Transition metal catalysts for the conversion of biomass inspired substrates
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Chapter 6

Application of Transition Metal Complexes Containing a Bidentate NHC-Amine Ligand in Direct α-Alkylation of Ketones with Alcohols

Abstract

The application of Ru, Ir and Rh complexes, containing an NHC-amine ligand \( \text{C}^{\text{NH}-\text{NH}_2} \), as hydrogen-borrowing catalyst in the direct \( \alpha \)-alkylation of ketones with alcohols was screened. All complexes showed activity in this reaction, but good selectivity remained an issue. It was found that the selectivity of the reaction strongly depended on two factors: 1) The hydrogenation activity of the catalyst and 2) the choice of substrate. A multitude of side-products was formed due to the fact that either the hydrogenation catalyst was too fast (hydrogenating the product ketone further towards the alcohol) or too slow, leaving the intermediate formed exposed to further alkylation. The reactivity of the substrate determined the degree of higher alkylation that took place.

Screening of the substrate scope showed that sterically more demanding substrates, in particular the substrate alcohol, ensured a lower degree of alkylation products. The catalyst \( \text{Ir(cod)Cl(C}^{\text{NH}-\text{NH}_2}) \) was found to be of the right "intermediate" hydrogenation activity, showing the most consistency in conversion and selectivity. We also screened the application of complexes with a deprotonated, anionic form of the NHC-amine motif, where a coordinated amine could function as internal base, omitting the need of addition of KOH. This approach proved successful, obtaining up to 45% conversion and 25% of the desired product using \( \text{Rh(cod)(C}^{\text{NH}-\text{NH})} \) before decomposition of the catalyst. The selectivity of the reaction did not increase.

The application of the catalysts was also extended to include biomass-inspired substrates ethylene glycol and geraniol. The functionalization of ethylene glycol was unsuccessful and resulted in poly-aldol products. Instead, geraniol could be successfully functionalized.

6.1 Introduction

The growing interest in sustainable chemistry is accompanied by a substantial development of the role of organometallic chemistry in this field. This is of no surprise, since much of the progress in organometallic catalysis has ‘green’ implications. The development of bifunctional catalysis and its application in, among others, hydrogenation reactions (see Chapter 5) is one example. Another example is the development of the hydrogen-borrowing concept. Hydrogen-borrowing activation of alcohols obviates the need for alkylating agents in an alkylation.\(^{[1,2]}\) Alcohols are frequently used as starting materials but are unreactive due to the poor leaving group ability of the OH-group. Traditionally, alcohols were activated by replacing them with a halide (or a sulfonate) but this brings about the problems of toxicity...
(of alkylbromides for example), the need of an additional reaction step and the waste generated when ultimately the halide needs to be removed as a salt. Instead, an organometallic catalyst can be applied to dehydrogenate the alcohol, thereby creating an aldehyde or a ketone which can subsequently undergo a reaction, such as a condensation reaction, as shown in Scheme 1.

Scheme 1. Representation of the hydrogen borrowing system. The inactive substrate is activated by the catalyst via temporary removal of hydrogen. This allows a condensation reaction (in this case with an amine) after which the hydrogen is returned to yield the product.

The hydrogen is then returned in a hydrogenation step (via the hydride species created in the first oxidation) to yield the product. The hydrogens are essentially borrowed from the starting material and returned in the final step, creating an overall redox-neutral reaction pathway.

There are several catalytic reactions that employ this hydrogen-borrowing system. Dehydrogenative coupling of two alcohols[3-5] or an alcohol with an amine[6] and direct α-alkylation of ketones with alcohols[7,8] are just a few examples (see Scheme 2).

Scheme 2. Overview of recent developments obtained using hydrogen-borrowing systems.
In the direct α-alkylation of ketones with alcohols, shown in more detail in Scheme 3. The first step is the dehydrogenation of the substrate alcohol (1). This is followed by a base catalyzed aldol condensation (2) where an α,β-unsaturated ketone is formed. Subsequent hydrogenation of the alkene bond (3) by the oxidized catalyst species generated in the first step, yields the desired product. Work-up in between steps is unnecessary – an additional advantage when three reaction steps are combined in one reaction.

Scheme 3. Reaction pathway of the direct α-alkylation of ketones with alcohols: Dehydrogenation of the alcohol (1), base catalyzed aldol condensation (2), shown in more detail in the frame, and hydrogenation of the alkene bond (3).

The fact that, in general, a hydrogenation catalyst is present in the reaction mixture means that the formed ketone can also be hydrogenated further, to provide the corresponding alcohol as a side product. Additionally, the α,β-unsaturated ketone formed in the aldol condensation can be further alkylated before the hydrogenation step.

The direct α-alkylation of ketones with alcohols is a variation on the Guerbet reaction, where two dehydrogenated alcohol substrates perform a homocoupling and the presence of two equivalents of oxidized catalyst ensures complete reduction of the formed ketone into the product alcohol. Cho, Yus and Ishii were among the first to develop this reaction into the α-alkylation reaction between ketones and alcohols. All three investigated the substrate scope of the reaction, a very short summary of which is given in Table 1. Cho reported on the addition of a hydrogen acceptor 1-dodecene to suppress further hydrogenation of the ketone to the alcohol. Good yields were obtained when aryl substrates were applied, but the selectivity dropped when smaller substrates were used. Ishii reported good selectivities for both aryl and aliphatic combinations, using the commercially available [Ir(cod)Cl]₂ and PPh₃. However, no explanation was given for the found selectivities. Yus performed the reactions in dioxane with stoichiometric amounts of KOH, obtaining fair selectivity towards
the product ketones when aryl substrates were used, but the reaction failed when using aliphatic methyl ketones.

The application of α,ω-diols as substrate has also been investigated by Ishii. An excess of ketone with an α,ω-diol would produce diketones, whereas an excess of diol would be expected to yield ω-hydroxy ketones. For long-chain α,ω-diols this seems to work. However, smaller 1,3-, 1,4- and 1,5-diols, with an excess of methyl ketones have been reported not to produce diketones at all. The aldehydes derived from these diols are believed to undergo a homo-aldol reaction instead of the presumed cross-aldol condensation reaction, resulting in a complex mixture of poly-aldol products. Most catalysts that have been applied in these α-alkylation reactions have been standard precursors that are commercially available, such as \([\text{Ir}({\text{cod}})\text{Cl}]_2\), \([\text{Rh}({\text{cod}})\text{Cl}]_2\), \(\text{IrCl(CO)(PPh}_3\text{)}_2\), \(\text{RuCl}_2(\text{dmso})_4\) or \(\text{RuCl}_2(\text{PPh}_3)_3\).

Table 1. Overview of results obtained in the direct α-alkylation of ketones with alcohols by Cho, Ishii and Yus with a set of substrates containing both aryl and aliphatic ketones and alcohols.

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Alcohol</th>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>product ketone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetophenone</td>
<td>n-Butanol</td>
<td>(\text{RuCl}_2(\text{PPh}_3)_3)</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Acetophenone</td>
<td>Benzyl alcohol</td>
<td>(\text{RuCl}_2(\text{PPh}_3)_3)</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Me-Pr ketone</td>
<td>Benzyl alcohol</td>
<td>(\text{RuCl}_2(\text{PPh}_3)_3)</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\text{Ir}({\text{cod}})\text{Cl}]_2)</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Acetophenone</td>
<td>Benzyl alcohol</td>
<td>(\text{Ir}({\text{cod}})\text{Cl}]_2)</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>Me-Pr ketone</td>
<td>n-Butanol</td>
<td>(\text{Ir}({\text{cod}})\text{Cl}]_2)</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Acetophenone</td>
<td>Benzyl alcohol</td>
<td>(\text{RuCl}_2(\text{dmso})_4)</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Me-nBu ketone</td>
<td>Benzyl alcohol</td>
<td>(\text{RuCl}_2(\text{dmso})_4)</td>
<td>&lt;5</td>
<td></td>
</tr>
</tbody>
</table>

Data taken from indicated references. Cho applied a hydrogen acceptor to prevent further hydrogenation to the alcohol. Ishii added 4 equiv. of PPh₃ for 1 equiv. cat. Yus performed the reactions in dioxane.

There has only been one other report where bidentate cyclometallated iridium pyrimidine complexes have been used, but application of these complexes did not significantly improve the activity or the selectivity of the reaction. Also, there is only one related example in literature where the authors attempt to introduce enantioselectivity in this type of reaction. This was done by adding a second, chiral catalyst to hydrogenate the product ketone into a chiral alcohol. Formation of the product ketone is achieved using an Ir-catalyst and at
the end of the reaction the second chiral Ru-catalyst was added to reduce the ketone to an alcohol.

The fact that the direct α-alkylation encompasses a halogen-free coupling route sparked our interest. Since iridium, rhodium and ruthenium were frequently reported as catalysts for these reactions, we were curious how our Ru, Ir and Rh catalysts, containing an $\text{CNHC-NH}_2$ moiety allowing bidentate, hemilabile and/or bifunctional behavior, would perform in this reaction. We decided to investigate the performance of several selected catalysts, containing both the M-arene and M-cod motif (described in Chapter 3 and 4 respectively). Their general structure is depicted in Figure 1.

Figure 1. General structures of the M(arene) and M(cod) complexes containing a $\text{CNHC-NH}_2$ ligand applied in this chapter.

An additional advantage of the $\text{CNHC-NH}_2$ motif is the possibility of the amine functionality to act as internal base in its deprotonated form. If the amine is strong enough to deprotonate the activated ketone substrate, the addition of KOH as base would become unnecessary, thus improving the reaction conditions.

The only reports of a similar coupling where addition of a strong base is not required comes from Baba,\textsuperscript{[19]} where an enol acetate was used as starting material instead of a ketone, circumventing the step where a strong base is needed to deprotonate the substrate ketone for the aldol condensation. To probe the feasibility of applying a complex with an internal base function, a deprotonated form of the M(cod) complexes, developed in Chapter 4, was tested in the direct α-alkylation of ketones with alcohols. Additionally, we investigated the performance of our complexes for several types of substrates, including the more bio-inspired alcohols such as geraniol and the 1,2-diol ethylene glycol as alcohol substrate.

6.2 Results and Discussion

In order to investigate the activity and applicability of an NHC-amine moiety, complexes containing the $\text{CNHC-NH}_2$ ligand motif were applied in the direct α-alkylation of ketones with
alcohols. First, we chose to use [Ru(p-cym)Cl(C\text{NHC-NH}_2)]PF_6 (A), IrCp*Cl(C\text{NHC-NH}_2)]PF_6 (B; developed and described in Chapter 3), Ir(cod)Cl(C\text{NHC-NH}_2)] (C) and Rh(cod)Cl(C\text{NHC-NH}_2)] (D; developed and described in Chapter 4) as the most suitable catalysts to employ in this initial investigation. The complexes, shown in Figure 2, are the complexes that were developed containing the neutral C\text{NHC-NH}_2 ligand.

Figure 2. Complexes with a charge-neutral C\text{NHC-NH}_2 ligand that were applied in in the direct α-alkylation catalysis runs: [Ru(p-cym)Cl(C\text{NHC-NH}_2)]PF_6 (A), IrCp*Cl(C\text{NHC-NH}_2)]PF_6 (B), Ir(cod)Cl(C\text{NHC-NH}_2)] (C) and Rh(cod)Cl(C\text{NHC-NH}_2)] (D).

Application of C\text{NHC-NH}_2 Containing Complexes in the Direct α-Alkylation of Acetophenone and Benzyl Alcohol

As a benchmark reaction the direct α-alkylation of acetophenone with benzyl alcohol was studied (see Scheme 4). In this reaction, acetophenone 1 is reacted with benzyl alcohol 2 to form the ketone 1,3-diphenylpropanone 3 as the desired product and the further hydrogenated alcohol 1,3-diphenyl propanol 4 as side product. From literature the optimum ratio of substrate ketone to alcohol was reported to be 1:2, which we used as starting point for our investigations. As was explained in the introduction, the side products are composed of higher alkylated products, of which 1,3,4-triphenylbutanone 5 was the major side product. Intermediate structures t-chalcone 6 and phenylethenol 7 were also observed in trace amounts in catalysis runs. The results of these runs are shown in Table 2.

Scheme 4. The benchmark direct α-alkylation of acetophenone 1 and benzyl alcohol 2 to form 3, 4 and 5, and intermediate structures t-chalcone 6 and phenylethenol 7.
All complexes show activity and (almost) fully convert acetophenone, but do not lead to high selectivities. Besides the products specified in Table 2, the remainder of the formed product is constituted of trace amounts of 6, 7 and unidentified compounds at higher retention times, indicating a higher degree of alkylation, or a non-completed aldol condensation (-OH group still present).

Table 2. Results of the direct α-alkylation of acetophenone 1 and benzyl alcohol 2 using complexes A-D.

<table>
<thead>
<tr>
<th>Entry[a]</th>
<th>Catalyst</th>
<th>Conversion[b] (%)</th>
<th>Yield[c] (%)</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>98</td>
<td>65</td>
<td>2</td>
<td>3</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>100</td>
<td>57</td>
<td>-</td>
<td>21</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>99</td>
<td>68</td>
<td>4</td>
<td>13</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>D</td>
<td>100</td>
<td>47</td>
<td>41</td>
<td>8</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

General conditions: [a] 2 mmol acetophenone 1 : 4 mmol benzyl alcohol 2, 1 mol% cat, 10 mol% KOH, 100 °C for 3 hr, neat. [b] Conversion is based on amount of 1 converted. [c] Yields determined based on GC-area%.

Ru(p-cym) complex A produces 3 in a good yield (entry 1, Table 2) but the product distribution shows that there are a lot of unidentified / higher functionalized products at higher retention time. Ir complexes B and C (entry 2 and 3) have less of these higher functionalized products, but B is more active in forming doubly alkylated product 5. Surprisingly, application of Rh(cod) complex D results in the highest yield of alcohol 4, indicating that it most actively hydrogenates product ketone 3, and also doesn't form too much unidentified side-products. The complexes in Figure 2 are relatively stable and are probably resistant to the H₂O that is formed during the aldol condensation and which is present when standard grade KOH (around 85% KOH / 15% H₂O due to its hygroscopic nature) is used. When a pure batch of KOH (99%, stored under N₂) was applied, we saw a drop in activity, but similar products ratios were achieved. This led us to the notion that the water present in standard grade KOH could also have played a role in dissolving the base in the reaction mixture, speeding up the reaction.

Further investigation of the catalytic performance was done using M(cod)(C^N,NH₂) complexes E and F shown in Figure 3, which were also applied in the benchmark reaction shown in Scheme 4. These complexes were developed in Chapter 4 and contain a monoanionic form of the C^N,NH₂ ligand and are M(cod) complexes in which the amine is coordinated to the metal center (in contrast to Ir(cod)Cl and Rh(cod)Cl). The results of these reactions are shown in Table 3.
Rhodium complex F shows only 37% yield of the desired product 3 (entry 2, Table 3), besides a large amount of higher alkylated products (18% of 5 and 45% of unidentified products). Additionally, we also found quite a large amount of non-hydrogenated intermediate 6 (9%) and 7 (8%, deprotonated 1). In the results shown in Table 1, these were only found in trace amounts. This indicates that the Rh species is not very active as hydrogenation catalyst and facilitates subsequent aldol condensations or Michael additions to form the higher alkylated products.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Ratio</th>
<th>Conversion (%)</th>
<th>Yield (%): 3</th>
<th>4</th>
<th>5</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>E</td>
<td>1:1</td>
<td>99</td>
<td>71</td>
<td>-</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>1:2</td>
<td>100</td>
<td>37</td>
<td>-</td>
<td>18</td>
<td>45</td>
</tr>
</tbody>
</table>

General conditions: [a] 2 mmol acetophenone 1: 1 or 2 mmol benzyl alcohol 2, 1 mol% cat, 10 mol% KOH, 100 °C for 3 hr, neat. [b] Conversion is based on amount of 1 converted. [c] Yields determined based on GC-area%.

To avoid these large amounts of higher alkylated products, we decided to change the ratio of ketone:alcohol to 1:1 when we applied Ir complex E (entry 1, Table 3). This resulted in highest yield of 3 obtained so far (71%). With both these catalysts it was found that using pure KOH, which contained less water and was stored under N₂, the reaction went faster. In Chapter 4 we already described that these catalysts are not very robust, and water / traces of O₂ would probably deactivate the catalyst.

**Application of the M(cod)(CNHC-NH) complexes as Internal Base**

Complexes E and F contain the deprotonated form of the CNHC-NH ligand which, as we suggested, could also function as an internal base and replace the role of KOH in the base catalyzed aldol condensation. A suggested mode of action is shown in Scheme 5. If the amine...
deprotonates the ketone substrate it would dissociate and facilitate binding of the substrate as enolate.

Scheme 5. Suggested role of the M(cod)(C\textsubscript{NM}-NH) complex in the aldol condensation, where the coordinated amine functions as internal base, deprotonating the substrate ketone.

The amine moiety of complexes A and B could in principle also be deprotonated, but these complexes were only developed and isolated in their protonated form. To test if our idea worked, we applied complexes E and F, and a deprotonated version of B in the direct α-alkylation of acetophenone 1 and benzyl alcohol 2 (Scheme 3).

The results of this are shown in Table 4. To obtain a deprotonated version of complex B, a standard procedure was followed. B was stirred with 1,2 equiv. of KO\textsubscript{t}Bu in THF to abstract the chloride and deprotonate the amine, forming KCl and HO\textsubscript{t}Bu. After removal of the salts, the resulting complex was immediately used in catalysis (entry 1). This procedure, however, did not result in the coupling of the acetophenone 1 and benzyl alcohol 2.

Table 4. Results of the direct α-alkylation of acetophenone 1 and benzyl alcohol 2 using Ir-complex E, Rh-complex F and deprotonated B, without the addition of KOH.

<table>
<thead>
<tr>
<th>Entry\textsuperscript{[a]}</th>
<th>Catalyst</th>
<th>Conversion\textsuperscript{[b]} (%)</th>
<th>Yield\textsuperscript{[c]} (%)</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 \textsuperscript{[d]}</td>
<td>B + KO\textsubscript{t}Bu</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>E</td>
<td>29</td>
<td>5</td>
<td>12</td>
<td>&lt;1</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>43</td>
<td>19</td>
<td>&lt;1</td>
<td>1</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>4 \textsuperscript{[e]}</td>
<td>F</td>
<td>47</td>
<td>25</td>
<td>5</td>
<td>3</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

General conditions: [a] 2 mmol acetophenone 1 : 2 mmol benzyl alcohol 2 and 1 mol% cat at 100 °C for 3 hr, neat. [b] Conversion is based on amount of acetophenone 1 converted. [c] Yields determined based on GC-area%. [d] catalyst B was stirred with 1,2 eq of KO\textsubscript{t}Bu to obtain the deprotonated form of the C\textsubscript{NM}-NH\textsubscript{2} ligand. [e] reaction time was 24 hr.

We did not proceed in trying to obtain an isolated version of the deprotonated B, but instead
we applied complexes **E** and **F** displayed in Figure 3. Both complexes proved to be successful in the direct α-alkylation of acetophenone 1 with benzyl alcohol 2 without the need of adding base (entry 2-4, Table 4). When Rh complex **F** was used as catalyst under standard conditions (entry 3) acetophenone 1 was converted for 43%, of which 19% towards the desired product 3. Higher alkylated products (5 and unidentified) constituted about 15%, and the other 7% was identified as phenylethenol 7.

The decreased amount of higher alklylation products in favor of the mono-alkylated products is likely due to the applied 1:1 alcohol:ketone ratio. Increasing the reaction time to 24 hr (entry 4) did not significantly increase the conversion, indicating that at some point the catalyst apparently becomes inactive or decomposes. This is supported by the formation of a black film on the Schlenk wall. The Ir complex **E** (entry 2) is less successful than its rhodium counterpart in converting acetophenone 1 and creating the desired product 3, but the yield of 4 is increased, indicating that **E** is a more active hydrogenation catalyst, but perhaps decomposes more quickly.

If we examine the total number of side products obtained in the catalytic reactions without base, using complex **E** and **F** (Table 4), we see a similar amount as compared to when complex **C-F** are applied with base (Table 2 and 3). Removing the external base KOH from the reaction apparently has no influence on the side product formation. This can indicate two things:

1) The formation of the side products is metal-catalyzed or

2) the internal base functions in a very similar manner in the aldol-condensation as a normal added base.

The first option can be explained by the fact that **E** and **F** are generated from **C** and **D** by applying a base able to remove the chloride and deprotonate the amine (as described in Chapter 4). When **E** and **F** function as internal base a suggested intermediate can be formed, as shown above in Scheme 5.

Essentially, applying **C** and **D** in a catalytic reaction with KOH and substrate can result, directly or indirectly, in a similar intermediate which in turn might be the reason that in a similar number of side products is formed, see Scheme 6. However, these options are purely hypothetical and no further experiments have been performed to investigate the two possibilities.
Chapter 6

Scheme 6. M(cod)Cl(CNHC-NH₂) complexes C and D forming a similar suggested intermediate via the addition of KOH and the presence of substrate ketone as the one mentioned in Scheme 5.

Extending the Substrate Scope

The protocol was extended to include other substrates. We decided to first include the linear alcohol n-butanol 8 and methyl-i-propylketone 12 and apply these together with 1 and 2 to explore which substrate combinations work well (see Scheme 7-9). Alkylating 1 with n-butanol 8 should yield hexanophenone 9 as the main product, shown in Scheme 7 together with the main side products. The results of this reaction are reported in Table 5. From these results it quickly becomes clear that changing the substrate alcohol to the linear n-butanol 8 makes the reaction less selective. In all cases the total amount of 1 converted is satisfactory, but only complexes A, B and C (entry 1-3) show to preferably form desired product 9. Typically, the Ru-complex A and Ir-complexes C and E quickly hydrogenate the product ketone to alcohol, yielding 10 (entry 1, 3 and 5) in larger amounts. Except for Ru(p-cym) A (entry 1), between 4 and 10% of homocoupled acetophenone 11 was observed. For Ir complexes B, E and Rh complex F (entry 2, 5 and 6) a large amount of higher alkylated products was observed.

Scheme 7. Direct α-alkylation of acetophenone 1 and n-butanol 8, forming products 9, 10, homocoupled acetophenone 11 and a multitude of higher alkylated and unidentified products.
Table 5. Results of the direct α-alkylation of acetophenone 1 and n-butanol 8 using the selected catalysts.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conversion (a) (%)</th>
<th>Yield (b) (%)</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>89</td>
<td>43</td>
<td>24</td>
<td>43</td>
<td>-</td>
<td>22</td>
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<tr>
<td>2</td>
<td>B</td>
<td>69</td>
<td>1</td>
<td>26</td>
<td>9</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>98</td>
<td>40</td>
<td>35</td>
<td>1</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>D</td>
<td>70</td>
<td>1</td>
<td>10</td>
<td>5</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>E</td>
<td>99</td>
<td>34</td>
<td>16</td>
<td>5</td>
<td>44</td>
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</tr>
<tr>
<td>6</td>
<td>F</td>
<td>71</td>
<td>1</td>
<td>8</td>
<td>1</td>
<td>56</td>
<td></td>
</tr>
</tbody>
</table>

General conditions: [a] 2 mmol acetophenone 1: 4 mmol n-butanol 8, 10 mol% KOH and 1 mol% cat at 100 °C for 3 hr, neat. [b] Conversion is based on amount of 1 converted. [c] Yields determined based on GC-area%.

Formation of these products was probably partially promoted by the excess of substrate alcohol present (ketone:alcohol 1:2, Table 5). For this reason, we decided to continue our investigation with a 1:1 ratio of substrate ketone:alcohol. Alkylating methyl-i-propylketone 12 with benzyl alcohol 2 should mainly yield 4-methyl-1-phenylpentanone 13 as product. In Scheme 8 the possible products and side-products found for this reaction are displayed. In Table 6 we report the results this combination of substrates. A clear preference for the desired product 13 was observed for all catalysts. However, except when Ru(p-cym) A (entry 1) was used, there is a significant amount of 15 formed, where a second molecule of methyl-i-propylketone 12 is incorporated. In general however, no higher alkylated products were observed.

Scheme 8. Direct α-alkylation of methyl-i-propylketone 12 and benzyl alcohol 2 forming 13, 14 and 15 and several other unidentified products.
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Table 6. Results of the direct α-alkylation of methyl-isopropylketone 12 and benzyl alcohol 2 using the selected catalysts.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conversion&lt;sup&gt;[b]&lt;/sup&gt; (%)</th>
<th>Yield&lt;sup&gt;[c]&lt;/sup&gt; (%)</th>
<th>Entry 13</th>
<th>Entry 14</th>
<th>Entry 15</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>87</td>
<td>67</td>
<td>19</td>
<td>3</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>74</td>
<td>55</td>
<td>2</td>
<td>17</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>94</td>
<td>62</td>
<td>5</td>
<td>27</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>D</td>
<td>88</td>
<td>54</td>
<td>8</td>
<td>26</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>E</td>
<td>96</td>
<td>48</td>
<td>3</td>
<td>22</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>95</td>
<td>56</td>
<td>4</td>
<td>30</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

General Conditions: [a] 2 mmol methyl-i-propylketone 12 : 2 mmol benzyl alcohol 2, 10 mol% KOH and 1 mol% cat at 100 °C for 3 hr, neat. [b] Conversion is based on amount of 12 converted. [c] Yields determined based on GC-area%.

We then proceeded to combine the two non-aromatic substrates methyl-i-propylketone 12 and n-butanol 8 in the direct alkylation reaction, shown in Scheme 9 and Table 7.

![Scheme 9](image)

Scheme 9. Direct α-alkylation of methyl-i-propylketone 12 and n-butanol 8 forming 16-19 and a multitude of unidentified peaks.

Now that n-butanol 8 is applied as substrate alcohol, the reaction returns to being very unselective. For the Ru and Ir catalysts (entry 1-3 and 5, Table 7) only 20 to 25% methyloc-tanone 16 was yielded, while application of the Rh catalysts (entry 4 and 6) yields around 40-50% of 16. For this reaction in particular, a very large number of side products was formed. For entry 5 and 6 especially, there is an incredible amount (>30) of small peaks that together constitute an estimate of 5% of the conversion.
Table 7. Results of the direct α-alkylation of methyl-i-propylketone 12 and n-butanol 8 using the selected catalysts.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conversion[^b] (%)</th>
<th>Yield[^c] (%)</th>
<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>60</td>
<td></td>
<td>20</td>
<td>-</td>
<td>2</td>
<td>6</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>37</td>
<td></td>
<td>16</td>
<td>3</td>
<td>8</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>61</td>
<td></td>
<td>14</td>
<td>&lt;1</td>
<td>16</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>D</td>
<td>85</td>
<td></td>
<td>39</td>
<td>5</td>
<td>16</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>5[^d]</td>
<td>E</td>
<td>86</td>
<td></td>
<td>25</td>
<td>8</td>
<td>21</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>6[^d]</td>
<td>F</td>
<td>93</td>
<td></td>
<td>50</td>
<td>5</td>
<td>12</td>
<td>15</td>
<td>11</td>
</tr>
</tbody>
</table>

General Conditions: [a] 2 mmol methyl-i-propylketone 12 : 2 mmol n-butanol 8, 10 mol% KOH and 1 mol% cat at 100 °C for 3 hr, neat. [b] Conversion is based on amount of 12 converted. [c] Yields determined based on GC-area%. [d] A very large amount of side-products (>30) form around 5% of the total GC-area% in these reactions.

From the previous examples we can conclude that, using our catalysts A-F, the direct α-alkylation of ketones with alcohols is in general not a very selective reaction. Higher selectivity has been obtained for some specific substrates though. For example, using benzyl alcohol 2 instead of n-butanol 8 appeared to yield much less side products. Complexes E and F should be tested without KOH for these substrates to obtain more data on the formation of side products and on the substrate scope of the reaction without base. The selectivity of the reaction, using our complexes, seems to be heavily depending on an ideal substrate combination, with a preference for bulkier substrates.

**Conversion of Natural Substrates**

Nonetheless, we were still intrigued if this catalytic system could be extended to include biomass inspired or natural substrates. We therefore decided to screen two additional alcohol substrates: the diol ethylene glycol 20 and geraniol 22. We already encountered ethylene glycol as the product of the fully hydrogenolysed ester dimethyl oxalate. Additionally, it can be obtained directly from cellulose via a heterogeneous process[^20] and is a common derivative of platform chemicals[^21]. In industry it finds widespread application as precursor to polymers. Geraniol (3,7-dimethylocta-trans-2,6-dienol) is a terpene alcohol that can be isolated from certain aromatic plants. It is known to exhibit insecticidal properties, has antimicrobial, antioxidant and anti-inflammatory activity and sparked interest in the pharmaceutical industry as, amongst others, a chemoprevention agent for cancer[^22]. Both are thus interesting substrates to functionalize. The anticipated reactions are displayed in Scheme 10.
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Scheme 10. The envisaged direct α-alkylation of acetophenone 2 with biomass inspired and natural substrates ethylene glycol 20 and geraniol 22.

Similar reaction conditions as used above were applied for these two reactions. Ketone and alcohol were reacted neat, using 10 mol% KOH and 1 mol% Ru(p-cym) A for 3 hr at 100 °C. When 20 was reacted with one or two equivalents of 2, however, it appeared that under these conditions 20 mostly polymerizes or dimerizes. GC and NMR of the mixture after 3 hr revealed only the presence of unreacted 2, together with an insoluble white film on the inside of the Schlenk tube. We did not attempt to further identify the white polymer but, in analogy to literature reports, one can imagine that due to the presence of KOH and the dehydrogenating/hydrogenating catalyst, poly-aldol products were formed. Compound 20 can be dehydrogenated to hydroxyacetaldehyde after which dimerization or polymerization can take place. Additionally, the product was filtered over silica, which in this case can promote aldol condensation and removal of the polymer from the final analyzed reaction mixture.

The larger substrate geraniol 22, however, reacted in a somewhat controlled manner with 2 under the standard conditions and in a 1:1 ratio. Investigation of the reaction products with GC showed full conversion of 22 into only four main products (see Scheme 11) and only a trace-amount of 11, the homocoupled product of 2, was observed (±1%).

$^1$H-NMR of the crude product mixture showed complete disappearance of the doublet at $\delta = 4.2$ ppm belonging to the alcoholic $CH_2$ protons characteristic of 22. The appearance of two signals at $\delta = 2.4$ ppm and 3.0 ppm, belonging to the bond formed via the aldol condensation and subsequent hydrogenation, indicate the successful coupling of 22 and 2 to form product. All signals are rather broad, which is due to the fact that the signals of the four products overlap. Two of the four products were found to both have m/z = 256.173, which could indicate two structural isomers of the desired product 23. The other two products peaks correlate to the product 24 where an additional double bond is hydrogenated. The formation of the different isomers can be ascribed to unselective hydrogenation of one or two of the three double bonds that the aldol product contains (step 2), and the hydrogenation catalyst
unselectively hydrogenates 1 or 2 double bonds, or the ketone (step 3).

Scheme 11. Catalytic scheme of the direct α-alkylation of acetophenone 2 with geraniol 22 forming four different products as observed by GC-MS. Multiple isomers of 23 and 24 are possible but not shown in this scheme.

Since these last two experiments only concerned a superficial screening of the potential of biomass inspired and natural substrates, there are several ambiguities and questions still to be answered and no proper product isolation was performed. For example, we did not test biogenic substrates where more functionalities are present (such as methyl levulinate which has an extra ester moiety, or hydroxymethylfurfural, which has an ether oxygen). We also did not test these biogenic substrates in a catalytic run without KOH, using a complex with an internal base. However, functionalization of geraniol 22 via this pathway is an option that could be considered and explored further, while small diols like ethylene glycol 20 should be excluded from the substrate scope.

6.3 Summary and Conclusions

The selected catalysts A-F all show activity in the direct α-alkylation of ketones with alcohols. Both conversions and selectivities that were obtained were similar to levels as reported in literature. The general aseletivity of this reaction stems from the fact that two different catalytic cycles are at work. The first is a hydrogen-borrowing system, where the selected catalysts function as dehydrogenation and hydrogenation catalysts. This can cause further hydrogenation of the product ketone to an alcohol. The second is the base catalyzed aldol condensation, where coupling of the ketone with the dehydrogenated alcohol takes place. For this step, a strong base is needed and further alkylation of the aldol product via a Michael addition or another aldol condensation, before it is hydrogenated, can give rise to a large part of the higher alkylated side-products that were observed. The selectivity of the
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reaction is thus balanced by a combination of two factors:

1) the hydrogenation activity of the catalyst

2) the choice of substrate.

Specific substrate-catalyst combinations lead to reasonable selectivity in this reaction. However, Ir(cod) complex C showed to have quite a constant activity and selectivity for all the applied substrates. C therefore could be said to have a correct intermediate hydrogenation activity: not too fast and not too slow. From the screening of different types of substrates it became clear that small, linear substrate alcohols such as n-butanol 8, (and to a lesser degree also small ketones) sterically allow multiple alkylations, creating an abundance of side-products both in combination with acetophenone 1 and methyl-i-propylketone 12. Applying, a 1:1 ratio of substrate ketone and alcohol instead of a 1:2 ratio diminishes the presence of side-products as well.

We succeeded to demonstrate that an internal base functionality, as is present in the deprotonated form of M(cod) complexes E and F, can replace an external base such as KOH. The stability of the catalyst needs to be improved to prevent its decomposition under the reaction conditions. We did not see improvement in selectivity when applying these catalysts without base. This means we cannot exclude the possibility that formation of the higher alkylated side products is metal-catalyzed, since complexes C and D can form similar intermediate structures in the presence of KOH and substrate ketone. If that is the case, further design of the complex with an internal base moiety might improve the selectivity. The substrate scope was extended and the natural alcohol geraniol was successfully functionalized.

A possible future development for the direct α-alkylation of ketones with alcohols is to make the last hydrogenation step enantioselective, by using a secondary alcohol combined with a chiral hydrogen-borrowing catalyst. This would generate a stereocenter after hydrogenation of the aldol-condensated product. The prospect of being able to incorporate enantioselectivity into this reaction and the ability to functionalize biogenic substrates, without the use of an external base, opens up opportunities for the application of this conversion in the field of sustainable chemistry. First, however, serious improvements on the selectivity issue have to be made.
6.4 Experimental Section

General Remarks

All experiments were carried out under an atmosphere of purified nitrogen using standard Schlenk techniques. p-xylene was distilled from CaCl₂ under a nitrogen atmosphere and stored over 4Å molecular sieves. Deuterated solvents (CDCl₃ and CD₂Cl₂), acetophenone and benzyl alcohol were distilled from CaH₂ under a nitrogen atmosphere and stored over 4Å molecular sieves prior to use. Methyl-i-propylketone, n-butanol, ethylene glycol and geraniol were degassed by three freeze-pump-thaw cycles and stored under a dried nitrogen atmosphere prior to use. Products were determined with gas chromatography using p-xylene as internal standard, on a Thermo Scientific Trace GC Ultra system with a Restek RTX®-200 (30 meters, 0.25 mmID) capillary column with a split injecting method. 3, 4, 5, 6, 7, 9, 10, 11, 13, 14 and 16 were known in literature and identified using either ¹H-NMR, GC and/or GC-MS. 15, 17, 18, 19 and 23 were not previously reported in literature, but have not been isolated in this research. Their identity has been reasoned based on the structure of their starting materials and the catalytic cycle combined with GC-MS and ¹H-NMR data. NMR spectra were recorded on either a Bruker AMX400 MHz, Bruker DRX 300 MHz, Varian Mercury 300 MHz or Varian INOVA 500 MHz. GC-MS was performed on a JEOL AccuTOF 4G GCv with a HP-5 MS (30 meters, 0.25 mmID) capillary column.

The synthesis of [Ru(p-cym)Cl(C₅H₄-NH₂)]PF₆ (A) and IrCp*(C₅H₄-NH₂)]PF₆ (B) are described in Chapter 3. The synthesis of Ir(cod)Cl(C₅H₄-NH₂) (C), Rh(cod)Cl(C₅H₄-NH₂) (D), Ir(cod)(C₅H₄-NH) (E) and Rh(cod)(C₅H₄-NH) (F) are described in Chapter 4.

General Procedure for Direct Alkylation Catalysis

Catalyst (0.02 mmol) and KOH (11.2 mg, 0.2 mmol) were weighed in a schlenk flask and ketone (2 mmol), alcohol (2 or 4 mmol) and p-xylene (17.2 μl, 0.14 mmol) were added. The schlenk flask was closed using a septum and a tie wrap. The mixture was immediately placed in a pre-heated oil-bath of 100 °C and stirred for 3 hr. The septum allowed sampling in time using a needle and a syringe, and samples were filtered over a short silica column. Conversions were determined with gas chromatography using the GC-area%. Several known or commercially available products were calibrated using p-xylene as internal standard. These calibrated products and substrates were used to check the reported conversions based on GC area%, as far as possible, to not deviate in a large extent: Numbers are accurate within 5 %. In none of the cases it was attempted to isolate the product or report isolated yields.
6.5 References