Sustainable pathways to chemicals and fuels from lignocellulose via catalytic cleavage and coupling reactions
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2018

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter 3

Upgrading of Lignin Derived Platform Chemicals

In Chapter 2, I designed the LignoFlex process which transformed lignocellulose to a range of attractive products including aromatic alcohols (4-propanolguaiacol and 4-propanolsyringol). In this chapter I will continue the work from Chapter 2 and focus on the upgrading of obtained aromatic alcohols. Amines play a central role in the chemical industry since nitrogen-containing compounds are key structural motifs in pharmaceutically active compounds, polymers or surfactants. The shortest and highly atom-economic route towards bio-based amines is the direct coupling of lignin-derived alcohols with ammonia and herein we presented a direct transformation of 4-propanolguaiacol with ammonia using commercially available Ni/SiO$_2$-Al$_2$O$_3$. The corresponding nitrile was obtained in good yield (69%) at 180 °C. The obtained nitrile could be converted to amine by the same catalyst (Ni/SiO$_2$-Al$_2$O$_3$) under hydrogen with excellent yield (95%) and also to acid by simply refluxing in aqueous solution of NaOH. Defunctionalizations to 4-ethylguaiacol or 4-ethylsyringol are also performed and good isolated yield (75% and 79%) are obtained by heated them to 220 °C in toluene with Ni/SiO$_2$-Al$_2$O$_3$ catalyst. Potential applications for obtained chemicals are discussed at the end of this chapter.

Part of this chapter has been published as: Z. Sun, G. Bottari, A. Afanasenko, M. C. A. Stuart, P. J. Deuss, B. Fridrich & K. Barta, Nat. Catal. 2018, 1, 82–92.
3.1 Introduction
The lignin derived monomers obtained are normally less complex than lignin itself; however keep some of the inherent structural features of the renewable starting material. These structures will inspire new research directions in chemical catalysis that will focus on a.) selective functionalization to emerging building blocks and fine chemicals; b.) selective defunctionalization to bulk chemicals (Figure 3.1).

![Figure 3.1 Strategies for the conversion of lignin derived monomers to emerging structures and bulk chemicals.](image)

Selective functionalization strategies should target atom economic and waste free pathways for the direct conversion of aliphatic and aromatic alcohols to amines or the formation of new C-C bonds to obtain value added products such as various polymer building blocks or pharmaceutical intermediates in few reaction steps, which will significantly contribute to achieving overall sustainability and meet green chemistry goals\(^1\). Novel and efficient defunctionalization methods hold the promise of producing simpler drop in molecules (e.g. BTX, phenol, catechol, cyclohexane), which have large market potential. The advantage of producing compounds equivalent to those obtained from petrochemicals is that these structures are fully compatible with existing infrastructure\(^2,3\).

In Chapter 2 I have proposed an efficient way (LignoFlex process) for the selective production of lignin monomers \(1G\) (4-propanolguaiacol) and \(1S\) (4-propanolsyringol). These intermediates maintain important functionalities that allow direct conversion to higher value products. Such pathways are direct and atom-economic and lead to value added chemicals with minimal amount of waste and energy input. The obtained compounds would enter the chemical supply chain at higher level of functionality ensuring competitiveness with fossil derived pathways. This offsets the need for multiple functionalization steps developed for petroleum derived simple building blocks via classical pathways that are associated with the
production of copious amounts of waste. Regarding lignin valorisation, such approach is a viable alternative to strategies that attempt to convert lignin into chemicals of very low functionality, in particular when products containing heteroatoms are desired. So in this Chapter I will focus on these two compounds and especially 1G for getting more valuable chemicals. Firstly, I focused on the functionalization on the aliphatic alcohol moiety. Amines play a central role in the chemical industry since nitrogen-containing compounds are key structural motives in pharmaceutically active compounds, polymers or surfactants.\textsuperscript{4,5} Surprisingly however, systematic chemo-catalytic approaches for the production of amines from lignin\textsuperscript{6} have, to the best of our knowledge, not been realized. The shortest, and highly atom economic route towards bio-based amines is the direct coupling of lignin-derived alcohols with ammonia, producing water as only by-product. However, merely a few homogeneous and heterogeneous catalytic methods are known to yield amines\textsuperscript{7,8} or nitriles\textsuperscript{9} from alcohols directly and the efficiency of these is largely limited by the structure of the substrate. As shown in Scheme 3.1, I have surprisingly found that a versatile building block, nitrile 4 can be obtained through the direct transformation of 4 with ammonia using the commercially available Ni/SiO\textsubscript{2}-Al\textsubscript{2}O\textsubscript{3}. Hydrogenation of 4 under mild reaction conditions provided amine 5 in analytical purity. Nitrile 4 could also be easily converted to acid 6 by refluxing in sodium hydroxide solution. Reductive defunctionalization of 1G resulted in the formation of 3G in high selectivity. The obtained chemicals have potential to be used as pharmaceutical or polymer building blocks.

\textbf{Scheme 3.1} Catalytic functionalization and defunctionalization of 1G.

Another interesting route is the selective HDO to oxygenated products such as substituted cyclohexanols which is an important precursor of polymer building blocks like caprolactam,
caprolactone and adipic acid. Sels and co-workers have investigated several commercial catalysts like 5 wt % Ru/C, 5 wt % Pd/C and 65wt % Ni/SiO$_2$–Al$_2$O$_3$ and home-made supported Ni catalysts for the conversion of 4-propylguaiaicol to 4-propylcyclohexanol. Rinaldi and co-workers demonstrated that RANEY @Ni could efficiently catalyse the transfer HDO of several lignin monomers using 2-PrOH as H- donor and solvent. And recently, they also pointed out the possibility of producing 4-(3-hydroxypropyl)cyclohexanol which could be a lignin-derived long-chain diol monomer as replacements for petroleum-derived 1,6-hexanediol, employed on the large-scale production of polyesters. However, in this study dehydro-p-coumaryl alcohol was selected as a model compound and neither 1G nor 1S was tested. As a result, in this chapter, I focused on the lignin derived platform chemical 1G as starting material (Scheme 3.2) to show the possibility of achieving high yield.

3.2 Results and discussion

3.2.1 Catalytic conversion of 1G to 4

I set out to study the reaction of the aliphatic alcohol moiety of 1G with ammonia directly using heterogeneous Ni catalysts. I envisioned that a Ni based heterogeneous catalyst will affect the dehydrogenation of the alcohol to the corresponding aldehyde, which will undergo condensation with ammonia to form the corresponding imine. Primary amine can then be generated by a “borrowing hydrogen” sequence or the imine can undergo further dehydrogenation to the corresponding nitrile (Scheme 3.3). Being aware that the key issue is product selectivity, I have first used a variety of heterogeneous Ni catalyst to elucidate ideal reaction conditions. Among the tested catalysts, Cu-Zn alloy, CuNi-PMO and Ni/C showed no substrate conversion under this reaction conditions. Raney Ni displayed good to excellent substrate conversion, however poor selectivity and delivered a mixture of different products including the expected nitrile, primary amine and secondary amine (Table 3.3). Additional products observed were 2G, obtained upon direct hydrogenolysis or dehydration/hydrogenation of 1G; and 3G, which likely formed upon decarbonylation of the aldehyde (Scheme 3.3). Compared to Raney Ni, Ni/SiO$_2$–Al$_2$O$_3$ was less active but displayed much better selectivity towards 3-(4-hydroxy-3-methoxyphenyl)propanenitrile (4).
Upgrading of Lignin Derived Platform Chemicals

Scheme 3.3 Proposed reaction mechanism for catalytic conversion of 1G to 4 via dehydrogenation and amination reaction.

Table 3.1 Screening of different catalysts for transforming 1G to the corresponding amines and nitrile.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalysts</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
<th>2G (GC Yield (%))</th>
<th>3G (GC Yield (%))</th>
<th>4 (GC Yield (%))</th>
<th>5 (GC Yield (%))</th>
<th>5DA (GC Yield (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ni/SiO₂-Al₂O₃</td>
<td>4</td>
<td>42.5</td>
<td>0.6</td>
<td>3.2</td>
<td>18.2</td>
<td>18.9</td>
<td>1.6</td>
</tr>
<tr>
<td>2</td>
<td>Ni/SiO₂-Al₂O₃</td>
<td>18</td>
<td>86.6</td>
<td>5.9</td>
<td>11.9</td>
<td>28.1</td>
<td>28.7</td>
<td>12.0</td>
</tr>
<tr>
<td>3</td>
<td>Ni/SiO₂-Al₂O₃</td>
<td>24</td>
<td>91.9</td>
<td>7.9</td>
<td>13.4</td>
<td>23.6</td>
<td>32.6</td>
<td>14.5</td>
</tr>
<tr>
<td>4</td>
<td>Raney Ni</td>
<td>4</td>
<td>61.3</td>
<td>2.1</td>
<td>13.1</td>
<td>4.3</td>
<td>37.9</td>
<td>5.0</td>
</tr>
<tr>
<td>5</td>
<td>Raney Ni</td>
<td>18</td>
<td>93.2</td>
<td>11.1</td>
<td>33.1</td>
<td>5.6</td>
<td>29.2</td>
<td>14.3</td>
</tr>
<tr>
<td>6</td>
<td>Raney Ni</td>
<td>24</td>
<td>97.6</td>
<td>13.8</td>
<td>33.1</td>
<td>12.3</td>
<td>25.2</td>
<td>13.2</td>
</tr>
<tr>
<td>7</td>
<td>Cu-Zn alloy</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Ni/C</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Cu-Ni-PMO</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Reaction conditions: a. Raney Ni (0.1 g wet) or other catalysts 0.05 g, NH₃-THF (0.5 M) 3 mL, substrate 0.09 g (0.5 mmol), 180 °C, NH₃:substrate = 3:1.

2G: 4-Propylguaiacol; 3G: 4-Ethylguaiacol; 4: 4-Propanenitrileguaiacol; 5: 4-(3-aminopropyl)guaiacol; 5DA: 4,4’-(azanediylbis(propane-3,1-diyl))bis(2-methoxyphenol).

Therefore we have selected the Ni/SiO₂-Al₂O₃ catalyst for further optimization of reaction conditions to get higher yield of nitrile 4 (Table 3.2). First, we increased the NH₃ to substrate ratio in order to facilitate the imine formation pathway and thereby suppress the formation of 4-ethylguaiacol (3G) by decarbonylation. To our surprise, when the NH₃ to substrate ratio increased from 3 to 10, we observed the formation of 4 in perfect selectivity, albeit at lower substrate conversion 12%. Therefore, we increased the reaction time and further increased...
the NH\textsubscript{3} amount. Finally 4 was obtained in very good selectivity (about 90\%) at full conversion. This reaction was repeated 4 times (limitations existed due to the small volume of the microreactor) and the pure product 4 was isolated in 69\% yield. This reaction is also performed under Ar atmosphere, without obvious differences in product selectivity and conversion showing that oxygen likely did not affect the reaction, thus a true dehydrogenation of both the alcohol 1G as well as the imine intermediate took place.

### Table 3.2 Optimizing reaction conditions for transforming 1G to 4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (g)</th>
<th>Solvent (mL)</th>
<th>NH\textsubscript{3}:Substrate</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
<th>GC Yield (%)</th>
<th>2G</th>
<th>3G</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.01</td>
<td>2</td>
<td>10</td>
<td>16</td>
<td>12.0</td>
<td></td>
<td>0</td>
<td>0</td>
<td>12.0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0.01</td>
<td>2</td>
<td>10</td>
<td>60</td>
<td>100</td>
<td>4.1</td>
<td>7.2</td>
<td>30.1</td>
<td>24.4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.02</td>
<td>3</td>
<td>15</td>
<td>16</td>
<td>68.1</td>
<td>2.7</td>
<td>7.5</td>
<td>57.8 (37%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.02</td>
<td>4</td>
<td>15</td>
<td>16</td>
<td>59.2</td>
<td>2.2</td>
<td>7.1</td>
<td>47.7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.02</td>
<td>5</td>
<td>15</td>
<td>16</td>
<td>54.4</td>
<td>1.9</td>
<td>6.6</td>
<td>41.3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.02</td>
<td>4</td>
<td>20</td>
<td>20</td>
<td>100</td>
<td>2.7</td>
<td>8.7</td>
<td>88.6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7\textsuperscript{b}</td>
<td>0.02</td>
<td>4</td>
<td>20</td>
<td>24</td>
<td>100</td>
<td>3.4</td>
<td>6.3</td>
<td>87.9 (69%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>8\textsuperscript{d}</td>
<td>0.02</td>
<td>4</td>
<td>20</td>
<td>24</td>
<td>100</td>
<td>1.2</td>
<td>7.4</td>
<td>80.7 (64%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9\textsuperscript{e}</td>
<td>0.02</td>
<td>4</td>
<td>20</td>
<td>24</td>
<td>100</td>
<td>1.8</td>
<td>7.2</td>
<td>86.3</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Reaction conditions: NH\textsubscript{3}-THF (0.5 M), substrate 0.02 g (0.1 mmol), 180 °C. a. isolated yield. b. reaction repeated for 4 times and give an average number. c. isolated yield from 4 reactions. d. using isolated 1G as starting material. e. reaction under Ar.

2G: 4-Propylguaiacol; 3G: 4-Ethylguaiacol; 4: 4-Propanenitrileguaiacol; 5: 4-(3-aminopropyl)guaiacol.

### 3.2.2 Further selective conversion of nitrile 4

Since nitrile 4 was obtained in excellent selectivity, it could be further catalytically converted to the amine, using the same Ni/SiO\textsubscript{2}-Al\textsubscript{2}O\textsubscript{3} catalyst simply by changing the reaction conditions. Thus, hydrogenation under 110 °C provided the desired primary amine in very good selectivity and high purity (Scheme 3.4). It should be noted, that such good selectivity could not be achieved despite several attempts though a “borrowing hydrogen” manner by using alcohol 1G directly due to the inevitable competing reaction involving the formation of the corresponding secondary amine typical for such reactions.

![Scheme 3.4 Selective conversion of nitrile 4 to amine 5.](image-url)
Scheme 3.5 Selective conversion of nitrile 4 to acid 6.

Next, the nitrile 4 was converted to acid as shown in Scheme 3.5 by refluxing with sodium hydroxide solution following the procedure reported by Chen et al. After purification an isolated yield of 72% is obtained.

3.2.3 Defunctionalization of 1G and 1S

As shown in Scheme 3.3, compound 3G is formed as by product via dehydrogenation and decarbonylation of the alcohol. Inspired by this reaction, I performed a similar reaction without addition of ammonia and resulted in the selective formation of compound 3G (Scheme 3.6). To provide evidence for a decarbonylation pathway and the existence of the aldehyde as crucial intermediate in our reaction pathways, I performed dehydrogenation of 1G (or 1S) over the Ni/SiO₂-Al₂O₃ catalyst in the presence of ethylene glycol. Gratifyingly, the aldehyde intermediate was captured in the form of its ethylene glycol acetal as well as a small amount of aldehyde itself as shown on Figure 3.1.

Scheme 3.6 Defunctionalization of 1G or 1S.

Figure 3.1 GC-MS chromatogram of products after reaction of 1G in presence of ethylene glycol. Reaction conditions: toluene 3 mL, catalyst 10 mg, substrate 90 mg (0.5 mmol), ethylene glycol 0.1 mL (1.8 mmol), 220 °C, 18 h.
3.2.4 Catalytic conversion of $1G$ to $7$

Scheme 3.7 Proposed reaction pathways for catalytic conversion of $1G$ to $7$.

As shown in Scheme 3.7, one-pot catalytic conversion of $1G$ to $7$ could be achieved via different pathways. Firstly, compound $1G$ could be converted to 4-propanolphenol (PNP) via demethoxylation reaction and this compound then converted to $7$ immediately by transfer hydrogenation reaction. Another possible reaction pathway could be first hydrogenation of $1G$ and the formed intermediate ($1GH$) was converted to $7$ through demethoxylation reaction. At the same time, several by products could be formed via hydrolysis or decarbonylation reactions.

Table 3.3 Influence of reaction time for the catalytic conversion of $1G$ to $7$.

<table>
<thead>
<tr>
<th>Time (Min.)</th>
<th>Conversion %</th>
<th>EC</th>
<th>PC</th>
<th>PP</th>
<th>3G</th>
<th>2G</th>
<th>7</th>
<th>1GH</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>23.9</td>
<td>1.9</td>
<td>9.9</td>
<td>4.8</td>
<td>11.9</td>
<td>4.6</td>
<td><strong>17.7</strong></td>
<td>41.2</td>
<td>8.0</td>
</tr>
<tr>
<td>30</td>
<td>52.3</td>
<td>8.0</td>
<td>12.7</td>
<td>7.8</td>
<td>8.4</td>
<td>3.6</td>
<td><strong>35.0</strong></td>
<td>14.1</td>
<td>10.4</td>
</tr>
<tr>
<td>60</td>
<td>65.1</td>
<td>10.9</td>
<td>14.1</td>
<td>9.1</td>
<td>7.4</td>
<td>3.5</td>
<td><strong>36.6</strong></td>
<td>6.9</td>
<td>11.5</td>
</tr>
<tr>
<td>120</td>
<td>77.0</td>
<td>14.3</td>
<td>15.1</td>
<td>8.2</td>
<td>6.5</td>
<td>3.6</td>
<td><strong>37.5</strong></td>
<td>2.9</td>
<td>11.9</td>
</tr>
<tr>
<td>180</td>
<td>84.1</td>
<td>16.1</td>
<td>16.5</td>
<td>7.6</td>
<td>6.2</td>
<td>3.9</td>
<td><strong>36.4</strong></td>
<td>1.2</td>
<td>12.1</td>
</tr>
<tr>
<td>240</td>
<td>97.0</td>
<td>18.2</td>
<td>30.9</td>
<td>3.1</td>
<td>3.1</td>
<td>4.5</td>
<td><strong>25.5</strong></td>
<td>1.1</td>
<td>13.6</td>
</tr>
</tbody>
</table>

Reaction conditions: Raney Ni 1 g (wet), $i$-propanol 7 mL, $1G$ 1 mmol, Dodecane 20 µL was used as internal standard, 120 °C.

As shown in Table 3.3 and Figure 3.2, intermediate $1GH$ is shown as the main products after 10 minutes reaction while intermediate PNP is not detected. This means the hydrogenation of aromatic ring is favored at the initial stage. With the reaction progress, the selectivity of $1GH$ decreased dramatically from 41.2% to 1.1% after 240 minutes while the selectivity of $7$ first increased to 37.5% and then decreased slightly to 25.5%. The low selectivity of $7$ could be explained as its further conversion to EC and PC as discussed above.
Figure 3.2 Product formation profile for the catalytic conversion of 1G to 7. Reaction conditions: Raney Ni 1 g (wet), i-propanol 7 mL, 1G 1 mmol, Dodecane 20 µL was used as internal standard, 120 °C.

3.2.5 Potential applications of obtained chemicals

Scheme 3.8 Potential applications of compound 1G.

1G can be used for the synthesis of XH-14 which has been widely used in China for the treatment of coronary heart diseases.\textsuperscript{19} It can be also used for the synthesis of novel epoxy resins. For example, van de Pas and co-workers reported using hydrogenolysis products derived from softwood lignin (which contain mainly 1G) and their use as replacements for BADGE in new epoxy thermosetting polymers.\textsuperscript{20}
Based on the strategy developed by Sels and co-workers, 3G can be converted to 4-ethylcyclohexanol by supported Ni catalysts and then dehydrogenated to 4-ethylcyclohexanone with high yield. Finally the alkylated ε-caprolactone (precursors for novel polymer building blocks) can be produced by tin-containing beta zeolite in high yields, according to a Baeyer–Villiger-type oxidation with H₂O₂. 3G can be also used for the production of bisphenolic polymer precursors like 5,5′-methylenebis(4-ethylguaiacol). The corresponding bisphenols can be polymerized to polycarbonates, cyanate ester and epoxy resins. Abu-Omar and co-workers did an in-depth research for the application of lignin derived monomers. Based on their researches lignin-derivable 4-alkylguaiacols can be used for the production of biobased epoxy nanocomposites, renewable thermoplastics and renewable thermoset polymers.

Compound 6 is a versatile polymer building block. It can be functionalized with epoxy, cyclic carbonates, allyl, amine, alcohol and carboxylic acid moieties. Through transesterification of compound 6 with bio-based polyols in the presence of lipase, different bisphenol building blocks can be obtained for polyester synthesis. 6 can also be used for preparing the aromatic polyester poly(dihydroferulic acid), which exhibits thermal properties functionally similar to those of polyethylene terephthalate (PET). Besides polymer building blocks, compound 6 also has potential to be used as pharma intermediates. For example, JBIR-94 was isolated from the culture broth of a new species of Streptomyces (strain R56-07) and it...
represents potential lead compounds in the development of a series of novel biologically active molecules with antioxidant and other useful properties.\textsuperscript{32,33} Through demethylation reaction, compound 6 could be converted to corresponding catechol structure, which then was developed as a new mussel-inspired dendritic polyglycerol (MI-dPG) that effectively mimics mussel foot proteins with regard to their functional groups, molecular weight, and molecular structure.\textsuperscript{34}

![Scheme 3.11](image)

\textbf{Scheme 3.11} Potential application of compound 5.

By functionalization of the aliphatic alcohol moiety to amine we obtained compounds 5. It could be directly react with acryloyl chloride and then incorporated into thermoplastic polymers by the radical polymerization.\textsuperscript{35}

\section*{3.3 Conclusion}

In summary, I reported herein the synthesis of several value added chemicals from lignin derived monomers. Notably, among these transformations is the direct coupling of 1G with ammonia and the obtained nitrile could be further converted to amine or acid. Both 1G and 1S can be defunctionalized to 3G or 3S with good selectivity by using commercial Ni catalyst. The obtained chemicals in this Chapter show potential applications as pharmaceutical and polymer building blocks. The established pathways show that the isolated pure compound 1G from LignoFlex process can serve as a lignin-derived platform chemical as it was obtained in high selectivity and converted to higher-value building blocks including amines.

Functionalization of other positions of 1G for getting more value-added chemicals would be an interesting topic in the future. For example, functionalization of the phenol group could produce aniline and substituted aniline. Selective functionalization of the aromatic ring and methoxyl group are also interesting but more challenging. All these functionalization strategies need participate of heterogeneous, homogeneous or bio-catalysts.

\section*{3.4 Experimental procedures}

\subsection*{3.4.1 Experimental procedures for synthesis of compounds}

\textbf{Compound 3G}

20 mg compound 1G was added in a 10 mL Swagelok stainless steel microreactor with 10 mg Ni/SiO\textsubscript{2}-Al\textsubscript{2}O\textsubscript{3} as catalyst, then 3 mL toluene was added.
as solvent. The reactor was sealed and placed in a pre-heated aluminum block at the 220 °C for 18 h. Then the reactor was cooled in ice-water. The catalyst was separated by filtration and the solution was analyzed by GC-MS and GC-FID. Herein, 4 reactions were set up at the same time. After reaction, the reaction mixtures were combined and then toluene was evaporated. The residue was purified by column chromatography on silica gel, using hexanes: ethyl acetate (1:1) as eluent. Yield: 51 mg, (75%).

\[ ^{1} \text{H NMR} \ (400 \text{ MHz, CDCl}_3): \delta \ 6.86 \ (d, J = 8.3 \text{ Hz, 1H}), \ 6.72 \ (d, J = 7.4 \text{ Hz, 2H}), \ 3.89 \ (s, 3H), \ 2.61 \ (q, J = 7.6 \text{ Hz, 2H}), \ 1.24 \ (t, J = 7.6 \text{ Hz, 3H}). \]

\[ ^{13} \text{C NMR} \ (100 \text{ MHz, CDCl}_3): \delta \ 149.02, \ 146.18, \ 138.93, \ 122.93, \ 116.86, \ 113.19, \ 58.50, \ 31.22, \ 18.60. \]

\[ \text{HMRS (ESI}^{+}) \text{ calculated for C}_{9}\text{H}_{11}\text{O}_{2} [\text{M+H}]^{+}: 151.07536, \text{ found 151.07643}. \]

**Compound 4**

20mg **4** was added in a 10 mL Swagelok stainless steel microreactor with 20mg Ni/SiO\textsubscript{2}-Al\textsubscript{2}O\textsubscript{3} as catalyst, and then 3 mL ammonia solution in THF (0.4 M) was added as a solvent. The reactor was sealed and placed in a pre-heated aluminum block at the 180 °C for 24h. Four reactions using 4 identical microreactors were used at the same time. After reaction the reactor was cooled in ice-water. The catalyst was separated by filtration and the solution was analyzed by GC-MS and GC-FID. For purification, we combined all 4 reaction mixtures and the solvent was removed. The residue was purified by column chromatography on silica gel, hexanes: ethyl acetate (2:1). Yield: 54 mg (69%).

\[ ^{1} \text{H NMR} \ (400 \text{ MHz, CDCl}_3): \delta \ 6.87 \ (d, J = 8.0 \text{ Hz, 1H}), \ 6.74 – 6.71 \ (m, 2H), \ 5.59 \ (s, 1H), \ 3.89 \ (s, 3H), \ 2.88 \ (t, J = 7.3 \text{ Hz, 2H}), \ 2.59 \ (t, J = 7.3 \text{ Hz, 2H}). \]

\[ ^{13} \text{C NMR} \ (100 \text{ MHz, CDCl}_3): \delta \ 149.29, \ 147.46, \ 132.64, \ 123.61, \ 121.91, \ 117.32, \ 113.54, \ 58.60, \ 33.99, \ 22.43. \]

\[ \text{HMRS (ESI}^{+}) \text{ calculated for C}_{10}\text{H}_{10}\text{NO}_{2} [\text{M+H}]^{+}: 176.07061, \text{ found 176.07161}. \]

**Compound 5**

Compound **4** (44 mg, 0.25 mmol) was placed in a 4 mL glass vial with a magnetic stirring bar and dissolved in MeOH (1.7 mL). The Ni/SiO\textsubscript{2}-Al\textsubscript{2}O\textsubscript{3} catalyst was added and the vial was quickly transferred to a 5 mL stainless steel reactor, which was pressurized with H\textsubscript{2} (20 bar). The reactor was placed into a pre-heated oil bath (110 °C) and the reaction was left under magnetic stirring for 5 hours. After this time, the reactor was cooled to room temperature and vented. The mixture was filtered on a PTFE filter (0.25 µm pore size) and the volatiles were evaporated under reduced pressure to give an analytically pure sample of **5**. Alternatively, the hydrochloride salt can be isolated as yellow solid (95%, 43 mg) by adding HCl solution in MeOH to a solution of amine **5** in diethyl ether (10 mL).
\[^1\text{H} \text{NMR} \text{ (400 MHz, CD}_3\text{OD): } \delta \text{ 6.74 (dd, } J = 5.3, 1.8 \text{ Hz, 1H), 6.68 (d, } J = 8.0 \text{ Hz, 1H), 6.60(d, } J = 7.6 \text{ Hz, 1H), 3.81 (s, 3H), 2.65-2.61 (t, } J = 7.2 \text{ Hz, 2H), 2.56-2.51 (m, 2H), 1.74 (q, } J = 7.2 \text{ Hz, 2H).} \]

\[^{13}\text{C} \text{NMR} \text{ (100 MHz, CD}_3\text{OD): } \delta 150.19, 147.03, 135.93, 122.98, 117.42, 114.33, 57.58, 43.29, 36.92, 35.03. \]

\text{HRMS (ESI)} \text{ calculated for C}_{10}\text{H}_{14}\text{NO}_{2} \text{ [M-H]: 180.1025; found: 180.1030.} \]

\text{Compound 6} \hspace{1cm} 100 \text{ mg (0.56 mmol) compound 4 was added to a 20 mL microwave vial, then 10mL 1M NaOH was added. The reactor was sealed and placed in a pre-heated aluminum block at the 100 °C for 24h. After cooling to room temperature, the mixture was extracted with Et}_2\text{O} \text{ (20 mL), and the aqueous phase was acidified with conc. HCl (pH = 2), extracted with Et}_2\text{O} \text{ (3 \times 20 mL) and the combined organic layers were washed with brine (20 mL), dried over anhydrous MgSO}_4, \text{ filtered, and concentrated under reduced pressure by rotary evaporation. Purification was carried out by flash column chromatography on silica gel, using ethyl acetate: methanol (20:1) as eluent. Yield: 80 mg (72%).} \]

\[^{1}\text{H} \text{NMR} \text{ (400 MHz, CDCl}_3): \delta \text{ 6.84 (d, } J = 7.8 \text{ Hz, 1H), 6.71-6.69 (m, 2H), 5.51 (b, 1H, OH), 3.87 (s, 3H), 2.89 (t, } J = 7.7 \text{ Hz, 2H), 2.65 (t, } J = 7.7 \text{ Hz, 2H).} \]

\[^{13}\text{C} \text{NMR} \text{ (100 MHz, CDCl}_3): \delta 181.00, 149.08, 146.75, 134.72, 123.49, 117.04, 113.56, 58.52, 38.52, 33.00. \]

\text{HRMS (ESI\textsuperscript{+}) calculated for C}_{10}\text{H}_{11}\text{O}_{4} \text{ [M+H]\textsuperscript{+}: 195.06519, found 195.06658.} \]

\textbf{3.6 References} \hspace{1cm} 1 \text{ P. Anastas and J. Warner, } \textit{Green Chemistry: Theory and Practice,} \text{ Oxford University Press Inc, 1998.} \]

2 \text{ L. Zhang and G. Hu, } \textit{Biomass Bioenergy,} \text{ 2013, 58, 238–250.} \]

3 \text{ R. A. Sheldon, } \textit{Green Chem.}, \text{ 2014, 16, 950–963.} \]

4 \text{ S. Imm, L. Neubert, H. Neumann and M. Beller, } \textit{Angew. Chem. Int. Ed.}, \text{ 2010, 49, 8126–8129.} \]


7 \text{ C. Gunanathan and D. Milstein, } \textit{Angew. Chem. Int. Ed.}, \text{ 2008, 47, 8661–8664.} \]

8 \text{ K. I. Shimizu, K. Kon, W. Onodera, H. Yamazaki and J. N. Kondo, } \textit{ACS Catal.}, \text{ 2013, 3, 112–117.} \]

9 \text{ R. V Jagadeesh, H. Junge and M. Beller, } \textit{Nat. Commun.}, \text{ 2014, 5, 4123.} \]

10 \text{ M. T. Musser, in } \textit{Ullmann’s Encyclopedia of Industrial Chemistry,} \text{ Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2000.} \]
