 4.8). Combining the Rh-source, 3-methoxybenzoic acid, and phosphine ligand resulted in an equilibrium mixture of Rh-complexes \textit{8a} and \textit{8a’}, each with 3-methoxybenzoate counterions. Upon treatment of this mixture with hydrocinnamaldehyde (\textit{1q}), we observed styrene (\textit{2q}) in high yields along with the regeneration of the benzoic acid derivative.\textsuperscript{33} Subsequent addition of PPh\textsubscript{3} enabled us to identify the organometallic product, Rh-hydrido-carbonyl \textit{9}, which is a catalyst for traditional hydroformylations.\textsuperscript{34} Although stoichiometric dehydroformylation takes place in the absence of the strained acceptor, our studies on the catalytic process revealed a correlation between the ring strain of the acceptor and the selectivity for dehydroformylation versus decarbonylation. Therefore, we propose that stoichiometric dehydroformylation in the absence of acceptor is thermodynamically downhill and reversible, but norbornadiene can irreversibly trap the Rh-hydrido-carbonyl intermediate to prevent decarbonylation and turn over the catalyst.

\begin{align*}
\textbf{Scheme 4.7} & \text{ Three step synthesis of (+)-yohimbenone.}
\end{align*}
Deuterium labelling studies and stoichiometric reactions.

A proposed catalytic cycle for transfer hydroformylation is depicted in Scheme 4.9. The neutral Rh-complex 8a activates the aldehyde C–H bond to generate acyl-Rh$^{\text{III}}$-hydride 8b. The 3-methoxybenzoate counterion can then undergo reductive elimination with the hydride ligand to generate acyl-Rh$^{\text{I}}$ 8c and 3-methoxybenzoic acid.\textsuperscript{35} In contrast, most hydroacylations and decarbonylations typically employ innocent counterions such as Cl$^{-}$ and BF$_4^-$\textsuperscript{-}. De-insertion of CO and subsequent β-hydride elimination forges Rh-hydrido-carbonyl 8e. Exchange of the olefin product with nbd (5a) generates 8f, which irreversibly leads to the transfer hydroformylation product 6a through similar mechanistic steps in reverse order (Figure 4C). Thus, the ring-strain of the olefin acceptor and the ability of the counterion to act as a proton-shuttle by reversible redox processes afford high reactivity and selectivity.

Scheme 4.9 Proposed mechanism of transfer hydroformylation.
4.3 Conclusions

A Rh catalyst was designed to enable transfer of a formyl group and hydride from an aldehyde substrate to a strained olefin acceptor. A Rh(Xantphos)(benzoate) catalyst activates aldehyde C–H bonds with high chemoselectivity to trigger C–C bond cleavage and generate olefins at low loadings (0.3 to 2 mol%) and temperatures (22 to 80 °C). This mild protocol was applied to various natural products and was used to achieve a three step synthesis of (+)-yohimbenone. A study of the mechanism revealed that the benzoate counterion acts as a proton-shuttle to enable transfer hydroformylation.
4.4 Experimental

4.4.1 Substrate Preparation

(5c, BNBD)

1,4-Dihydro-1,4-methanonaphthalene

BNBD was prepared according to a procedure in literature (ref. 36).
Biscyclopentadiene was heated at 170 °C for one hour using a distillation apparatus to obtain cyclopentadiene monomer as the distillate. A THF (20 ml) solution of cyclopentadiene (0.85 ml, 10.06 mmol, 1.1 equiv) and 1-bromo-2-fluorobenzene (1.00 ml, 9.15 mmol, 1 equiv) was added to Mg turnings (267 mg, 10.98 mmol, 1.2 equiv). The Grignard formation was initiated with a small I₂ crystal, and the resulting solution was heated at reflux for one hour. The solution was quenched with saturated aq. NH₄Cl solution and extracted with ethyl acetate three times. The combined organic fractions were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography to afford a colourless liquid (0.781 g, 60% yield). The ¹H NMR spectrum matched the literature values (36).

¹H NMR (400 MHz, CDCl₃) δ 7.24 (dd, J = 5.1, 3.1 Hz, 1H), 6.94 (dd, J = 5.1, 3.1 Hz, 1H), 6.82 – 6.78 (m, 1H), 3.92 – 3.87 (m, 1H), 2.33 (dt, J = 7.0, 1.4 Hz, 1H), 2.28 – 2.23 (m, 1H).

(Scheme 4.5, 1b)

trans-6-Heptyl-3,4-dimethylcyclohex-3-ene-1-carbaldehyde

BF₃·Et₂O (0.20 mL, 1.6 mmol, 0.3 equiv) was added to a stirring solution of trans-2-decenal (1.00 mL, 5.5 mmol, 1 equiv) and 2,3-dimethylbutadiene (0.75 mL, 6.6 mmol, 1.2 equiv) in 1,2-dimethoxyethane (5.5 mL). The reaction mixture was stirred at room temperature for 6 hours. The resulting solution was diluted with ethyl acetate and quenched with saturated aq. NaHCO₃ solution. The organic layer was separated, dried with MgSO₄, filtered, and concentrated. The resulting oil was purified by Kuglerohr distillation to afford the product as a colourless oil (0.734
g, 56% yield). \textbf{\textsuperscript{1}H NMR} (500 MHz, CDCl$_3$) $\delta$ 9.60 (d, $J = 3.0$ Hz, 1H), 2.32 – 2.24 (m, 1H), 2.24 – 2.16 (m, 1H), 2.16 – 2.04 (m, 1H), 2.04 – 1.90 (m, 2H), 1.74 – 1.59 (m, 7H), 1.43 – 1.21 (m, 12H), 0.89 (t, $J = 6.7$ Hz, 3H). \textbf{\textsuperscript{13}C NMR} (126 MHz, CDCl$_3$) $\delta$ 205.58, 124.96, 122.55, 51.83, 35.57, 33.93, 33.35, 31.83, 29.78, 29.71, 29.26, 26.79, 22.64, 19.07, 18.73, 14.09. \textbf{HRMS} (Cl$^+$): calculated for [C$_{16}$H$_{28}$O]$^+$, 236.2140, found 236.2144.

(Scheme 4.5, 1c)

trans-6-Phenyl-3,4-dimethylcyclohex-3-ene-1-carbaldehyde

BF$_3$-Et$_2$O (0.30 mL, 2.4 mmol, 0.3 equiv) was added to a stirring solution of trans-cinnamaldehyde (1.00 mL, 8.0 mmol, 1 equiv) and 2,3-dimethylbutadiene (1.00 mL, 8.8 mmol, 1.1 equiv) in 1,2-dimethoxyethane (8 mL). The solution was stirred at room temperature for 12 hours. The solution was diluted with EtOAc and saturated aq. NaHCO$_3$ solution was added. The organic layer was separated, dried with MgSO$_4$, filtered, and concentrated. The resulting oil was purified by Kuglerohr distillation followed by column chromatography (0 to 5% EtOAc in Hexane) to afford the pure product as a colourless oil (1.050 g, 61% yield). The \textbf{\textsuperscript{1}H NMR} spectrum matched the literature reported values (37). \textbf{\textsuperscript{1}H NMR} (500 MHz, CDCl$_3$) $\delta$ 9.47 (d, $J = 2.8$ Hz, 1H), 7.35 – 7.29 (m, 2H), 7.26 – 7.18 (m, 3H), 3.14 – 3.03 (m, 1H), 2.87 – 2.75 (m, 1H), 2.36 – 2.16 (m, 3H), 2.14 – 2.02 (m, 1H), 1.71 (s, 3H), 1.67 (s, 3H).

(Scheme 4.5, 1d)

(cis-6-formyl-3,4-dimethylcyclohex-3-en-1-yl)methylbenzoate

Step 1: 2,3-dimethylbutadiene (1.00 mL, 8.79 mmol, 1 equiv) was added dropwise to a stirring solution of maleic anhydride (0.862 g, 8.79 mmol, 1 equiv) in THF (2 mL). CAUTION: The reaction is highly exothermic. After 45 minutes, an additional 45 mL of THF were added and
the vessel was cooled in an ice bath. LiAlH₄ (1.335 g, 35.2 mmol, 4 equiv) was added slowly. The solution was stirred for 5 hours and then quenched using the Fieser method. The solution was dried with MgSO₄, filtered, and concentrated. The residue was dissolved in EtOAc and precipitated with hexane to give the pure diol as a white solid (0.860 g, 57% yield). The ¹H NMR spectrum matched the literature reported values (38). ¹H NMR (400 MHz, CDCl₃) δ 3.75 (dd, J = 11.0, 6.9 Hz, 2H), 3.62 (dd, J = 11.1, 3.8 Hz, 2H), 3.19 (s, 2H), 2.17 – 2.05 (m, 4H), 1.98 (t, J = 12.8 Hz, 2H), 1.64 (s, 6H).

Step 2: Benzoyl chloride (0.59 mL, 4.70 mmol, 1 equiv) was added dropwise to a stirring solution of diol (0.800 g, 4.70 mmol, 1 equiv) in pyridine (10 mL). After 3 hours, the solution was concentrated and then re-dissolved in EtOAc. The solution was washed with saturated aq. NH₄Cl solution and then water. The organic layer was separated, dried with MgSO₄, filtered, and concentrated. The resulting residue was subjected to silica gel chromatography (0 to 35% EtOAc in hexane) to afford a 10:1 mixture of mono- to di-benzoylated products (0.7266 g, 56% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.09 (dd, J = 8.2, 1.0 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.7 Hz, 2H), 4.48 (dd, J = 11.0, 6.1 Hz, 1H), 4.23 (dd, J = 10.9, 7.6 Hz, 1H), 3.83 (s, J = 57.9 Hz, 1H), 3.76 – 3.62 (m, 1H), 2.48 – 2.40 (m, 1H), 2.28 – 1.81 (m, 6H), 1.68 (s, 6H).

Step 3: DMSO (0.41 mL, 5.82 mmol, 2.2 equiv) was added dropwise to a stirring solution of oxalyl chloride (0.25 mL, 2.91 mmol, 1.1 equiv) in DCM (10 mL) at -78 °C. The solution was stirred until gas evolution ceased (ca. 10 min), then the alcohol from step 2 (0.7266 g, 2.65 mmol, 1 equiv) in DCM (2 mL) was added dropwise. After 10 minutes, triethylamine (1.85 mL, 13.2 mmol, 5 equiv) was added. The solution was stirred for 2 hours and then the cold bath was removed and the solution was stirred for a further 15 minutes. Saturated aq. NH₄Cl was added. The product was extracted with DCM, and the resulting solution was dried with MgSO₄, filtered, and concentrated. The resulting oil was subjected to silica gel chromatography (0 to 15% EtOAc in Hexane) to afford the pure product as a clear, colourless oil (0.566 g, 78% yield). ¹H NMR (500 MHz, CDCl₃) δ 9.86 (s, 1H), 8.05 (d, J = 7.6 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.7 Hz, 2H), 4.47 – 4.33 (m, 2H), 2.83 – 2.71 (m, 2H), 2.43 – 2.25 (m, 3H), 2.10 (d, J = 17.1 Hz, 1H), 1.73 (s, 3H), 1.70 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 204.02, 166.51, 133.10, 129.98,
129.67, 128.48, 124.41, 123.64, 65.42, 48.22, 33.96, 33.47, 29.19, 19.11, 19.04. **HRMS (ESI+):** calculated for $[\text{C}_{17}\text{H}_{20}\text{O}_{3}\text{Na}]^+$, 295.1310, found 295.1312.

(Scheme 4.5, 1e)

4-Phenylbutanal

Step 1: A solution of 4-phenylbutyric acid (4.00 g, 24.4 mmol, 1 equiv) in THF (ca. 10 mL) was added to stirring suspension of LiAlH$_4$ (2.1 equiv) in THF (50 mL) at 0 °C. The cooling bath was removed and the solution was stirred at room temperature for 2 hours. The solution was cooled to 0 °C and quenched using the Fieser method. The resulting solution was dried with MgSO$_4$, filtered, and concentrated to afford the product as a colourless oil 3.10 g (85% yield) which was used in the next step without further purification.

Step 2: DMSO (2.91 mL, 41.0 mmol, 2.2 equiv) was added dropwise to a stirring solution of oxalyl chloride (1.92 mL, 22.4 mmol, 1.1 equiv) in DCM (80 mL) at -78 °C. The solution was stirred until gas evolution ceased (ca. 10 min), then 4-phenyl-1-butanol (2.80 g, 18.6 mmol, 1 equiv) in DCM (5 mL) was added dropwise. After 20 minutes, triethylamine (13.00 mL, 93.2 mmol, 5 equiv) was added. The solution was stirred for 16 hours and the cold bath was allowed to warm to room temperature. The reaction mixture was quenched with saturated aq. NH$_4$Cl solution. The product was extracted with DCM, and the resulting solution was dried with MgSO$_4$, filtered, and concentrated. The resulting oil was purified by Kugelrohr distillation to afford the pure $1b$ as a colourless oil (1.653 g, 60% yield). The $^1$H NMR spectrum matched the literature reported values (39). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.82 (s, 1H), 7.42 – 7.18 (m, 5H), 2.77 – 2.68 (m, 2H), 2.56 – 2.48 (m, 2H), 2.09 – 1.97 (m, 2H).
Step 1: Acrolein (10.3 mL, 153.6 mmol, 3 equiv), and morpholine-TFA salt (2.57 g, 12.8 mmol) was added to a solution of indole (6.0 g, 51.2 mmol, 1 equiv) in THF (200 mL) at room temperature. After 2 hours at 30 °C, the reaction mixture was concentrated in vacuo. The resulting residue was dissolved in MeOH (100 mL) and cooled to 0 °C. To the resulting solution was added NaBH₄ (3.875 g, 102.4 mmol, 2 equiv) portionwise. After addition of NaBH₄, the ice bath was removed and the solution was stirred at room temperature for 30 minutes. The solution was then concentrated in vacuo, extracted with EtOAc and washed with brine. The organic layer was dried with anhydrous MgSO₄, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography to afford a dark yellow oil (3.891 g, 43% yield). The ¹H NMR spectrum matched the literature reported values (40). ¹H NMR (400 MHz; CDCl₃): δ 7.63 (dd, J = 7.9, 0.7 Hz, 1H), 7.36 (dd, J = 8.1, 0.7 Hz, 1H), 7.20 (td, J = 7.6, 0.9 Hz, 1H), 7.13 (td, J = 7.4, 1.0 Hz, 1H), 6.99 (s, 1H), 3.74 (t, J = 6.4 Hz, 2H), 2.87 (t, J = 7.5 Hz, 2H), 2.04-1.97 (m, 2H).

Step 2: NaH (0.354 g, 8.85 mmol, 1.1 equiv) was added portionwise to a stirring solution of 3-(1H-indol-3-yl)-propan-1-ol in DMF at 0 °C and stirred for 1 h at 0 °C. Tosyl chloride (1.687g, 8.85 mmol, 1.1 equiv) and DMAP (99 mg, 0.81 mmol, 0.1 equiv) were added at 0 °C. The solution was allowed to warm to room temperature before heating to 60 °C for 24 h. The solution was quenched with saturated aq. NH₄Cl solution and extracted with EtOAc. The organic layer was washed with water, dried with anhydrous MgSO₄, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography to afford a dark orange oil (1.15 g, 43%
yield, <10% free indole). \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta 7.99-7.96\) (d, 1H), 7.75-7.71 (d, 2H), 7.50-7.47 (d, 1H), 7.35-7.28 (dt, 2H), 7.25-7.17 (m, 3H), 3.72-3.67 (t, 2H), 2.78-2.73 (t, 2H), 2.33-2.31 (s, 3H), 1.98-1.91 (m, 2H); \(^1\)C NMR (126 MHz; DMSO): \(\delta 145.3, 134.6, 134.2, 130.8, 130.2, 126.6, 124.7, 123.23, 123.14, 123.04, 119.8, 113.3, 60.0, 39.5, 31.7, 21.0, 20.6\); HRMS (ESI+): calculated for \([C_{18}H_{19}NO_3S+Na]^+\), 352.0983, found 352.0984.

Step 3: DMSO (0.30 mL, 4.18 mmol, 2.2 equiv) was added dropwise to a solution of oxalyl chloride (0.18 mL, 2.09 mmol, 1.1 equiv) and DCM (40 mL) at -78 °C, then stirred for 5 minutes. A solution of N-tosyl indole alcohol in DCM was added dropwise at -78 °C and stirred for 5 minutes. Triethylamine (1.3 mL, 9.50 mmol, 5 equiv) was added dropwise at -78 °C. The resulting solution was then warmed to room temperature and stirred for 2 hours. The reaction mixture was quenched with a solution of saturated aq. NH\(_4\)Cl and extracted with DCM. The organic layer was washed with water, dried with anhydrous MgSO\(_4\), filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography to afford a red solid (0.355 g, 57% yield). The \(^1\)H NMR spectrum matched the literature reported values (41). \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta 9.84\) (s, 1H), 7.99-7.97 (m, 1H), 7.73 (d, \(J = 8.3\) Hz, 2H), 7.48-7.46 (m, 1H), 7.34-7.30 (m, 2H), 7.24-7.20 (m, 3H), 3.02-2.98 (m, 2H), 2.86-2.83 (m, 2H), 2.33 (s, 3H).

(Scheme 4.5, 1h)

(E)-2-(2-(1,3-dioxoisindolin-2-yl)ethyl)-5-phenylpent-4-enal

The title compound was prepared according a literature procedure (42). Cinnamyl acetate (0.387 mL, 2.30 mmol, 1 equiv) was added to a stirring suspension of Pd(PPh\(_3\))\(_4\) (0.133 g, 0.115 mmol, 0.05 equiv) in DMSO (7 mL). The solution was sonicated for 5 minutes, and then a solution of 4-(1,3-dioxoisindolin-2-yl)butanal (prepared according to a procedure in literature (43), 0.600 g, 2.76 mmol, 1.2 equiv) in DMSO (1 mL) was added. After 24 hours, the mixture was diluted with EtOAc and extracted with water. The organic layer was dried with MgSO\(_4\), filtered, and concentrated. The resulting residue was subjected to silica gel chromatography to yield the pure
product as a yellow oil (0.415 g, 54% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.79 (d, $J = 1.2$ Hz, 1H), 7.95 – 7.84 (m, 2H), 7.84 – 7.73 (m, 2H), 7.39 – 7.32 (m, 4H), 7.29 – 7.24 (m, 1H), 6.53 (d, $J = 15.8$ Hz, 1H), 6.17 (dt, $J = 15.6$, 7.1 Hz, 1H), 3.84 (t, $J = 7.0$ Hz, 2H), 2.77 – 2.54 (m, 3H), 2.28 – 2.17 (m, 1H), 1.97 – 1.84 (m, 1H). HRMS (ESI+): calculated for [C$_{21}$H$_{19}$NO$_3$+Na]$^+$, 356.1263, found 356.1259.

(Scheme 4.5, 1i)

2-(4-Methoxyphenyl)-5-phenoxypentanal

Step 1: To a stirring solution of the ester (1.91 mL, 10.57 mmol) in DMF (30 mL) at 0 °C was added NaH (60 wt% in mineral oil, 0.507 g, 12.68 mmol, 1.2 equiv) portionwise. After 5 minutes, the alkyl bromide (2.00 mL, 12.68 mmol, 1.2 equiv) was added. After 6 hours, the mixture was diluted with EtOAc and extracted with saturated aq. NH$_4$Cl solution. The organic layer was separated and dried over MgSO$_4$, filtered, and concentrated to afford the crude α-alkylated ester.

Step 2: The crude material from step 1 was dissolved in dry THF (60 mL) and the solution was cooled to 0°C. LiAlH$_4$ (0.802 g, 21.14 mmol, 2 equiv) was added slowly. The reaction mixture was stirred for 16 hours and then quenched using the Fieser method. The resulting solution was dried with MgSO$_4$, filtered, and concentrated to afford the crude alcohol.

Step 3: DMSO (1.57 mL, 22.10 mmol, 2.4 equiv) was added dropwise to a stirring solution of oxalyl chloride (0.87 mL, 10.13 mmol, 1.1 equiv) in DCM (100 mL) at -78 °C. The solution was stirred until gas evolution ceased (ca. 5 min), then the alcohol from step 2 (2.62 mmol, 1 equiv) in DCM was added dropwise. After 10 minutes, triethylamine (6.42 mL, 46.04 mmol, 5 equiv) was added. The solution was stirred for 1 hour and then the cold bath was removed and the reaction mixture was stirred for a further 1 hour. Saturated aq. NH$_4$Cl was added. The product was extracted with DCM, and the resulting solution was dried with MgSO$_4$, filtered, and concentrated. The resulting oil was subjected to silica gel chromatography (0 to 20% EtOAc in
Hexane) to afford the pure product as a clear colourless oil (1.3089 g, 38% yield over 3 steps).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.75 (d, $J = 1.3$ Hz, 1H), 7.41 – 7.29 (m, 3H), 7.00 (t, $J = 7.3$ Hz, 1H), 6.95 – 6.90 (m, 3H), 6.88 (d, $J = 7.6$ Hz, 1H), 6.81 (s, 1H), 4.01 (t, $J = 6.2$ Hz, 2H), 3.87 (s, 3H), 3.63 (t, $J = 7.3$ Hz, 1H), 2.37 – 2.25 (m, 1H), 2.05 – 1.92 (m, 1H), 1.91 – 1.75 (m, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 200.40, 160.21, 158.88, 137.55, 130.21, 129.49, 121.21, 120.71, 114.68, 114.45, 112.97, 67.33, 58.89, 55.31, 26.86, 26.26; HRMS (Cl+): calculated for [C$_{18}$H$_{20}$O$_3$+NH$_4$]$^+$, 302.1756, found 302.1756.

(Scheme 4.5, 1j)

2-Isopropyldecane

Step 1: Sodium bis(trimethylsilyl)amide solution (7.5 ml, 2.0 M solution in THF, 15 mmol, 1.5 equiv.) was added to THF solution of methyl isobutyrate (1.16 g, 10 mmol, 1 equiv.) at -78 °C. The solution was stirred for 1 hour. Then, hexamethylphosphoramide (1.8 ml, 10 mmol, 1 equiv.) and 1-iododecane (3.2 ml, 15 mmol, 1.5 equiv.) were added. The solution was warmed to room temperature and stirred for 12 hours. The reaction mixture was quenched with aq. NH$_4$Cl solution, and extracted with ethyl acetate for 3 times. The collecting organic layer was dried over MgSO$_4$, filtered, and concentrated. The ester was obtained after column chromatography as colourless oil (1.3 g, 58% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.67 (s, 3H), 2.03-2.08 (m, 1H), 1.88-1.79 (m, 1H), 1.63-1.46 (m, 2H), 1.25 (m, 16H), 0.93-0.87 (m, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 176.6, 53.0, 51.2, 31.2, 30.8, 29.9, 29.8, 29.7, 29.6, 29.5, 28.0, 22.8, 20.7, 20.4, 14.3; HRMS (Cl+): calculated for [C$_{16}$H$_{32}$O$_2$+NH$_4$]$^+$ 274.2740, found 274.2746.

Step 2: LiAlH$_4$ (0.472 g, 12.5 mmol, 2.5 equiv) was added slowly to a stirring solution of ester (1.3 g, 5 mmol, 1 equiv) in 30 mL THF at 0 °C. The ice bath was removed and the solution was allowed to stir at room temperature for 4 hours. The reaction mixture was quenched using the Fieser method and the resulting solution was dried with MgSO$_4$, filtered, and concentrated. The alcohol was obtained after column chromatography (1.1 g, 94% yield). DMSO (0.51 mL, 7.2
mmol, 3 equiv) was added dropwise to a DCM solution of oxalyl chloride (0.25 mL, 2.88 mmol, 1.2 equiv) at -78 °C, then stirred for 30 minutes. A solution of alcohol (550 mg, 2.4 mmol, 1 equiv.) in DCM (5 ml) was added dropwise at -78 °C and stirred for 30 minutes. Triethylamine (1.7 mL, 12 mmol, 5 equiv) was added dropwise at -78 °C. The reaction mixture was then warmed to room temperature and stirred for additional 30 min. The solution was quenched with water and extracted with DCM. The organic layer was washed with water, dried with anhydrous MgSO₄, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography to afford pure Ij as colourless oil (0.373 g, 68% yield). ¹H NMR (400 MHz, CDCl₃): δ 9.61 (d, J=3.5 Hz, 1H), 2.06-1.93 (m, 2H), 1.68-1.59 (m, 1H), 1.50-1.42 (m, 1H), 1.26 (m, 1H), 0.96 (d, J=3.1 Hz, 6H), 0.88 (t, J=7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 206.3, 58.6, 32.1, 29.9, 29.7, 29.6, 29.5, 28.5, 27.8, 26.3, 22.8, 20.4, 20.0, 14.3. HRMS (Cl⁺): calculated for [C₁₅H₃₀O⁺NH₄⁺]⁺ 244.2640, found 244.2633.

(Scheme 4.5. 1k)

2-Methyl-4-phenylbutanal

Step 1: Methyl diethylmalonate (3.5 ml, 20.75 mmol, 1 equiv.) was added to the DMF (50 ml) solution of NaH (60%, 954 mg, 24.9 mmol, 1.5 equiv.), and the mixture was stirred at room temperature. Phenethyl bromide (3.4 ml, 24.9 mmol, 1.2 equiv.) was added to the reaction mixture and stirred 4 hours. The solution was quenched with saturated aq. NH₄Cl solution, diluted with ethyl acetate, and washed with H₂O for 3 times. The organic layer was dried over MgSO₄, filtered and concentrated under reduced procedure. The malonate was isolated by column chromatography as colourless oil (4.12 g, 71% isolated yield). The ¹H NMR spectrum matched the literature reported values (44). ¹H NMR (400 MHz, CDCl₃): δ 7.31-7.18 (m, 2H), 4.20 (q, J = 7.2 Hz, 4H), 2.71-2.57 (m, 2H), 2.20-2.16 (m, 2H), 1.51 (s, 3H), 1.27 (t, J = 7.2 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 172.4, 141.7, 128.6, 128.5, 126.2, 61.4, 53.8, 37.7, 31.0, 20.1, 14.2.

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Step 2: 2 M KOH (4.43 g, 79 mmol, 10 equiv.) aqueous solution was added to an ethanol (30 ml) solution of malonate (2.2 g, 7.9 mmol, 1 equiv.), and the solution was stirred for 12 hours at 80 °C. Excess amount of 2 M HCl solution was added to the solution and extracted with ethyl acetate for 3 times. The collected organic layer was dried over MgSO₄, filtered, and concentrated. The crude malonic acid was heated at 155 °C for 3 hours. The resulting brown liquid was subject to column chromatography to obtain acid as a yellow liquid (1.10 g, 78%). The ¹H NMR spectrum matched the literature reported values (45). ¹H NMR (400 MHz; CDCl₃): δ 7.33-7.29 (m, 2H), 7.23-7.19 (m, 3H), 2.72-2.68 (m, 2H), 2.53 (sextet, J=7.2 Hz, 1H), 2.12-2.03 (m, 1H), 1.82-1.73 (m, 2H), 1.26 (d, J = 7.0 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 183.2, 141.6, 128.6, 128.5, 126.1, 39.0, 35.3, 33.5, 17.1.

Step 3: LiAlH₄ (0.472 g, 12.5 mmol, 2.5 equiv) was added slowly to a stirring solution of acid (1.0 g, 7.3 mmol, 1 equiv) in 30 mL THF at 0 °C. The ice bath was removed and the reaction mixture was allowed to stir at room temperature for 4 hours. The reaction mixture was quenched using the Fieser method and the resulting solution was dried with MgSO₄, filtered, and concentrated. DMSO (1.55 mL, 21.9 mmol, 3 equiv) was added dropwise to a DCM solution of oxalyl chloride (0.75 mL, 8.76 mmol, 1.2 equiv) at -78 °C, then stirred for 30 minutes. A solution of crude alcohol in DCM (5 ml) was added dropwise at -78 °C and stirred for 30 minutes. Triethylamine (5.1 mL, 36.5 mmol, 5 equiv) was added dropwise at -78 °C. The reaction mixture was then warmed to room temperature and stirred for additional 30 min. The solution was quenched with water and extracted with DCM. The organic layer was washed with water, dried with anhydrous MgSO₄, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel column chromatography to afford 1k as a colourless liquid (0.781 g, 85% yield). The ¹H NMR spectrum matched the literature reported values (46). ¹H NMR (400 MHz, CDCl₃) δ 9.64 (d, J = 1.6 Hz, 1H), 7.33-7.29 (m, 2H), 7.23-7.19 (m, 3H), 2.71-2.66 (m, 2H), 2.44-2.34 (m, 1H), 2.13-2.03 (m, 1H), 1.73-1.64 (m, 1H), 1.16 (d, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 204.9, 141.5, 128.6, 128.5, 126.2, 45.8, 33.2, 32.3, 13.5.
Step 1: NaHMDS solution (2.0 M solution in THF, ca. 2.6 ml, 5.12 mmol, 1.5 equiv.) was added to THF solution (10 ml) of Ph₃PMeI (1.83 g, 5.12 mmol, 1.5 equiv.) at -78 °C dropwise. The mixture was stirred for an hour. Then, ketone (650 mg, 2.56 mmol, 1 equiv.) in THF (3 ml) was added to the solution, and stirred for 3 hours. The reaction mixture was quenched with aq. NH₄Cl, and extracted with DCM for 3 times. The collecting organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The product (alkene) was isolated by column chromatography as a clear colourless oil (480 mg, 74% yield). ¹H NMR (400 MHz; CDCl₃): δ 7.21-7.18 (m, 2H), 7.15-7.11 (m, 1H), 7.06-7.01 (m, 4H), 6.80-6.78 (m, 2H), 4.92 (m, 1H), 4.85 (m, 1H), 3.78 (s, 3H), 3.47 (t, J = 7.6 Hz, 1H), 3.16 (dd, J= 13.5, 6.4 Hz, 1H), 2.98 (dd, J = 13.6, 8.4 Hz, 1H), 1.62 (s, 3H); ¹³C NMR (400 MHz; CDCl₃): δ 158.2, 147.9, 140.9, 135.1, 129.1, 129.0, 128.1, 125.9, 113.6, 110.7, 55.3, 53.7, 40.2, 21.6; HRMS (Cl+): calculated for [C₁₈H₂₀O+NH₄]⁺ 270.1858, found 270.1857.

Step 2: BH₃·THF solution (1.0 M, 3.6 ml, 3.6 mmol, 2 equiv.) was added to alkene (460 mg, 1.8 mmol, 1 equiv.), and the solution was stirred at room temperature overnight. After evaporating solvent, the crude product was dissolved in MeOH (5 ml), and KOH (1.0 g, 18 mmol, 10 equiv.) in H₂O (5 ml) and H₂O₂ (30% aq., 0.4 ml, 20 equiv.) was added and stirred for 12 hours. The solution was quenched with aq. Na₂SO₃ solution and extracted with ethyl acetate for 3 times. The collected organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure. The product (alcohol) was isolated by column chromatography as a clear colourless oil (382 mg, 77% yield). ¹H NMR (400 MHz; CDCl₃): δ 7.21-7.12 & 6.98-6.94 (m, 5H), 7.10-7.05 (m, 2H), 6.81-6.75 (m, 2H), 3.78 & 3.76 (s each, 3H, ratio=1:2), 3.52-3.46 & 3.31-3.27 (m each, 2H, ratio=2:1); 3.19-3.16 & 2.97-2.93 (m each, 1H, ratio=2:1), 3.10-3.05 & 2.82-2.72 (m each, 2H,
ratio=1:2), 1.99-1.89 (m, 1H), 1.15 & 0.83 (d each, J = 6.8 Hz, 3H, ratio=2:1); $^{13}$C NMR (400 MHz; CDCl$_3$): $\delta$ 158.0, 141.0, 135.2, 130.0, 129.4, 129.2, 129.2, 128.3, 128.1, 125.9, 125.7, 113.7, 113.5, 66.6, 55.3, 50.2, 47.6, 40.9, 39.7, 39.4, 15.8, 12.9; HRMS (CI+): calculated for [C$_{18}$H$_{22}$O$_2$+NH$_4$]$^+$ 288.1964, found 288.1972.

Step 3: DMSO (0.28 mL, 4 mmol, 3 equiv) was added dropwise to a DCM solution of oxalyl chloride (0.14 mL, 1.6 mmol, 1.2 equiv) at -78 °C, then stirred for 30 minutes. A solution of alcohol (360 mg 1.33 mmol, 1 equiv) in DCM was added dropwise at -78 °C and stirred for 30 minutes. Triethylamine (0.94 mL, 6.67 mmol, 5 equiv) was added dropwise at -78 °C. The reaction mixture was then warmed to room temperature and stirred for additional 30 min. The resulting solution was quenched with water and extracted with DCM. The organic layer was washed with water, dried with anhydrous MgSO$_4$, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography to afford 3-(4-methoxyphenyl)-2-methyl-4-phenylbutanal (I) a colourless liquid (0.182 g, 47% yield). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 9.68 & 9.54 (d each, J = 2.6 Hz, 1H, ratio=1:2.16), 7.21-7.12 (m, 3H), 7.03-6.98 (m, 4H), 6.81-6.78 (m, 2H), 3.78 & 3.77 (s each, 3H, ratio=1:2.2), 3.29-3.00 m, 2H), 2.95-2.88 (m, 1H), 2.71-2.60 (m, 1H), 1.19 & 0.93 (d each, J = 7.0 Hz, 3H, ratio=2.1:1); $^{13}$C NMR (400 MHz; CDCl$_3$): $\delta$ 204.9, 204.8, 158.4, 138.9, 138.8, 133.4, 132.8, 129.6, 129.5, 129.3, 129.3, 126.3, 126.2, 113.9, 113.9, 55.3, 51.1, 51.0, 48.7, 47.4, 40.7, 39.0; HRMS (CI+): calculated for [C$_{18}$H$_{20}$O$_2$]$^+$ 268.1463, found 268.1473.

(Scheme 4.5, 1m)

2-Cyclopentyl-2-phenylacetaldehyde

\[
\begin{align*}
\text{Ph} & \text{CH}_{\text{OH}} \quad \text{i) (COCl)}_2 \text{ / cat. DMF} \\
\text{Ph} & \text{CH}_{\text{OMe}} \quad \text{DCM, 0 °C to rt} \\
\text{Ph} & \text{CH}_{\text{OMe}} \quad \text{DIBAL-H} \\
\text{Et}_{\text{2}O} & -78 ^{\circ} \text{C, 4 h} \\
\end{align*}
\]

Step 1: 2-Cyclopentyl-2-phenylacetic acid (550 mg, 2.7 mmol, 1 equiv.) and oxalyl chloride (350 μl, 4.05 mmol, 1.5 equiv.) were dissolved in dichloromethane (10 ml). Then, N,N’-dimethylformamide (4 drops) was added to the mixture dropwise. The mixture was warmed to rt and stirred for 4 hours. Then, the solution was concentrated in vacuo. The acid chloride was used
for the next step without further purification. The crude acid chloride and N,O-dimethylhydroxylamine hydrochloride (316 mg, 3.24 mmol, 1.2 equiv.) was dissolved in dichloromethane (10 ml). Then, triethylamine (0.95 ml, 6.75 mmol, 2.5 equiv.) was added dropwise. The reaction mixture was stirred for 4 hours at room temperature. Then, distilled water was added to the mixture, and the solution was extracted with dichloromethane for 3 times. The collecting organic layer was dried over anhydrous MgSO₄, and concentrated in vacuo. Pure weinreb amide [CAS: 169805-28-1] was obtained after column chromatography as a white solid (n-Hex:ethyl acetate=3:1, isolated yield: 93% (620 mg)). ¹H NMR (400 MHz; CDCl₃): δ 7.38-7.35 (m, 2H), 7.31-7.27 (m, 2H), 7.23-7.20 (m, 1H), 3.77-3.71 (br m, 1H), 3.54 (s, 3H), 3.15 (s, 3H), 2.66-2.59 (m, 1H), 1.67-1.53 (m, 3H), 1.50-1.43 (m, 1H), 1.40-1.32 (m, 1H), 1.22-1.13 (m, 1H), 1.10-1.00 (m, 1H).

LRMS (EI): calculated for [C₁₅H₂₂NO₂-H]⁺, 247.16, found 247.1.

Step 2: DIBAL (1 M solution in heptane, 3.75 ml, 3.75 mmol, 1.5 equiv.) was added to the diethyl ether (10 ml) solution of weinreb amide (620 mg, 2.5 mmol, 1 equiv.) precooled to -78 °C dropwise. The mixture was stirred for 4 hours at -78 °C. Then, aqueous HCl (1 M, 20 ml) solution was added slowly, and the solution was warmed to room temperature. The solution was extracted with diethyl ether for 3 times. Pure aldehyde In was obtained after column chromatography as a colourless liquid (n-Hex:ethyl acetate=40:1, isolated yield: 78% (366 mg). The ¹H NMR spectrum matched the literature reported values (47). ¹H NMR (400 MHz, CDCl₃) δ 9.69 (d, J = 3.0 Hz, 1H), 7.38-7.34 (m, 2H), 7.31-7.29 (m, 1H), 7.23-7.21 (m, 2H), 3.31 (dd, J = 10.5, 3.0 Hz, 1H), 2.02-1.90 (m, 1H), 1.71-1.43 (m, 6H), 1.33-1.22 (m, 1H), 1.13-1.02 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 201.0, 136.4, 129.2, 129.1, 127.6, 65.4, 40.4, 31.2, 30.9, 25.4, 24.6.

(Scheme 4.5, In)

2-((1S,8aS)-5,5,8a-trimethyl-2-methyleneoctahydropyrrolo[1,2-c]cycloheptene-1-yl)acetaldehyde

Sclareolide aldehyde derivative In was synthesized according to the procedure in literature (48).
Step 1: To a DCM (40 ml) solution of N,O-dimethylhydroxylamine hydrochloride (1.70 g, 10.0 mmol, 1.0 equiv.) at 0 ºC was added AlMe₃ (2.0 M in hexanes, 10.4 mL, 20.8 mmol, 2.08 equiv.) dropwise. The solution was warmed to room temperature and was stirred for 2 h. A solution of (+)-sclareolide (1.70 g, 10.0 mmol, 1.0 equiv.) in dichloromethane (20 mL) was added. The reaction mixture was stirred for another 2 h. After cooling to 0 ºC the reaction mixture was quenched with aq. H₂SO₄ (10%, 15 mL) carefully with evolution of a large amount of gas. The reaction mixture was allowed to warm to room temperature and the organic layer was separated. The aqueous phase was extracted with dichloromethane (50 ml) for 3 times. The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced procedure. Pure sclareolide weinreb amide was obtained by silica gel chromatography as a white solid (1.52 g, 71%). The ¹H NMR spectrum matched the literature reported values (48). ¹H NMR (400 MHz; CDCl₃) δ 3.71 (s, 3H), 3.17 (s, 3H), 2.59-2.41 (m, 3H), 1.96-1.90 (m, 2H), 1.68-1.65 (m, 1H), 1.58-1.24 (m, 6H), 1.15 (m, 4H), 1.03-0.93 (m, 2H) 0.86 (s, 3H), 0.81 (s, 3H), 0.78 (s, 3H).

Step 2: Pyridine (360 ml, 4.5 mmol, 2 equiv.) was added to DCM solution (5 ml) of sclareolide-weinreb amide (700 mg, 2.24 mmol, 1 equiv.). After cooling to -78 ºC, thionyl chloride (0.82 ml, 11.2 mmol, 5 equiv.) in DCM (10 ml) and pyridine (1.5 ml, 18.8 mmol, 8.4 equiv.) were added dropwise. The reaction mixture was stirred for 30 min, and quenched with NaHCO₃ (20 ml) at -78 ºC. The solution was warmed to room temperature and extracted with DCM for 3 times. The collected organic layer was dried over MgSO₄, filtered and concentrated under reduced procedure. Pure sclareolide-aldehyde derivative (1o) was obtained after column chromatography as a white solid (n-Hex:ethyl acetate=1:3, isolated yield: 79% (520 mg). The ¹H NMR spectrum matched the literature reported values (48). ¹H NMR (400 MHz, CDCl₃): δ 4.42 (m, 1H), 4.42 (m, 1H), 3.73 (s, 3H), 3.16 (s, 3H), 2.69 (dd, J = 15.8, 10.8 Hz, 1H), 2.50 (br d, J = 10.2 Hz, 1H), 2.43-2.36 (m, 2H), 2.15 (br ddd, J = 13.0, 12.7, 5.2 Hz, 1H), 1.77-1.72 (m, 1H), 1.62-1.12 (m, 8H), 0.89 (s, 3H), 0.82 (s, 3H), 0.74 (s, 3H).

Step 3: Diethyl ether solution of weinreb amide (500 mg, 1.7 mmol, 1 equiv.) was cooled to -78 ºC and DIBAL (1 M solution in toluene, 2.55 ml, 2.55 mmol, 1.5 equiv.) was added to the solution dropwise. The mixture was stirred for 4 hours at -78 ºC. Then, aqueous HCl (1 M, 20 ml) solution was added slowly, and the reaction mixture was warmed to room temperature. The
solution was extracted with diethyl ether for 3 times. The collected organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure. Pure sclareolide-aldehyde (1n) was obtained after column chromatography as a colourless liquid (n-Hex:ethyl acetate=40:1, isolated yield: 71% (282 mg). The ¹H and ¹³C NMR spectra matched the literature reported values (48).

¹H NMR (400 MHz, CDCl₃): δ 9.65 (dd, J = 2.9, 1.4 Hz, 1H), 4.83 (m, 1H), 4.40 (m, 1H), 2.50-2.40 (m, 3H), 2.14-2.07 (m, 1H), 1.80-1.74 (m, 1H), 1.60-1.48 (m, 4H), 1.43 (dm, J = 13.6 Hz, 1H), 1.35 (m, 1H), 1.25-1.18 (m, 1H), 1.14-1.06 (m, 1H), 0.91 (s, 3H), 0.83 (s, 3H), 0.72 (s, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 203.7, 148.7, 108.2, 55.4, 51.1, 42.2, 40.0, 39.5, 39.1, 37.6, 33.7, 24.1, 21.9, 19.4, 14.7.

(Scheme 4.5, 1o)

3α,12α-Dihydroxy-5β-cholanal-(24)

Step 1: LiAlH₄ (0.773 g, 20.4 mmol, 4 equiv) was added slowly to a stirring solution of deoxycholic acid (2.0 g, 5.1 mmol, 1 equiv) in 150 mL THF at 0 °C. The ice bath was removed and the reaction mixture was allowed to stir at room temperature for 16 hours. The solution was quenched using the Fieser method and the resulting solution was dried with MgSO₄, filtered, and concentrated. The residue was dissolved in DCM and hexanes to precipitate a white powder, then concentrated in vacuo to afford a white powder (1.5121 g, 78% yield). ¹H NMR spectrum matched the literature reported value (49). ¹H NMR (400 MHz, CDCl₃): δ 4.00 (s, 1H), 3.70 – 3.52 (m, 3H), 1.93 – 0.93 (m, 38H), 0.92 (s, 3H), 0.69 (s, 3H).
Step 2: TEMPO (16.6 mg, 0.106 mmol, 0.1 equiv) and PhI(OAc)₂ (0.3865 g, 1.2 mmol, 1.1 equiv) were added to a solution of 3α,12α,24-trihydroxy-5β-14α-cholane (0.400 g, 1.06 mmol, 1 equiv) in DCM (16 mL) at room temperature. The mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated in vacuo and purified by silica gel column chromatography to afford a white solid (286 mg, 76% yield). \(^1H\) NMR (500 MHz; CDCl₃): δ 9.76 (s, 1H), 3.98 (t, 1H), 3.65-3.58 (m, 1H), 2.50-2.33 (m, 2H), 1.90-1.46 (m, 16H), 1.46-1.29 (m, 6H), 1.28-1.22 (m, 2H), 1.17-1.00 (m, 3H), 0.97 (d, J = 7.6 Hz, 3H), 0.93-0.87 (s, 3H), 0.67 (s, 3H); \(^13C\) NMR (126 MHz; CDCl₃): δ 203.3, 73.3, 71.9, 48.4, 47.4, 46.6, 42.2, 41.1, 36.5, 36.1, 35.31, 35.20, 34.2, 33.8, 30.6, 28.8, 28.0, 27.6, 26.2, 23.8, 23.3, 17.5, 12.9 HRMS (ESI+): calculated for [C₂₄H₄₀O₃Na]^+, 399.2875, found 399.2872.

(Scheme 4.5, 7b)

Yohimbinal

Step 1: LiAlH₄ (0.556 g, 14.7 mmol, 3.46 equiv) was added slowly to a stirring solution of (+)-yohimbine (7a, 1.500 g, 4.23 mmol, 1 equiv) in THF (75 mL) at 0 °C. The ice bath was removed and the reaction mixture was stirred for 1.5 hours at room temperature. The solution was quenched using the Fieser method and the resulting solution was dried with MgSO₄, filtered, and concentrated. The residue was dissolved in DCM and then concentrated to afford an off-white foamy solid (1.302 g, 94% yield). \(^1H\) NMR (500 MHz, DMSO) δ 10.74 (s, 1H), 7.35 (d, J = 7.7 Hz, 1H), 7.29 (d, J = 7.9 Hz, 1H), 7.02 (t, J = 7.4 Hz, 1H), 6.95 (t, J = 7.4 Hz, 1H), 4.42 – 4.37 (m, 1H), 4.36 – 4.29 (m, 1H), 4.11 – 4.04 (m, 1H), 3.73 – 3.68 (m, 1H), 3.16 (d, J = 11.1 Hz, 1H), 2.99 (dd, J = 10.5, 5.0 Hz, 1H), 2.92 – 2.71 (m, 2H), 2.60 (d, J = 14.3 Hz, 1H), 2.50 – 2.40 (m, 2H), 2.06 (t, J = 10.5 Hz, 1H), 1.57 – 1.34 (m, 4H), 1.32 – 1.22 (m, 2H), 0.99 (dd, J = 23.9, 12.0 Hz, 1H). \(^13C\) NMR (126 MHz, DMSO) δ 136.56, 136.38, 127.17, 120.66, 118.71, 117.85, 111.41, 106.53, 66.03, 62.02, 61.01, 60.71, 53.07, 47.95, 41.70, 36.63, 33.59, 33.08, 24.31, 22.05. HRMS (ESI+): calculated for [C₂₀H₂₆N₂O₂+H]^+, 327.2072, found 327.2076. [α]₂⁰⁰ = -34.8 (c = 1.0, DCM)

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Step 2: The crude alcohol (400 mg, 1.23 mmol, 1 equiv) from step 1 was added to a stirring solution of NEt₃ (1.71 mL, 12.3 mmol, 10 equiv) in DMSO (8 mL). Separately, SO₃-pyridine (0.585 g, 3.67 mmol, 3 equiv) was dissolved in DMSO (2 mL) and the solution was shaken for 2 minutes. The solution of SO₃-pyridine was added to the solution of the alcohol. After 30 minutes, the transformation was approximately 60% complete as judged by LC-MS. Another solution of SO₃-pyridine (0.390 g, 2.45 mmol, 2 equiv) in DMSO (2 mL) was prepared and shaken for 2 minutes, and then added to the reaction mixture. After an additional 30 minutes, the transformation was quantitative as judged by LC-MS. DCM (100 mL) was added and the resulting solution was shaken with 10% w/w aq. NaSO₃H solution (100 mL) for 5 minutes. The layers were separated, and the process was repeated. The aqueous layers were combined and extracted with 100 mL DCM. To the resulting aqueous solution was added DCM (100 mL) and saturated aq. Na₂CO₃ solution (200 mL). The mixture was shaken and then the layers were separated. The aqueous layer was extracted with a further 2 x 100 mL of DCM. The three organic washes were combined, dried with MgSO₄, filtered, and concentrated. The resulting solid was triturated with 5 mL of 1:1 THF:hexane and the liquid was removed, leaving behind solid yohimbinal. The solid was dried in vacuo to afford pure yohimbinal (7h, 361 mg, 91% yield).

**¹H NMR** (500 MHz, DMSO) δ 10.74 (s, 1H), 9.71 (s, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.01 (t, J = 7.4 Hz, 1H), 6.94 (t, J = 7.4 Hz, 1H), 4.81 (s, 1H), 4.26 (s, 1H), 3.30 (d, J = 10.8 Hz, 1H), 3.05 – 2.93 (m, 1H), 2.88 (d, J = 10.8 Hz, 1H), 2.79 (t, J = 11.9 Hz, 1H), 2.60 (d, J = 15.9 Hz, 1H), 2.52 (s, 1H), 2.45 (d, J = 12.2 Hz, 1H), 2.17 (t, J = 10.6 Hz, 1H), 2.12 (d, J = 11.4 Hz, 1H), 2.03 (q, J = 10.7 Hz, 1H), 1.79 (d, J = 12.9 Hz, 1H), 1.61 – 1.26 (m, 4H), 1.02 (q, J = 11.9 Hz, 1H).

**¹³C NMR** (126 MHz, CDCl₃) δ 206.24, 136.45, 136.10, 120.71, 118.72, 117.85, 111.49, 106.61, 65.88, 61.61, 60.43, 58.45, 53.01, 40.82, 35.11, 34.13, 32.95, 23.49, 22.04.  

**HRMS** (ESI-): calculated for [C₂₀H₂₃N₂O]⁺, 323.1760, found 323.1755.  

[α]²⁰= -16.8 (c = 1.0, DCM)
4.4.2 Olefin Synthesis

**Method 4.1** Transfer hydroformylation with strained olefins

To a 1 dram vial was added the indicated amount of [Rh(COD)OMe]₂, xantphos, 3-OMeBzOH, and any solid substrates (aldehyde or acceptor). The indicated amounts of THF and liquid substrates (aldehyde or acceptor) were then added. When norbornadiene was used as an acceptor, it was crucial to add the norbornadiene last to achieve the fastest reaction rates. The vial was then sealed with a Teflon-lined screw cap and heated at the indicated temperature and time. Chemo- and regio-selectivity were determined from analysis of the reaction mixture by ¹H NMR analysis. The olefin product was isolated by either column chromatography or preparatory TLC. Alternatively, the yields of volatile products were determined either by GC-FID or ¹H NMR analysis.

*(Scheme 4.5, 2a)*

2,6-Dimethylhepta-1,5-diene

The title compound was synthesized according to Method 4.1 using [Rh(COD)OMe]₂ (1.9 mg, 0.004 mmol, 0.5 mol%), xantphos (4.6 mg, 0.008 mmol, 1 mol%), 3-OMeBzOH (1.2 mg, 0.008 mmol, 1 mol%), citronellal (144 µL, 0.8 mmol, 1 equiv), norbornadiene (98 µL, 0.96 mmol, 1.2 equiv), and THF (200 µL). After stirring at 60 °C for 24 hours, the yield was determined by GC-FID analysis using durene as an internal standard. 99% yield, >99:1 dehydroformylation:decarbonylation.

*(Scheme 4.5, 2b)*

5-Heptyl-1,2-dimethylcyclohexa-1,3-diene

The title compound was synthesized according to Method 4.1 using [Rh(COD)OMe]₂ (1.9 mg, 0.004 mmol, 0.5 mol%), xantphos (4.6 mg, 0.008 mmol, 1 mol%), 3-OMeBzOH (1.2 mg, 0.008 mmol, 1 mol%), aldehyde 1b (171.5 mg, 0.8 mmol, 1 equiv), norbornadiene (97.6 mL, 0.96 mmol, 1.2 equiv), and THF (200 mL). After stirring at 100 °C for 12 hours, the ¹H NMR of the reaction mixture showed 93:7 regioselectivity in favour of the conjugated diene. The product was isolated by column chromatography (100% pentanes) as a clear colorless oil (148.0 mg, 90% yield). ¹H NMR (500
MHz, CDCl$_3$) $\delta$ 5.78 (d, $J = 9.5$ Hz, 1H), 5.61 (d, $J = 9.5$ Hz, 1H), 2.34 – 2.22 (m, 1H), 2.16 (dd, $J = 16.6$, 8.2 Hz, 1H), 1.94 (t, $J = 14.7$ Hz, 1H), 1.79 (s, 3H), 1.75 (s, 3H), 1.50 – 1.27 (m, 12H), 0.94 (t, $J = 6.7$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 129.10, 128.86, 127.36, 123.64, 36.40, 34.96, 33.97, 31.95, 29.86, 29.39, 26.98, 22.74, 19.41, 17.17, 14.18. HRMS (Cl+): calculated for [C$_{15}$H$_{26}$-H$_2$]$^+$, 204.1878, found 204.1882.

(Scheme 4.5, 2c and 2c')

3,4-Dimethyl-1,2-dihydro-1,1'-biphenyl and 3,4-dimethyl-2,5-dihydro-1,1'-biphenyl

Dehydroformylation of 1e was performed according to Method 4.1 using [Rh(COD)OMe]$_2$ (2.0 mg, 0.004 mmol, 1 mol%), xantphos (4.6 mg, 0.008 mmol, 2 mol%), 3-OMeBzOH (1.2 mg, 0.008 mmol, 2 mol%), 4,5-dimethyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-carbaldehyde (1c, 85.6 mg, 0.4 mmol, 1 equiv), norbornadiene (44 mg, 0.48 mmol, 1.2 equiv), and THF (100 $\mu$L). After stirring at 80 °C for 24 hours, the yield and regioselectivity were determined by $^1$H NMR analysis (20 second relaxation delay) using 1,3,5-trimethoxybenzene as an internal standard (97% NMR yield, 2e/2e'=76/24). The product 2c was isolated by column chromatography (100% hexane) as a colourless oil (48.5 mg, 66% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.53 – 7.23 (m, 5H), 5.97 (d, $J = 9.4$ Hz, 1H), 5.76 (d, $J = 9.4$ Hz, 1H), 3.63 (t, $J = 10.7$ Hz, 1H), 2.53 – 2.24 (m, 2H), 1.83 (s, 3H), 1.80 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 146.04, 130.20, 128.43, 127.60, 127.08, 126.97, 126.23, 121.97, 41.02, 39.13, 19.23, 17.25. HRMS (Cl+): calculated for [C$_{14}$H$_{16}$-H$_2$]$^+$, 182.1095, found 182.1089.

(Scheme 4.5, 2d)

(4,5-Dimethylcyclohexa-2,4-dien-1-yl)methyl benzoate

The title compound was synthesized according to Method 4.1 using [Rh(COD)OMe]$_2$ (1.9 mg, 0.004 mmol, 0.5 mol%), xantphos (4.6 mg, 0.008 mmol, 1 mol%), 3-OMeBzOH (1.2 mg, 0.008 mmol, 1 mol%), 6-formyl-3,4-dimethylcyclohex-3-en-1-yl)methyl benzoate (1d, 218.0 mg, 0.8 mmol, 1 equiv), norbornadiene (98 $\mu$L, 0.96 mmol, 1.2 equiv), and THF (200 $\mu$L). After stirring at 90 °C for 8 hours, the regioselectivity (>95:5) was assessed by $^1$H NMR analysis of the reaction mixture. The product 2d was isolated by column chromatography (0→10% ethyl acetate in hexanes) as a clear
colorless oil (193 mg, 99% yield). The experiment was repeated using an identical procedure and an 85% yield was obtained in that case (92% average yield over two experiments). **¹H NMR** (500 MHz, CDCl₃) δ 8.11 (d, J = 7.3 Hz, 2H), 7.62 (t, J = 7.3 Hz, 1H), 7.50 (t, J = 7.3 Hz, 2H), 5.92 (d, J = 9.5 Hz, 1H), 5.67 (d, J = 9.5 Hz, 1H), 4.30 (d, J = 6.8 Hz, 2H), 2.81 (s, 1H), 2.39 – 2.27 (m, 1H), 2.24 – 2.14 (m, 1H), 1.82 (s, 3H), 1.78 (s, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 166.69, 132.94, 131.39, 130.42, 129.63, 128.40, 126.79, 123.85, 123.10, 66.93, 33.75, 32.81, 19.41, 17.22; **HRMS** (CI⁺): calculated for [C_{16}H_{18}O₂-H₂]⁺, 240.1150, found 240.1161.

**(Scheme 4.5, 2e)**

**3-Phenyl-1-propene**

The title compound was synthesized according to Method 4.1 using [Rh(COD)OMe]₂ (1.9 mg, 0.004 mmol, 0.5 mol%), xantphos (4.6 mg, 0.008 mmol, 1 mol%), 3-OMeBzOH (1.2 mg, 0.008 mmol, 1 mol%), 4-phenylbutanal (1e, 119 μL, 0.8 mmol, 1 equiv), norbornadiene (98 μL, 0.96 mmol, 1.2 equiv), and THF (200 μL). After stirring at 60 °C for 24 hours, the yield was determined by ¹H NMR analysis (20 second relaxation delay) using durene as an internal standard. 90% yield, >95:5 α:β.

**(Scheme 4.5, 2f)**

**1-(Phenylmethyl)-1,2,3,6-tetrahydropyridine**

The title compound was synthesized according to Method 4.1 using [Rh(COD)OMe]₂ (1.9 mg, 0.004 mmol, 1 mol%), Xantphos (4.6 mg, 0.008 mmol, 2 mol%), 3-OMeBzOH (1.2 mg, 0.008 mmol, 2 mol%), 4-carboxaldehyde-1-phenylmethylpiperidine (1f, 81.3 mg, 0.4 mmol, 1 equiv), norbornadiene (49 μL, 0.48 mmol, 1.2 equiv), and THF (100 μL). After stirring at 60 °C for 72 hours, the product 2f was isolated by column chromatography (30% diethyl ether in pentanes) as a clear colourless oil (47 mg, 67% yield). The ¹H NMR spectrum matched the literature reported values (50). **¹H NMR** (400 MHz, CDCl₃) δ 7.38-7.24 (m, 5H), 5.76 (d, J = 21.3 Hz, 1H), 5.66 (d, J = 20.2 Hz, 1H), 3.60 (s, 2H), 2.99 (quintet, J = 2.7 Hz, 2H), 2.58 (t, J = 5.7 Hz, 2H), 2.17 (qd, J = 5.6, 2.8 Hz, 2H).

**(Scheme 4.5, 2g)**

**3-Ethenyl-1-[(4-methylbenzene)sulfonyl]-1H-indole**
The title compound was synthesized according to Method 4.1 using [Rh(COD)OMe]₂ (1.0 mg, 0.002 mmol, 1 mol%), xantphos (2.3 mg, 0.004 mmol, 2 mol%), 3-OMeBzOH (0.6 mg, 0.004 mmol, 2 mol%), 3-(1-tosyl-1H-indol-3-yl)propanal (1g, 65.5 mg, 0.2 mmol, 1 equiv), norbornadiene (24 μL, 0.24 mmol, 1.2 equiv), and THF (50 μL). After stirring at 80 °C for 24 hours, the product 2g was isolated by column chromatography (10% EtOAc in Hexanes) as white solid (50 mg, 84% yield). The ¹H NMR spectrum matched the literature reported values (51).

¹H NMR (400 MHz; CDCl₃): δ 8.01 (d, J = 8.2 Hz, 1H), 7.79-7.73 (m, 3H), 7.62 (s, 1H), 7.34 (ddd, J = 8.2, 7.2, 1.1 Hz, 1H), 7.26 (s, 1H), 7.22-7.19 (m, 2H), 6.78 (ddd, J = 17.8, 11.3, 0.7 Hz, 1H), 5.80 (dt, J = 17.8, 0.6 Hz, 1H), 5.35 (dd, J = 11.3, 1.1 Hz, 1H), 2.32 (s, 3H).

(Scheme 4.5, 2h)

6-Phenylhexa-3,5-dien-1-yl)isoindoline-1,3-dione

The title compound was synthesized according to Method 4.1 using [Rh(COD)OMe]₂ (1.9 mg, 0.004 mmol, 1 mol%), xantphos (4.6 mg, 0.008 mmol, 2 mol%), 3-OMeBzOH (1.2 mg, 0.008 mmol, 2 mol%), 2-(2-(1,3-dioxoisindolin-2-yl)ethyl)-5-phenylpent-4-enal (1h, 133 mg, 0.4 mmol, 1 equiv), norbornene (114 mg, 1.2 mmol, 3 equiv), and THF (150 μL). After stirring at 80 °C for 16 hours, ¹H NMR analysis of an aliquot of the reaction mixture showed a 2.3:1 ratio of stereoisomers. The product was isolated by column chromatography (0→40% EtOAc in Hexanes) as white solid (97 mg, 80% yield). Major product (trans): ¹H NMR (500 MHz, CDCl₃) δ 7.90 (dd, J = 4.7, 3.0 Hz, 2H), 7.77 (dd, J = 4.7, 3.0 Hz, 2H), 7.46 – 7.21 (m, 5H), 6.78 (dd, J = 15.5, 10.5 Hz, 1H), 6.47 (d, J = 15.6 Hz, 1H), 6.29 (dd, J = 24.8, 13.7 Hz, 1H), 5.91 – 5.76 (m, 1H), 3.94 – 3.82 (m, 2H), 2.61 (q, J = 7.0 Hz, 2H). Minor product (cis): ¹H NMR (500 MHz, CDCl₃) δ 7.83 (dd, J = 4.8, 2.9 Hz, 2H), 7.68 (dd, J = 4.7, 3.0 Hz, 2H), 7.46 – 7.21 (m, 5H), 7.03 (dd, J = 15.4, 11.3 Hz, 1H), 6.47 (d, J = 15.6 Hz, 1H), 6.29 (dd, J = 24.8, 13.7 Hz, 1H), 5.59 (dd, J = 17.7, 8.3 Hz, 1H), 3.94 – 3.82 (m, 2H), 2.77 (q, J = 7.1 Hz, 2H). Combined ¹³C NMR (126 MHz, CDCl₃) δ 168.56, 168.41, 137.34, 137.23, 133.98, 133.84, 133.28, 132.12, 132.02, 131.87, 131.32, 130.33, 128.75, 128.61, 128.58, 127.60, 127.51, 127.40, 126.44, 126.30, 123.62, 123.31, 123.20, 37.59, 37.49, 32.10, 27.09. LRMS (EI+): calculated for [C₂₀H₁₇NO₂]⁺, 303.1, found 303.0.
(Scheme 4.5, 2i)

**1-Methoxy-4-(4-phenoxybut-1-en-1-yl)benzene**

The title compound was synthesized according to Method 4.1 using [Rh(COD)OMe]₂ (1.9 mg, 0.004 mmol, 1 mol%), xantphos (4.6 mg, 0.008 mmol, 2 mol%), 3-OMeBzOH (1.2 mg, 0.008 mmol, 2 mol%), 2-(4-methoxyphenyl)-5-phenoxypentanal (1i, 114 mg, 0.4 mmol, 1 equiv), norbornene (112 mg, 1.2 mmol, 3 equiv), and THF (100 μL). After stirring at 40 °C for 24 hours, the product 2i was isolated by column chromatography as colourless oil (79 mg, 78% yield).

**¹H NMR** (500 MHz, CDCl₃) δ 7.30 (t, J = 7.4 Hz, 2H), 7.23 (t, J = 7.5 Hz, 1H), 7.01 – 6.90 (m, 5H), 6.79 (d, J = 8.0 Hz, 1H), 6.51 (d, J = 15.9 Hz, 1H), 6.36 – 6.27 (m, 1H), 4.10 (t, J = 6.7 Hz, 2H), 3.83 (s, 3H), 2.72 (q, J = 6.7 Hz, 2H).

**¹³C NMR** (126 MHz, CDCl₃) δ 159.83, 158.89, 138.90, 132.12, 129.54, 129.51, 126.56, 120.78, 118.83, 114.63, 112.93, 111.43, 67.32, 55.27, 33.01.

**HRMS** (CI+): calculated for [C₁₇H₁₈O₂+NH₄]⁺, 272.1650, found 272.1643.

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(Scheme 4.5, 2j and 2j’)

**Dehydroformylation of 1j**

Dehydroformylation of 2-isopropyldecanal (1j) was performed according to Method 4.1 using [Rh(COD)OMe]₂ (1.0 mg, 0.002 mmol, 1 mol%), xantphos (2.3 mg, 0.004 mmol, 2 mol%), 3-OMeBzOH (1.2 mg, 0.004 mmol, 2 mol%), 1j (45.2 mg, 0.2 mmol, 1 equiv), norbornene (56.4 mg, 0.6 mmol, 3 equiv), and THF (100 μL). After stirring at 80 °C for 48 hours, the yield and regioselectivity of 2j and 2j’ was determined by ¹H NMR analysis (20 second relaxation delay) using 1,3,5-trimethoxybenzene as an internal standard (97% yield, 2j:2j’ = 65:32; E/Z of 2j=88/12)).

**¹H NMR** (400 MHz; CDCl₃): for 2j, δ 5.37-5.26 (m, 2H, trans), 5.23-5.14 (m, 2H, cis), 2.65-2.56 (m, 1H, cis), 2.29-2.18 (m, 1H, trans), 1.99-1.94 (m, 2H), 1.35-1.27 (m, 14H), 0.97 (d, J = 6.8 Hz, 6H), 0.89 (t, J = 6.8 Hz, 3H); for 2j’, δ 5.09 (tm, J = 7.2 Hz, 1H), 2.05-2.01 (m, 2H), 1.70 (s, 3H), 1.61 (s, 3H), 1.35-1.27 (m, 16H), 0.89 (t, J = 6.8 Hz, 3H).

**HRMS** (CI+): calculated for [C₁₄H₂₈]⁺, 196.2191, found 196.2187.
(Scheme 4.5, 2k and 2k’)

Dehydroformylation of 1k

Dehydroformylation of 2-methyl-4-phenylbutanal (1k) was performed according to Method 4.1 using [Rh(COD)OMe]₂ (1.0 mg, 0.002 mmol, 1 mol%), xantphos (2.3 mg, 0.004 mmol, 2 mol%), 3-OMeBzOH (1.2 mg, 0.004 mmol, 1 mol%), 1k (37.6 mg, 0.4 mmol, 1 equiv), norbornadiene (22 mg, 0.24 mmol, 1.2 equiv), and THF (100 μL). After stirring at 80 °C for 36 hours, the yield was determined by ¹H NMR analysis (20 second relaxation delay) using 1,3,5-trimethoxybenzene as an internal standard (71% yield, 2k:2k’ = 41:30). The combined product was isolated by column chromatography (100% pentanes) as a colourless oil (32.2 mg, 59% yield). ¹H NMR (400 MHz; CDCl₃): for 2k, δ 7.33-7.29 (m, 2H), 7.22-7.19 (m, 3H), 5.64-5.56 (m, 2H), 3.43 (d, J = 5.2 Hz, 2H, cis), 3.34 (d, J = 6.3 Hz, 2H, trans), 1.75 (dm, J = 4.9 Hz, 3H, cis) 1.71 (dm, J = 6.1 Hz, 3H, trans); for 2k’, δ 7.33-7.29 (m, 2H), 7.22-7.19 (m, 3H), 5.93-5.84 (m, 1H), 5.09-4.99 (m, 2H), 2.74 (t, J = 7.8 Hz, 2H) 2.42-2.37 (m, 2H).

(Scheme 4.5, 2l)

1-Methoxy-4-(1-phenylbut-3-en-2-yl)benzene

The title compound was synthesized according to Method 4.1 using [Rh(COD)OMe]₂ (1.0 mg, 0.002 mmol, 1 mol%), xantphos (2.3 mg, 0.004 mmol, 2 mol%), 3-OMeBzOH (1.2 mg, 0.004 mmol, 1 mol%), 3-(4-methoxyphenyl)-2-methyl-4-phenylbutanal (1l, 53.6 mg, 0.2 mmol, 1 equiv, 2/1 mixture of diastereomers), norbornadiene (22 mg, 0.24 mmol, 1.2 equiv), and THF (50 μL). After stirring at 80 °C for 24 hours, the product 2l was isolated by preparatory TLC as a colourless oil (39 mg, 81% yield). ¹H NMR (400 MHz; CDCl₃): δ 7.24-7.21 (m, 2H), 7.18-7.14 (m, 1H), 7.09-7.06 (m, 4H), 6.84-6.82 (m, 2H), 6.02 (td, J = 7.4, 1.0 Hz, 1H), 5.03-4.92 (m, 2H), 3.80 (s, 3H), 3.54 (q, J = 7.2 Hz, 1H), 3.0 (m, 2H); ¹³C NMR (100 MHz): δ 158.2, 141.8, 140.3, 135.8, 129.4, 128.9, 128.2, 126.0, 114.5, 113.9, 55.4, 50.8, 42.4; HRMS (CI+): calculated for [C₁₇H₁₈O₂+NH₄]⁺, 256.1701, found 256.1706.
(Scheme 4.5, 2m)

(Cyclopentylidenemethyl)benzene

The title compound was synthesized according to Method 4.1 using [Rh(COD)OMe]₂ (1.9 mg, 0.004 mmol, 1 mol%), xantphos (4.6 mg, 0.008 mmol, 2 mol%), 3-OMeBzOH (2.4 mg, 0.008 mmol, 2 mol%), 2-cyclopentyl-2-phenylacetaldehyde (1m, 75.2 mg, 0.4 mmol, 1 equiv), norbornadiene (44 mg, 0.48 mmol, 1.2 equiv), and THF (100 μL).

After stirring at 80 °C for 24 hours, the yield was determined by ¹H NMR analysis (20 second relaxation delay) using 1,3,5-trimethoxybenzene as an internal standard (95% yield). The product 2m was isolated by column chromatography (100% pentanes) as a clear colourless oil (53.2 mg, 84% yield). The ¹H and ¹³C NMR spectra matched the literature reported values (52). ¹H NMR (400 MHz; CDCl₃): δ 7.33-7.30 (m, 4H), 7.20-7.14 (m, J = 1 Hz), 6.371 (quintet, J = 2.4 Hz, 1H), 2.58-2.54 (m, 2H), 2.52-2.48 (m, 2H), 1.80 (quintet, J = 7.2 Hz, 2H), 1.68 (quintet, J = 6.4 Hz, 2H). ¹³C NMR (100 MHz): δ 147.4, 139.0, 128.3, 128.1, 125.7, 120.9, 36.1, 31.3, 27.4, 25.8.

(Scheme 4.5, 2n)

(4aS,8aS)-1,1,4a-trimethyl-5,6-dimethylenedecahyronaphthalene

The title compound was synthesized according to Method 4.1 using [Rh(COD)OMe]₂ (1.0 mg, 0.002 mmol, 1 mol%), xantphos (2.3 mg, 0.004 mmol, 2 mol%), 3-OMeBzOH (1.2 mg, 0.004 mmol, 1 mol%), sclareolide-aldehyde (1n, 46.8 mg, 0.2 mmol, 1 equiv), norbornadiene (22 mg, 0.24 mmol, 1.2 equiv), and THF (100 μL).

After stirring at 80 °C for 24 hours, the yield was determined by ¹H NMR analysis (20 second relaxation delay) using 1,3,5-trimethoxybenzene as an internal standard (97% yield). The pure diene 2n was isolated by column chromatography (100% pentane) as a colourless oil (33.3 mg, 82% yield). The ¹H and ¹³C NMR spectra matched the literature reported values (53). ¹H NMR (400 MHz; CDCl₃): δ 4.80 (t, J = 2.6 Hz, 1H), 4.77 (d, J = 1.9 Hz, 1H), 4.66 (t, J = 2.6 Hz, 1H), 4.54 (t, J = 1.9 Hz, 1H), 2.48 (dq, J = 13.6, 2.2 Hz, 1H), 2.18-2.09 (m, 1H), 1.77-1.71 (m, 1H), 1.69-1.61 (m, 2H), 1.61-1.52 (m, 2H), 1.51-1.48 (m, 1H), 1.47-1.41 (m, 2H), 1.24-1.16 (m, 1H), 1.13 (dd, J = 16.4, 2.8 Hz, 1H), 0.96 (d, J = 0.8 Hz, 1H), 0.89 (s, 3H), 0.87 (s, 3H); ¹³C NMR (100 MHz): δ 162.0, 150.2, 109.0, 103.2, 52.7, 42.4, 40.4, 37.7, 36.1, 34.0, 33.6, 22.9, 22.2, 20.8, 19.3.
(Scheme 4.5, 2o)

24-Nor-5β-chol-22-ene-3α,12α-diol

The title compound was synthesized according to Method 4.1 using [Rh(COD)OMe]₂ (1.0 mg, 0.004 mmol, 1 mol%), Xantphos (2.3 mg, 0.008 mmol, 2 mol%), 3-OMeBzOH (0.6 mg, 0.008 mmol, 2 mol%), 3α,12α-dihydroxy-5β-cholanal-(24) (1o, 75.3 mg, 0.2 mmol, 1 equiv), norbornadiene (24 μL, 0.24 mmol, 1.2 equiv), and THF (50 μL). After stirring at 80 °C for 72 hours, the product 2o was isolated by column chromatography (50% EtOAc in Hexanes) as a clear pale yellow solid (45 mg, 64% yield). ¹H NMR (500 MHz; CDCl₃): δ 5.73-5.63 (m, 1H), 4.95-4.87 (dd, 1H), 4.86-4.78 (dd, 1H), 4.01-3.94 (t, 1H), 3.66-3.56 (m, 1H), 2.11-2.00 (m, 1H), 1.88-1.75 (m, 3H), 1.75-1.64 (m, 3H), 1.64-1.48 (m, 6H), 1.48-1.30 (m, 4H), 1.31-1.18 (m, 2H), 1.19-1.10 (m, 1H), 1.10-1.05 (d, 2H), 1.05-0.94 (dt, 2H), 0.94-0.89 (s, 2H), 0.89-0.82 (m, 1H), 0.74-0.67 (s, 2H); ¹³C NMR (126 MHz; CDCl₃): δ 145.0, 112.0, 73.3, 72.0, 48.5, 47.1, 46.6, 42.2, 41.1, 36.6, 36.2, 35.4, 34.3, 33.9, 30.7, 28.8, 27.9, 27.3, 26.3, 23.8, 23.3, 19.5, 13.1; HRMS (ESI+): calculated for [C₂₃H₃₈O₂+Na]⁺, 369.2769, found 369.2777.

(Scheme 4.5, 2p)

Spiramycin derivative

The title compound was synthesized according to Method 4.1 using [Rh(COD)OMe]₂ (3.1 mg, 0.0064 mmol, 4 mol%), xantphos (7.4 mg, 0.00128 mmol, 8 mol%), 3-OMeBzOH (1.9 mg, 0.00128 mmol, 8 mol%), spiramycin I (1p, 135 mg, 0.16 mmol, 1 equiv), norbornadiene (50 μL, 0.48 mmol, 3 equiv), and THF (2.56 mL). After stirring at 80 °C for 3 days, the product 2p was isolated by preparative thin-layer chromatography (1:1:0.2:0.05 ethyl acetate:dichloromethane:methanol:ammonium hydroxide) as a white solid (105 mg, 80% yield). ¹H NMR (500 MHz, CDCl₃) δ 6.12 (dd, J = 15.1, 10.5 Hz, 1H), 6.03 (dd, J = 14.7, 10.7 Hz, 1H), 5.80 (dd, J = 15.2, 7.7 Hz, 1H), 5.56 (ddd, J = 14.9, 10.9, 4.2 Hz, 1H), 5.33 – 5.23 (m, 2H), 5.13 (d, J = 3.0 Hz, 1H), 5.07 (s, 1H), 4.50 (d, J = 8.0 Hz, 1H), 4.40 – 4.30 (m, 3H), 4.12 (s, J = 23.3
Hz, 1H), 3.70 (t, \( J = 9.3 \) Hz, 2H), 3.62 (s, 3H), 3.57 – 3.48 (m, 1H), 3.33 (d, \( J = 5.1 \) Hz, 2H), 3.16 (d, \( J = 8.3 \) Hz, 1H), 3.00 (d, \( J = 9.8 \) Hz, 1H), 2.77 (dd, \( J = 15.9, 10.5 \) Hz, 1H), 2.64 – 2.44 (m, 8H), 2.31 (d, \( J = 17.1 \) Hz, 8H), 2.29 – 2.17 (m, 2H), 2.17 – 2.03 (m, 2H), 2.02 – 1.87 (m, 2H), 1.84 – 1.72 (m, 2H), 1.64 – 1.49 (m, 2H), 1.43 – 1.22 (m, 19H), 1.09 (d, \( J = 6.7 \) Hz, 3H).

\[ ^{13}C \text{ NMR} \ (126 \text{ MHz, CDCl}_3) \delta 173.85, 144.31, 132.60, 132.49, 131.34, 130.60, 114.33, 110.01, 104.21, 101.52, 96.21, 93.34, 87.29, 84.17, 81.35, 76.49, 73.70, 73.41, 71.99, 69.54, 69.39, 68.80, 67.72, 66.12, 64.97, 62.26, 42.09, 41.66, 40.96, 40.74, 38.69, 33.96, 32.26, 31.66, 31.21, 25.49, 20.21, 19.33, 19.23, 18.69, 18.34, 16.30. \]

HRMS (ESI\(^+\)): calculated for [C\(_{42}\)H\(_{72}\)N\(_2\)O\(_{13}\)+Na], 835.4932, found 835.4932.

(Scheme 4.5, 7c)

(+-)Yohimbenone

The title compound was synthesized according to Method 4.1 using [Rh(COD)OMe]\(_2\) (1.9 mg, 0.004 mmol, 2 mol%), xantphos (4.6 mg, 0.008 mmol, 4 mol%), 3-OMeBzOH (1.2 mg, 0.008 mmol, 1 mol%), yohimbinal (65.0 mg, 0.2 mmol, 1 equiv), norbornene (110 mg, 1.2 mmol, 6 equiv), and THF (200 mL). After stirring at 70 °C for 24 hours, the product was isolated by thin-layer chromatography (5% NEt\(_3\) in ethyl acetate) as a light yellow solid (38 mg, 65% yield). The \(^1\)H and \(^{13}\)C NMR data match those reported in the literature (31); however, one previous report appears to have mis-tabulated the data and reported a water signal as a key peak. Aside from this discrepancy, all other data is consistent with the literature. \(^1\)H NMR (500 MHz, DMSO): \( \delta \) 10.89 (s, 1H), 7.42 (d, \( J = 7.8 \) Hz, 1H), 7.33 (d, \( J = 8.0 \) Hz, 1H), 7.07 (t, \( J = 7.5 \) Hz, 1H), 6.99 (t, \( J = 7.4 \) Hz, 1H), 5.87 (s, 1H), 3.23 (dd, \( J = 11.2, 6.0 \) Hz, 1H), 3.17 – 3.09 (m, 2H), 2.91 – 2.75 (m, 2H), 2.74 – 2.67 (m, 1H), 2.63 – 2.54 (m, 2H), 2.46 – 2.29 (m, 3H), 2.22 (t, \( J = 11.1 \) Hz, 1H), 2.11 – 2.03 (m, 1H), 1.62 (ddd, \( J = 24.4, 14.0, 4.8 \) Hz, 1H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \( \delta \) 198.6, 163.6, 136.2, 134.8, 126.8, 124.7, 120.8, 118.6, 117.8, 111.2, 106.8, 61.0, 59.0, 51.8, 38.3, 36.7, 36.4, 25.7, 21.6. Changing the temperature and equivalents of acceptor changes the selectivity for the enone versus the allylic alcohol: 60 °C, 3 equiv NBE, 24 h, full conversion, 1:1 enone:allylic alcohol; 60 °C, 5 equiv NBE, 24 h, full conversion, 4:1 enone:allylic alcohol; 50 °C, 3 equiv NBE, 24 h, full conversion, 1:3 enone:allylic alcohol.
4.4.3 Mechanistic Studies

(Scheme 4.8, 6c)

1,2,3,4-Tetrahydro-1,4-methanonaphthalene-2-carbaldehyde

The mixture of [Rh(COD)OMe]₂ (7.8 mg, 0.016 mmol, 0.02 equiv.), xantphos (18.4 mg, 0.032 mmol, 0.04 equiv.), 3-OMeBzOH (4.9 mg, 0.032 mmol, 0.04 equiv.), and THF (200 μl) was stirred for 5 min at room temperature. Citronellal (1a, 123.2 mg, 0.8 mmol, 1 equiv.) and BNBD (5c, 0.96 mmol, 1.2 equiv.) was added and the vial was then sealed with a Teflon-lined screw cap and heated at 60 °C for 6 hours. The 1,2,3,4-tetrahydro-1,4-methanonaphthalene-2-carbaldehyde (6c) was isolated by column chromatography (96.7 mg, 70% isolated yield based on citronellal). \(^1\)H NMR (400 MHz; CDCl₃): δ 9.91 (d, \(J = 1.6\) Hz, 1H), 7.25-7.20 (m, 2H), 7.21-7.01 (m, 3H), 3.66 (s, 1H), 3.46-3.45 (m, 1H), 2.47-2.43 (m, 1H), 2.28 (ddd, \(J = 12.4, 4.0, 4.8\) Hz, 1 H), 1.78-1.74 (m, 1H), 1.60 (dt, \(J = 9.6, 1.5\) Hz, 1H); \(^13\)C NMR (100 MHz; CDCl₃): δ 203.1, 148.8, 148.6, 126.3, 126.1, 121.1, 120.9, 53.4, 46.9, 45.5, 43.7, 29.1; HRMS (Cl+): calculated for [C₁₂H₁₂O+N₄H]⁺, 190.1232, found 190.1233.

(Scheme 4.8, 2r, d-6c)

The reaction was performed according to Method 4.1 using [Rh(COD)OMe]₂ (2.4 mg, 0.005 mmol, 5 mol%), xantphos (5.8 mg, 0.01 mmol, 10 mol%), 3-OMeBzOH (1.5 mg, 0.01 mmol, 10 mol%), 13.2 μL, 0.1 mmol, 1 equiv), 5c (17.1 mg, 0.12 mmol, 1.2 equiv), and THF (200 μL). After stirring at 22 °C for 24 hours, the yield and deuterium content were determined by \(^1\)H and \(^2\)H NMR analysis of the resulting mixture using durene as an internal standard. 72% yield of 2r, 91% yield of d-6c with 91% d-content at the formyl position. The ~9% loss of the deuterium label is likely due the formation of 10 mol% protio-methanol upon mixing the catalyst components.
The reaction was performed according to a modified version of Method 4.1 using [Rh(COD)OMe]₂ (2.4 mg, 0.005 mmol, 5 mol%), xantphos (5.8 mg, 0.01 mmol, 10 mol%), 3-OMeBzOH (1.5 mg, 0.01 mmol, 10 mol%), d-1r (13.2 μL, 0.1 mmol, 1 equiv), 5c (17.1 mg, 0.12 mmol, 1.2 equiv), and THF (200 μL). Deuterated methanol (4.1 μL, 0.1 mmol, 1 equiv) was added to the reaction vessel immediately after the aldehyde was added. After stirring at 22 °C for 24 hours, the yield and deuterium content were determined by ¹H and ²H NMR analysis of the crude material using durene as an internal standard. 86% yield of 2r, 96% yield of h/d-6c with 41% d-content at the formyl position.

(Scheme 4.8, 8a, 8a’, 2r, 9)

To a 1 dram vial was added [Rh(COD)OMe]₂ (10.0 mg, 0.00206 mmol, 0.5 equiv), xantphos (23.9 mg, 0.00412 mmol, 1 equiv), 3-OMeBzOH (6.3 mg, 0.00412 mmol, 1 equiv), durene (10 mg) as an internal standard, and d₈-THF (700 μL). Analysis of the crude material by ³¹P NMR revealed a 3.6:1 mixture 8a’ to 8a. ³¹P NMR (162 MHz, d₈-THF) δ 36.74 (d, J = 208.6 Hz), 5.53 (d, J = 90.3 Hz). The peak at 5.53 ppm corresponds to 8a’ based on comparison to an authentic sample of [Rh(Xantphos)(COD)]BF₄. We assign the peak at 36.74 ppm based on analogy to a [Rh(BIPHEP)(2,6-dimethoxybenzoate)] complex as in the previous report (54). Hydrocinnamaldehyde (16.3 μL, 0.01236 mmol, 3 equiv) was added to the reaction mixture and the solution was heated at 60° for 5 minutes. ¹H NMR analysis of the crude material revealed the formation of styrene in 70% yield. The peaks for the regenerated 3-OMeBzOH were very broad thus precluding an assessment of the yield. An analogous experiment with 4-F-BzOH confirmed quantitative regeneration of the benzoic acid derivative as judged by ¹⁹F NMR. The ³¹P NMR spectrum of the reaction mixture displayed a broad multiplet at 36-24 ppm, which has not been
assigned. Triphenylphosphine (32.4 mg, 0.01236 mmol, 3 equiv) was added to the reaction mixture and the solution was heated at 60 °C for 5 minutes. Analysis of the crude material by $^{31}$P NMR spectroscopy and $^1$H NMR spectroscopy revealed the presence of 9 (83% yield) based on comparison to an authentic sample of 9 that was prepared according to ref (36). $^{31}$P NMR (162 MHz, d$_8$-THF) δ 45.22 (dt, $J = 168.0, 128.7$ Hz), 27.92 (dd, $J = 147.8, 128.7$ Hz). $^1$H NMR (400 MHz, d$_8$-THF) δ -9.75 (dt, $J = 19.4, 12.1$ Hz, 1H).

4.5 References


32. See the supplementary materials for detailed experimental conditions.

33. The peaks for the regenerated benzoic acid are very broad in the NMR spectra, possibly due to reversible reductive elimination. Analogous results were obtained using 4-fluorobenzoic acid as a surrogate, which enabled us to follow the reaction by 19F NMR and confirm the results.


Appendix A – NMR Spectra for Phosphinite Directed Hydroacylation

(8j) 2-hydroxy-5-fluoro-styrene
(8k) 2-hydroxy-4-methoxy-styrene
(II) 5-(4-pyridyl)-salicylaldehyde
(Scheme 1.7, 5a) 2-(2-hydroxybenzoyl)propan-1-ol
(Table 1.1, entry 1, 5b)

2-(2-hydroxybenzoyl)pentan-1-ol

\[
\begin{align*}
\text{OH} & \quad \text{O} \quad \text{OH} \\
\text{nPr} &
\end{align*}
\]
(Table 1.1, entry 3, 5d)

2-(2-hydroxybenzoyl)-6-hepten-1-ol
(Table 1.1, entry 5, 5f)

2-(2-hydroxybenzoyl)-2-methylpropan-1-ol

\[
\begin{array}{c}
\text{OH} & \text{O} & \text{OH} \\
\text{Me} & \text{Me} & \\
\end{array}
\]

\[
\begin{array}{c}
\text{212.8} & \text{163.9} & \text{136.1} & \text{130.8} & \text{119.6} & \text{118.2} & \text{117.7} & \text{71.5} & \text{49.4} & \text{23.8} \\
\end{array}
\]
(Table 1.2, entry 2, 5h)

2-(2-hydroxy-5-chlorobenzoyl)-2-methylpropan-1-ol

\[
\begin{align*}
\text{OH} & \quad \text{O} & \quad \text{OH} \\
\text{Cl} & \quad \text{Me} & \quad \text{Me}
\end{align*}
\]
(Table 1.2, entry 3, 5i)

3-hydroxy-1-(2-hydroxy-5-methoxyphenyl)-2,2-dimethylpropan-1-one
(Table 1.2, entry 4, 5j)

2-(2-hydroxy-3-methylbenzoyl)-2-methylpropan-1-ol

![Chemical structure](image-url)
(Table 1.2, entry 5, 5k)

2-(2-hydroxy-6-methylbenzoyl)-2-methylpropan-1-ol
(Table 1.2, entry 6, 5f)

3-hydroxy-1-(2-hydroxynaphthalen-1-yl)-2,2-dimethylpropan-1-one
(Table 1.2, entry 7, 5m)
1-(2,4-dihydroxyphenyl)-3-hydroxy-2,2-dimethylpropan-1-one
(Table 1.4, entry 1, 9a)

3-(2-hydroxybenzoyl)-1-butanol

![Chemical Structure Image]

---

195
(Table 1.4, entry 2, 9b)

3-(2-hydroxy-5-fluorobenzoyl)-1-butanol
(Table 1.4, entry 3, 9c)

3-(2-hydroxy-5-chlorobenzoyl)-1-butanol

\[ \text{Chemical Structure} \]

\[ \text{NMR Spectra} \]
(Table 1.4, entry 4, 9d)

3-(2-hydroxy-5-iodobenzoyl)-1-butanol
(Table 1.4, entry 5, 9e)

3-(2-hydroxy-4-methoxybenzoyl)-1-butanol
(Table 1.4, entry 6, 9f)

3-(2-hydroxy-5-methoxybenzoyl)-1-butanol
(Table 1.4, entry 7, 9g)

3-(2-hydroxy-3-methoxybenzoyl)-1-butanol
(Table 1.4, entry 8, 9h)

3-(2-hydroxy-6-methylbenzoyl)-1-butanol
(Table 1.4, entry 9, 9i)

4-hydroxy-1-(2-hydroxy-5-pyridin-5-yl)-phenyl-2-methylbutan-1-one
(Table 1.5, entry 2 and 3, 9k)

3-(2-hydroxybenzoyl)-1-hexanol
(Table 1.5, entry 4, 91)

3-(2-hydroxybenzoyl)-2-methyl-1-butanol (major isomer)
(Table 1.5, entry 4, 9l)

3-(2-hydroxybenzoyl)-2-methyl-1-butanol (minor isomer)
(Table 1.5, entry 5, 9m)

3-(2-hydroxybenzoyl)-1-phenyl-1-butanol
(Table 1.5, entry 6, 9n)

3-(2-hydroxybenzoyl)-2-methyl-1-pentanol (major)
(Table 1.5, entry 6, 9n)

3-(2-hydroxybenzoyl)-2-methyl-1-pentanol (minor)
(Table 1.6, entry 1, 9q)

1,2-bis(2-hydroxybenzoyl)-1-propanone
(Table 1.6, entry 2, 9r)

1-(2-hydroxyphenyl)-2-(2-hydroxy-5-fluorophenyl)-1-propanone

![Chemical structure of the compound](image)

![NMR spectrum](image)
Table 1.6, entry 3, 9s

1-(2-hydroxyphenyl)-2-(2-hydroxy-4-methoxyphenyl)-1-propanone
(Table 1.6, entry 4, 9t)

1,2-bis(2-hydroxybenzoyl)-1-butanone

![Chemical structure of 1,2-bis(2-hydroxybenzoyl)-1-butanone](image)
(Scheme 1.9, 10)

2-(3-methyl-tetrahydrofuran-2-yl)-phenol (major)
Appendix B – NMR Spectra for 2-Vinylphenol Hydroacylation

(Table 2.1, 2a)
4-chloro-2-vinylphenol
4-nitro-2-vinylphenol
(Table 2.3, 2c)

6-methoxy-2-vinylphenol
(Table 2.3, 2d)

5-methoxy-2-vinylphenol

![Chemical Structure Image]

![NMR Spectrum Image]
(Table 2.3, 2e)

4-methoxy-2-vinylphenol
Table 2.3, 2f

4-fluoro-2-vinylphenol

![Chemical Structure](image_url)

![NMR Spectrum](image_url)
(Table 2.3, 2g)

6-methyl-2-vinylphenol

![Chemical Structure of 6-methyl-2-vinylphenol]

![NMR Spectra of 6-methyl-2-vinylphenol]
(Table 2.3, 2h)

3-methyl-2-vinylphenol
(Table 2.3, 2i)

4,6-di-tert-butyl-2-vinylphenol

![Chemical structure of 4,6-di-tert-butyl-2-vinylphenol](image)

[Chemical structure image]

---

223
(Scheme 2.9)

d$_7$-2-naphthaldehyde
(Scheme 2.9)

d$_1$-hydrocinnamaldehyde
(Table 2.1, 3a)

4-(5-chloro-2-hydroxyphenyl)-1-phenylpentan-3-one
(Table 2.2, 3b)
4-(2-hydroxy-5-nitrophenyl)-1-phenylpentan-3-one
(Table 2.2, 3d)

2-(2-hydroxy-5-nitrophenyl)-5-methylhexan-3-one

![Chemical structure of 2-(2-hydroxy-5-nitrophenyl)-5-methylhexan-3-one]

![NMR spectra of 2-(2-hydroxy-5-nitrophenyl)-5-methylhexan-3-one]
(Table 2.2, 3e)

2-(2-hydroxy-5-nitrophenyl)-4-phenylbutan-3-one

![Chemical Structure](image)
Table 2.2, 3f)

1-((tert-butyldimethylsilyl)oxy)-4-(2-hydroxy-5-nitrophenyl)pentan-3-one
(Table 2.2, 3g)

(2R,5R)-2-(2-hydroxy-5-nitrophenyl)-5,9-dimethyldec-8-en-3-one and (2S,5R)-2-(2-hydroxy-5-nitrophenyl)-5,9-dimethyldec-8-en-3-one
(Table 2.2, 3h)

1-cyclopropyl-2-(2-hydroxy-5-nitrophenyl)propan-1-one
(Table 2.2, 3i)

1-cyclohexyl-2-(2-hydroxy-5-nitrophenyl)propan-1-one
(Table 2.2, 3j)

(E)-4-(2-hydroxy-5-nitrophenyl)-1-phenylpent-1-en-3-one

```
-100 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230
16.49
47.91
77.16
117.80
123.61
125.26
125.98
126.83
128.99
129.20
129.21
131.61
133.85
141.22
146.74
161.35
203.54
77.16
47.91
16.49

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

234
```
(Table 2.2, 3k) 2-(2-hydroxy-5-nitrophenyl)-5-methylhex-4-en-3-one
**(Table 2.2, 3l)**

**(E)-2-(2-hydroxy-5-nitrophenyl)-4-methylhex-4-en-3-one**

<table>
<thead>
<tr>
<th>Chemical Shift (ppm)</th>
<th>0.80</th>
<th>0.804</th>
<th>2.01</th>
<th>2.18</th>
<th>2.183</th>
<th>3.09</th>
<th>3.094</th>
<th>3.097</th>
<th>3.11</th>
<th>4.678</th>
<th>4.679</th>
<th>4.68</th>
<th>4.683</th>
<th>1.992</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Peaks</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>12</td>
<td>13</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

**NMR Spectra**

The NMR spectra show the characteristic peaks for the compound, with the chemical shifts indicating the presence of the hydroxy, nitro, and alkene functionalities. The spectra are consistent with the structural formula shown above.
(Table 2.2, 4d)

N,N-dimethyl-4-(3-methyl-5-nitrobenzofuran-2-yl)aniline

\[
\text{Me}_2\text{N}-\begin{array}{c}
\text{O} \\
\text{Me} \\
\text{NO}_2
\end{array}
\]

\[1.09 \delta, 1.09 \delta, 2.04 \delta, 1.09 \delta, 2.04 \delta, 5.95 \delta, 2.92 \delta\]

\[156.5, 128.0, 128.0, 115.0, 108.5, 117.4, 132.9, 115.0, 110.7, 40.2, 9.3\]
(Table 2.2, 4c)

2-(4-methoxyphenyl)-3-methyl-5-nitrobenzofuran
(Table 2.2, 3o)

2-(2-hydroxy-5-nitrophenyl)-1-phenylpropan-1-one

\[
\text{\begin{align*}
\text{Me} & \quad \text{OH} \\
\text{NO}_2 & \\
\end{align*}}\]

\[
\begin{align*}
\text{f}_1 \text{ (ppm)} & \\
\text{f}_2 \text{ (ppm)} & \\
\end{align*}
\]
methyl 4-(2-(2-hydroxy-5-nitrophenyl)propanoyl)benzoate

(Table 2.2, 3p)
(Table 2.2, 3q)

1-(4-hydroxy-3-methoxyphenyl)-2-(2-hydroxy-5-nitrophenyl)propan-1-one
(Table 2.2, 3r)

4-(2-hydroxy-3-methoxyphenyl)-1-phenylpenten-3-one

![Chemical structure and spectra](image)
(Table 2.2, 4b)

4-(2-hydroxy-4-methoxyphenyl)-1-phenylpent-3-one
(Table 2.2, 3t)

4-(2-hydroxy-5-methoxyphenyl)-1-phenylpentan-3-one
(Table 2.2, 3u)

4-(2-hydroxy-5-fluorophenyl)-1-phenylpentan-3-one
(Table 2.2, 3v)
4-(2-hydroxy-3-methylphenyl)-1-phenylpentan-3-one
(Table 2.2, 3w)

4-(2-hydroxy-6-methylphenyl)-1-phenylpentan-3-one
(Table 2.2, 3x)

5,7-di-tert-butyl-3-methyl-2-phenethyl-2,3-dihydrobenzofuran-2-ol
(Table 2.2, 3y)

1-cyclohexyl-2-(2-hydroxy-5-methoxyphenyl)propan-1-one
(Table 2.2, 3z)

1-cyclohexyl-2-(2-hydroxy-5-methoxyphenyl)propan-1-one
(Table 2.2, 3aa)

1-cyclohexyl-2-(2-hydroxy-3-methylphenyl)propan-1-one

\[
\text{Me} \quad \text{OH}
\]

\[
\begin{align*}
\text{Me} & \quad \text{OH} \\
\end{align*}
\]
(Table 2.2, 3ab)

1-cyclohexyl-2-(2-hydroxy-6-methylphenyl)propan-1-one
(E)-4-(2-hydroxy-3-methoxyphenyl)-1-phenylpent-1-en-3-one
(Table 2.2, 3ad)

(E)-4-(2-hydroxy-5-methoxyphenyl)-1-phenylpent-1-en-3-one

\[
\begin{align*}
\text{Ph} & \quad \text{OMe} \\
\text{Me} & \quad \text{OH}
\end{align*}
\]

\[
\begin{array}{c}
\text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \\
1.05 \quad 1.97 \quad 2.03 \quad 2.04 \quad 3.05 \\
-1.0 \quad -0.5 \\
10.5 \quad 10.0 \quad 9.5 \quad 9.0 \quad 8.5 \quad 8.0 \quad 7.5 \quad 7.0 \quad 6.5 \quad 6.0 \quad 5.5 \quad 5.0 \quad 4.5 \quad 4.0 \quad 3.5 \quad 3.0 \quad 2.5 \quad 2.0 \quad 1.5 \quad 1.0 \quad 0.5 \quad 0.0 \quad -0.5
\end{array}
\]

\[
\begin{array}{c}
\text{f1 (ppm)} \\
135.9 \quad 145.5 \quad 129.5 \quad 128.8 \quad 128.8 \quad 124.5 \quad 124.5 \quad 113.7 \quad 113.7 \quad 55.9 \quad 47.7 \quad 16.3
\end{array}
\]

\[
\begin{array}{c}
\text{f1 (ppm)} \\
230 \quad 220 \quad 210 \quad 200 \quad 190 \quad 180 \quad 170 \quad 160 \quad 150 \quad 140 \quad 130 \quad 120 \quad 110 \quad 100 \quad 90 \quad 80 \quad 70 \quad 60 \quad 50 \quad 40 \quad 30 \quad 20 \quad 10 \quad 0 \quad -10
\end{array}
\]
(Table 2.2, 3ae)

(E)-4-(2-hydroxy-3-methylphenyl)-1-phenylpent-1-en-3-one
(Table 2.2, 3af)
(E)-4-(2-hydroxy-6-methylphenyl)-1-phenylpent-1-en-3-one

![Chemical structure](image)

![NMR spectrum](image)
(Table 2.2, 3ag)

2-(2-hydroxy-3-methoxyphenyl)-1-phenylpropan-1-one
(Table 2.2, 3ah)

2-(2-hydroxy-5-methoxyphenyl)-1-phenylpropan-1-one
(Table 2.2, 3ai)

2-(2-hydroxy-3-methylphenyl)-1-phenylpropan-1-one
(Table 2.2, 3aj)

2-(2-hydroxy-6-methylphenyl)-1-phenylpropan-1-one
(Scheme 2.10, 3al)

1-cyclopropyl-2-(2-hydroxy-5-nitrophenyl)propan-1-one
(Table 2.7)

4-(2-hydroxy-5-nitrophenyl)-1-phenylpentan-3-one-5-d
(Table 2.7)

4-(2-hydroxy-5-nitrophenyl)-1-phenylpentan-3-one-5-d
(Scheme 2.10)

4-chloro-2-(1-cyclopropyl-1-oxopropan-2-yl)phenyltrifluoromethanesulfonate
(Scheme 2.10, 5a)

2-(4-chloro-4'-methoxy-[1,1'-biphenyl]-2-yl)-1-cycloprolylpropan-1-one
(Scheme 2.10, 4a)

5-chloro-3-methyl-2-phenethylbenzofuran

![Chemical structure of 5-chloro-3-methyl-2-phenethylbenzofuran]
6-formyleugenol
6-vinyleugenol
6-formyl-isoegenol
6-vinyl-isoeugenol
(Table 2.4, 4h, eupomateno 17)

5-allyl-7-methoxy-2-(3,4-dimethoxyphenyl)-3-methylbenzofuran
(Table 2.4)

(E)-1-(3,4-dimethoxyphenyl)-2-(2-hydroxy-3-methoxy-5-(prop-1-en-1-yl)phenyl)propan-1-one

![Chemical structure diagram]
(Table 2.4, 4e, eupomatenoid 12)

\[(E)-2-(3,4\text{-dimethoxyphenyl})-7\text{-methoxy-3-methyl-5-(prop-1-en-1-yl)benzofuran}\]
(Table 2.4, 4g, eupomatenoid 17)

5-allyl-7-methoxy-2-(4-methoxyphenyl)-3-methylbenzofuran
(Table 2.4, 4f, eupomatenoid 16)

(E)-2-(4-methoxyphenyl)-7-methoxy-3-methyl-5-(prop-1-en-1-yl)benzofuran

![Chemical structure of (E)-2-(4-methoxyphenyl)-7-methoxy-3-methyl-5-(prop-1-en-1-yl)benzofuran]
[Rh(dcpm)]_2Cl
$[\text{Rh(4-nitro-2-vinyl-phenolate)}_2][(18\text{-crown-6})\text{K}]$
[Rh(dcpm)]_2[Rh(4-nitro-2-vinyl-phenolate)]_2
[Rh(dcpm)(COD)]BF_4
[Rh(dcpm)(4-nitro-2-vinylphenolate)]
[Rh(dcpm)(4-nitro-2-vinylphenolate)(hydrocinnamaldehyde)]
(from a reaction with excess aldehyde and olefin at steady state concentration, peaks in red brackets correspond to the title compound)
[Rh(dcpm)(COD)][4-nitro-2-(3-oxo-5-phenylpentan-2-yl)phenolate]
Appendix C – Crystallographic Data for 2-Vinylphenol Hydroacylation

Table 1. Crystal data and structure refinement for vmd13.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>vmd13</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>$C_{28}H_{36}K_{2}N_{2}O_{12} \cdot C_4H_8O$</td>
</tr>
<tr>
<td>Formula weight</td>
<td>806.70</td>
</tr>
<tr>
<td>Temperature</td>
<td>88(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>$Cc$</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>(a = 13.6052(6) \text{ Å}) (a = 90^\circ).</td>
</tr>
<tr>
<td></td>
<td>(b = 19.6523(9) \text{ Å}) (b= 105.5588(5)^\circ).</td>
</tr>
<tr>
<td></td>
<td>(c = 14.3113(7) \text{ Å}) (g = 90^\circ).</td>
</tr>
</tbody>
</table>
Volume 3686.2(3) Å³

Z 4

Density (calculated) 1.454 Mg/m³

Absorption coefficient 0.640 mm⁻¹

F(000) 1672

Crystal color yellow

Crystal size 0.315 x 0.175 x 0.144 mm³

Theta range for data collection 1.868 to 27.103°

Index ranges -17 ≤ h ≤ 17, -25 ≤ k ≤ 25, -18 ≤ l ≤ 18

Reflections collected 20977

Independent reflections 8111 [R(int) = 0.0170]

Completeness to theta = 25.242° 99.9 %

Absorption correction Numerical

Max. and min. transmission 0.9581 and 0.8741

Refinement method Full-matrix least-squares on F²

Data / restraints / parameters 8111 / 2 / 423

Goodness-of-fit on F² 1.067

Final R indices [I>2sigma(I) = 7920 data] R1 = 0.0258, wR2 = 0.0650

R indices (all data, 0.78Å) R1 = 0.0267, wR2 = 0.0658

Absolute structure parameter 0.51(3)

Largest diff. peak and hole 0.550 and -0.336 e.Å⁻³
Appendix D – NMR Spectra for Enantioselective Ketone Hydroacylation

(Table 3.1, 4a)

4-Oxo-4-phenyl-1-butanol

\[
\text{\includegraphics[width=0.5\textwidth]{4-oxo-4-phenyl-1-butanol.png}}
\]
(Table 3.1, 4b)

4-Oxo-4-(3-chlorophenyl)-1-butanol

![Chemical Structure](image)

![NMR Spectrum](image)
(Table 3.1, 4c)

4-Oxo-4-(3-methoxyphenyl)-1-butanol

![Chemical structure](image)

![NMR spectrum](image)
(Table 3.1, 4d)

4-Oxo-4-(4-bromophenyl)-1-butanol
Table 3.1, 4e

4-Oxo-4-(4-fluorophenyl)-1-butanol

\[ \text{Formula Image} \]

\[ \text{NMR Spectra Image} \]

293
(Table 3.1, 4f)

4-Oxo-4-(4-methoxyphenyl)-1-butanol

(Table 3.1, 4g)
4-Oxo-4-(2-napthyl)-1-butanol

\[
\begin{align*}
\text{O} & \quad \text{C} \\
\text{H} & \quad \text{C} \\
\text{H} & \quad \text{C} \\
\text{H} & \quad \text{C} \\
\text{H} & \quad \text{C} \\
\text{H} & \quad \text{C} \\
\text{H} & \quad \text{C} \\
\text{H} & \quad \text{C} \\
\text{H} & \quad \text{C} \\
\text{H} & \quad \text{C} \\
\text{H} & \quad \text{C} \\
\text{H} & \quad \text{OH}
\end{align*}
\]
(Table 3.1, 4h)

4-Oxo-4-(2-furyl)-1-butanol
(Table 3.1, 4i)

4-Oxo-4-(2-phenylethynyl)-1-butanol
(Table 3.1, 4j)

4-Oxo-4-(2-butylenyl)-1-butanol

![Chemical structure of 4-Oxo-4-(2-butylenyl)-1-butanol]

![NMR spectrum of 4-Oxo-4-(2-butylenyl)-1-butanol]
Table 3.2, 4k

5-Oxo-5-phenyl-1-pentanol
5-Oxo-5-(4-chlorophenyl)-1-pentanol

(Table 3.2, 4l)
(Table 3.2, 4m)

5-Oxo-5-(3-methoxyphenyl)-1-pentanol
(Table 3.2, 4n)

5-Oxo-5-(3-methylphenyl)-1-pentanol
(Table 3.2, 4o)

5-Oxo-5-(2-benzofuryl)-1-pentanol
(Table 3.2, 4q)

5-Oxo-5-(2-butylethynyl)-1-pentanol

![Chemical structure of 5-Oxo-5-(2-butylethynyl)-1-pentanol](image)

![NMR spectrum](image)
(Table 3.2, 4r)
5-Oxo-5-(2-phenylethynyl)-1-pentanol

![Chemical structure of 5-Oxo-5-(2-phenylethynyl)-1-pentanol]

![NMR spectrum of 5-Oxo-5-(2-phenylethynyl)-1-pentanol]
3,3-dimethyl-5-Oxo-5-(2-furyl)-1-pentanol
(Table 3.2, 4t)

3,3-dimethyl-5-Oxo-5-(2-hexylethynyl)-1-pentanol
3,3-dimethyl-5-Oxo-5-(2-phenylethynyl)-1-pentanol
(Table 3.1, 8a)

(+)-(R)-γ-Phenyl-γ-butyrolactone
(Table 3.1, 8b)

(+)-(R)-γ-(3-Chlorophenyl)-γ-butyrolactone
(Table 3.1, 8c)

(+)-(R)-γ-(3-Methoxyphenyl)-γ-butyrolactone

![Chemical structure image]

![NMR spectrum image]

![Second NMR spectrum image]
(Table 3.1, 8d)

(+)-(R)-γ-(4-Bromophenyl)-γ-butyrolactone

![Chemical structure of (+)-(R)-γ-(4-Bromophenyl)-γ-butyrolactone]
(Table 3.1, 8e)

(+)-(R)-γ-(4-Fluorophenyl)-γ-butyrolactone

\[
\text{\begin{tabular}{c}
\end{tabular}}
\]
(Table 3.1, 8f)

(+)-(R)-γ-(4-methoxyphenyl)-γ-butyrolactone

![Chemical structure diagram]

![NMR spectrum diagram]
(+)-(R)-γ-(2-Naphthyl)-γ-butyrolactone
(-)-(R)-\(\gamma\)-(2-Furyl)-\(\gamma\)-butyrolactone

(Table 3.1, 8h)
(Table 3.1, 8i)

(-)-(R)-γ-(2-Phenylethynyl)-γ-butyrolactone

![Chemical Structure](image-url)
(Table 3.1, 8j)

(-)-(R)-γ-[(2-Butylethynyl)-γ-butyrolactone}
(+)-(R)-δ-(phenyl)-δ-valerolactone

( Table 3.2, 8k)
(Table 3.2, 8I)

(+)-(R)-δ-(4-chlorophenyl)-δ-valerolactone
(+)-(R)-δ-(3-methoxyphenyl)-δ-valerolactone
(Table 3.2, 8n)

(+)-(R)-δ-(3-methylphenyl)-δ-valerolactone

![Chemical Structure Image]
(Table 3.2, 80)

(+)-(R)-δ-(2-benzofuryl)-δ-valerolactone
(+)-(R)-δ-(2-butylethynyl)-δ-valerolactone

(Table 3.2, 8q)
(Table 3.2, 8r)

(+)-(R)-δ-(2-phenylethynyl)-δ-valerolactone
(Table 3.2, 8s)

(R)-β,β-dimethyl-δ-(2-furyl)-δ-valerolactone
(Table 3.2, 8t)

(R)-β,β-dimethyl-δ-(phenylethynyl)-δ-valerolactone
(Table 3.2, 8u)

(R)-β,β-dimethyl-δ-(2-hexethyl)-δ-valerolactone

![Chemical Structure](Image)

![NMR Spectrum](Image)

![NMR Spectrum](Image)
(Scheme 3.2, 9a)

(+)-(R)-3,5-dimethylisobenzofuran-1(3H)-one
Appendix E – SFC and GC-FID Chromatograms for Enantioselective Ketone Hydroacylation

*Note:* Because a racemic version of Noyori’s asymmetric transfer hydrogenation catalysts is not commercially available, each substrate was subjected to two reactions to obtain chiral analyses: one with [(R,R)-II] (data reported in table 1 of the manuscript, top chromatogram in this appendix) and one with [(S,S)-I] (data reported in table 2 of SI, bottom chromatogram in this appendix). Racemic 8a and 8k were available and their SFC or GC-FID analyses are displayed as the bottom chromatogram for those substrates.
(Table 3.1, 8a)

(+)-(R)-γ-Phenyl-γ-butyrolactone

(racemate)
(Table 3.1, 8b)

(+)-(R)-γ-(3-Chlorophenyl)-γ-butyrolactone
(+)-(R)-γ-(3-Methoxyphenyl)-γ-butyrolactone

(Table 3.1, 8c)
(Table 3.1, 8d)

(+)-(R)-γ-(4-Bromophenyl)-γ-butyrolactone

![Chemical Structure Diagram]

**Table 3.1:**

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<th>Height</th>
<th>Width</th>
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<th>Symmetry</th>
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(Table 3.1, 8e)

(+)-(R)-\(\gamma\)-(4-Fluorophenyl)-\(\gamma\)-butyrolactone
(+)-(R)-\gamma-(4-methoxyphenyl)-\gamma-butyrolactone

![Molecular Structure](image)

(Table 3.1, 8f)

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(Table 3.1, 8g)

(+)-(R)-γ-(2-Naphthyl)-γ-butyrolactone
(Table 3.1, 8h)

(-)-(R)-γ-(2-Furyl)-γ-butyrolactone
(-)-(R)-γ-(2-Phenylethynyl)-γ-butyrolactone

(Table 3.1, 8i)
(Table 3.1, 8j)

(-)-(R)-\(\gamma\)-(2-Butylethynyl)-\(\gamma\)-butyrolactone
(+)-(R)-δ-(phenyl)-δ-valerolactone
(Table 3.2, 81)

(+)-(R)-δ-(4-chlorophenyl)-δ-valerolactone

![Chemical Structure](image)

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(Table 3.2, 8m)

(+)-(R)-δ-(3-methoxyphenyl)-δ-valerolactone

![Chemical Structure](image)

---

### Table 3.2

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</table>
(+)-(R)-δ-(3-methylphenyl)-δ-valerolactone

![Chemical structure](image)

### Table 3.2, 8n

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</table>
(Table 3.2, 8o)

(+)-(R)-δ-(2-benzofuryl)-δ-valerolactone

![Diagram of the molecule]

Table 3.2, 8o: Data for the characterization of (+)-(R)-δ-(2-benzofuryl)-δ-valerolactone.
(Table 3.2, 8q)

(+)-(R)-δ-(2-butythynyl)-δ-valerolactone
(Table 3.2, 8r)

(+)-(R)-δ-(2-phenylethynyl)-δ-valerolactone
(Table 3.2, 8s)

(R)-β,β-dimethyl-δ-(2-furyl)-δ-valerolactone

![Chemical Structure Image]
(Table 3.2, 8u)

(R)-β,β-dimethyl-δ-(2-hexylethynyl)-δ-valerolactone
(Table 3.2, 8t)

(R)-β,β-dimethyl-δ-(phenylethynyl)-δ-valerolactone

![Chemical structure of (R)-β,β-dimethyl-δ-(phenylethynyl)-δ-valerolactone]
(Scheme 3.2, 9a)

(+)-(R)-3,5-dimethylisobenzofuran-1(3H)-one
Appendix F – NMR Spectra for Aldehyde Dehydroformylation

(5c, BNBD)

1,4-Dihydro-1,4-methanonaphthalene

![NMR Spectrum]

The NMR spectrum shows the chemical shifts and peaks for the 1,4-dihydro-1,4-methanonaphthalene. The peaks are labeled with their respective frequencies (in ppm).
(Scheme 4.5, 1e)

4-Phenylbutanal
(Scheme 4.5, 1b)

trans-6-Heptyl-3,4-dimethylcyclohex-3-ene-1-carbaldehyde

\[
\text{Me} \quad \begin{array}{c}
\text{H} \\
\text{Me}
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{Me}
\end{array} \quad \text{H} \\
\text{C}_7\text{H}_{15}
\]
(Scheme 4.5, 1c)

trans-6-Phenyl-3,4-dimethylcyclohex-3-ene-1-carbaldehyde
(Scheme 4.5, 1d)

(cis-6-formyl-3,4-dimethylcyclohex-3-en-1-yl)methylbenzoate
(Scheme 4.5, 1h)

(E)-2-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-5-phenylpent-4-enal
(Scheme 4.5, 1i)

2-(4-Methoxyphenyl)-5-phenoxypentanal
(Scheme 4.5, 1g)

3-(1-Tosyl-1H-indol-3-yl)propanal
(Scheme 4.5, 1j)
2-Isopropyldecanal

![Chemical Structure](image)

![NMR Spectrum](image)
(Scheme 4.5, 1k)

2-Methyl-4-phenylbutanal
(dr=2:1)
(Scheme 4.5, II)

3-(4-Methoxyphenyl)-2-methyl-4-phenylbutanal

(dr=2:1)
(Scheme 4.5, 1m)

2-Cyclopentyl-2-phenylacetaldehyde
(Scheme 4.5, 1n)

2-((1S,8aS)-5,5,8a-trimethyl-2-methylenedecahydropinaphthalen-1-yl)acetaldehyde
(Scheme 4.5, 10)

3α,12α-Dihydroxy-5β-cholanal-(24)
(Scheme 4.5, 7b)

Yohimbinal
(Scheme 4.5, 2b)

5-Heptyl-1,2-dimethylcyclohexa-1,3-diene

![Chemical Structure](image)

![NMR Spectra](image)
(Scheme 4.5, 2c and 2c')

3,4-Dimethyl-1,2-dihydro-1,1'-biphenyl and 3,4-dimethyl-2,5-dihydro-1,1'-biphenyl
(Scheme 4.5, 2d)

(4,5-Dimethylcyclohexa-2,4-dien-1-yl)methyl benzoate
(Scheme 4.5, 2f)

1-(Phenylmethyl)-1,2,3,6-tetrahydropyridine
6-Phenylhexa-3,5-dien-1-ylisoindoline-1,3-dione
(Scheme 4.5, 2i)

1-Methoxy-4-(4-phenoxybut-1-en-1-yl)benzene

\[
\begin{align*}
\text{MeO} & \quad \text{OPh} \\
& \quad \text{MeO}
\end{align*}
\]
(Scheme 4.5, 2g)

3-Ethenyl-1-([(4-methylbenzene)sulfonyl]-1H-indole
(Scheme 4.5, 2j and 2j')

Dehydroformylation of 1j

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
n-C_9H_{19} & \quad n-C_9H_{19} \\
2j & \quad 2j' 
\end{align*}
\]

\[ {^1}\text{H NMR spectra of the crude reaction mixtures:} \]

![NMR spectra](image-url)
$^1$H NMR spectra of the isolated materials:
(Scheme 4.5, 2k and 2k’)
Dehydroformylation of 1k

\[ \text{\textsuperscript{1}H NMR spectra of the crude reaction mixtures:} \]
$^1$H NMR spectra of the isolated materials:
(Scheme 4.5, 21)

1-Methoxy-4-(1-phenylbut-3-en-2-yl)benzene
(Scheme 4.5, 2m)

(Cyclopentyldienemethyl)benzene

![Chemical Structure](image)
(Scheme 4.5, 2n)

(4aS,8aS)-1,1a-trimethyl-5,6-dimethyleneoctahydronaphthalene
(Scheme 4.5, 2o)

24-Nor-5β-chol-22-ene-3α,12α-diol
(Scheme 4.5, 2p)

Spiramycin derivative
(Scheme 4.5, 7c)

(+)-Yohimbenone
(Scheme 4.8, 6c)

1,2,3,4-Tetrahydro-1,4-methanonaphthalene-2-carbaldehyde