CARBON MONOXIDE AS REAGENT IN THE FORMYLATION OF AROMATIC COMPOUNDS

by

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Phillipians 4:13: “I can do all things through Christ, who strengthens me”
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Abbreviations

NMR          nuclear magnetic resonance
MO           molecular orbital
M.p.         melting point
B.p.         boiling point
FID          flame ionisation detector
PHBAld.      para-hydroxy-benzaldehyde
p-Toluald.   para-tolualdehyde
PAA          para-anisaldehyde
OAA          ortho-anisaldehyde
BCD          beta-cyclodextrin
THF          tetrahydrofuran
TMS          tetramethylsilane
[bmim]       1-butyl-3-methylimidazolium
[hexmim]     1-hexyl-3-methyl-imidazolium
[omim]       1-octyl-3-methyl-imidazolium
[bmim]BTA    1-butyl-3-methylimidazolium trifluoromethane sulfonimide
h            hour
eq           equivalents
psi          pounds per square inch
atm          atmospheric
min          minutes
Press.       pressure
Conv.        conversion
Sec. Prod.   secondary products
SYNOPSIS

Sasol endeavors to expand its current business through the beneficiation of commodity feedstreams having marginal value into high-value chemicals via cost-effective processes. In this regard Merisol, a division of Sasol has access to phenolic and cresylic feedstreams, which have the potential to be converted to fine chemicals.

Targeted products include para-anisaldehyde, ortho- and para-hydroxybenzaldehyde which are important intermediates for the manufacture of chemicals used in the flavor and fragrance market and various other chemicals. The use of CO technology (HF/BF$_3$) to produce these aldehydes in a two-step process from phenol as reagent is economically attractive due to the relative low cost and other benefits associated with syngas as reagent. The aim of the study was to evaluate and understand this relatively unexplored approach to the formylation of aromatic compounds.

The reactivity of both phenol and anisole proved to be much lower than that of toluene. The main aldehyde isomer (para) produced in these HF/BF$_3$/CO formylations as well as of other ortho-para directing mono-substituted benzenes tested in our laboratories were in accordance with published results. Efforts to increase substrate conversion resulted in substantial secondary product formation and mechanistic investigations showed this to be a consequence of the inherent high acidity of the reaction environment.

The effect of different substituents on the relative formylation rates of benzene derivatives was investigated. These results showed that methyl groups are activating while halogens are deactivating relative to benzene as substrate. The decrease in reactivity from fluorobenzene> chlorobenzene> bromobenzene is in accordance with formylation trends observed in other acidic systems.

Deuterium labeling experiments were applied to gain additional information on the formylation reaction mechanism. This study provided interesting but inconclusive results in support of the so-called intra-complex mechanism.

All reported studies as well as our own work suggested that HF and BF$_3$ in (at least) stoichiometric amounts are required for effective formylation with CO. Under these conditions this methodology for effecting aromatic formylation is not economically viable. Industrial application of formylation using CO will require the development of new catalysts or methodology to allow the use of HF/BF$_3$ in a catalytic way. In this regard
Ionic liquids as a new and ecological-friendly field was explored. Chloro-aluminate ionic liquids promote the carbonylation of alkylated aromatic compounds, but fails in the case of oxygenated aromatics. Aldehyde yields of formylation in the acidified neutral ionic liquids were generally similar compared to reactions conducted in HF as solvent/catalyst. Formylation of anisole and toluene, but not of phenol in the neutral ionic liquids resulted in increased secondary product formation in comparison with hydrogen fluoride used as solvent/catalyst. This difference in behavior is not understood at present, but suggests that phenol is a good substrate for formylation in this medium, particularly with the development of a system catalytic with respect to HF/BF₃ in mind.
OPSOMMING

Ten einde sy huidige omset te verhoog, streef Sasol daarna om kommoditeitsvoerstrome met marginale waarde deur ekonomies lewensvatbare prosesse na hoëwaarde chemikalieë om te skakel. In hierdie verband beskik Merisol, ‘n divisie van Sasol, oor fenoliese- en kresielsuur strome wat potensiël na fyn chemikalieë omgeskaakel kan word. Produkte soos para-anysaldehied, en orto- en para-hidroksiebensaldehied, wat belangrike intermediere in hoofsaaklik die reuk- en smaakmiddel mark is, is as moontlike teiken verbindings hiervoor geidentifiseer.

Aangesien CO tegnologie (met HF/BF₃ as katalisator) nuttig aangewend kan word om genoemde aldehiede ekonomies in ‘n twee-stap proses vanaf fenol te vervaardig en as gevolg van die lae koste en ander voordele wat met sintesegas binne Sasol geassosieer kan word, is hierdie studie rakende die relatief onbekende veld van aromatiese formilering mbv CO onderneem.

In teenstelling met die algemeen aanvaarde orde van reaktiwiteit, is tydens hierdie studie gevind dat die reaktiewiteit van beide fenol en anisole in HF/BF₃/CO formilerings, veel laer as die van toluueen is. Wat selektiwiteite betref is in ooreenstemming met literatuur resultate gevind dat by alle substrate met orto-para rigtende substituente, die para-isomeer as hoofproduk gevorm word. Pogings gerig op die verbetering van fenol omsetting was onsuksesvol en het tot substansiële sekondêre produkvolming geleid. Meganistiese studies het getoon dat die hoë suurgehalte van die reaksiemedium waarskynlik hiervoor verantwoordelik is.

Die effek van substituente op die relatiewe formileringsreaktiwiteit van verskillende benseen derivate het getoon dat metielgroepe aktiverend en halogene deaktiverend tov benseen optree. Die waargenome afname in die reaktiewiteit van fluoor- > chloor- > broombenseen is ook in ooreenstemming met formileringsneigings wat by ander suursisteme waargeneem is.

Ten einde meer insig mbt die meganisme van die HF/BF₃/CO formilerings reaksie te verkry, is deuterium verrykkingsexperimente uitgevoer. Hoewel interessante resultate aanduidend van die sogenaamde intra-kompleks meganisme verkry is, was dit nie eenduidig nie en kon geen finale gevolgtrekking ivm die meganisme van die reaksie dus hieruit gemaak word nie.
In ooreenstemming met literatuur bevindinge, is ook tydens hierdie ondersoek bevind dat beide HF en BF₃ in stoichiometriese hoeveelhede benodig word vir effektiewe formilering van fenoliese substrate met CO. Die hoe koste van HF en BF₃ sou die toepassing hiervan op industriële skaal egter onekonomies maak, met die gevolg dat enige industriële formilering van fenole met CO dus die ontwikkeling van nuwe katalisatore of metodologie vir die katalitiese benutting van HF en BF₃ noodsaak. Aangesien die gebruik van ioniese vloeistowwe 'n moontlike oplossing vir hierdie probleem kon bied, is die effek van hierdie ekologies vriendelike verbindinge op die formileringsreaksie van fenole met CO vervolgens bestudeer.

Weens die feit dat formilering van alkibelensene mbv chloro-aluminaat ioniese vloeistowwe bekend is, is die effek van hierdie reagense op die reaksie van geoksigeneerde aromate aanvanklik ondersoek. Aangesien slegs demetilering van anisool met hierdie reagens waargeneem kon word, is die fokus van die ondersoek vervolgens na die benutting van aangesuurde neutrale ioniese vloeistowwe verskuif en is bevind dat aldehyd opbrengste in ooreenstemming is met die opbrengste van reaksies waar HF as oplosmiddel/katalisator gebruik is. In teenstelling met die reaksies van fenol, het die formilering van anisool en tolue onder hierdie kondisies tot verhoogde sekondêre produk vorming in vergelyking met reaksies van HF as oplosmiddel/katalisator, gelei. Hoewel onverklaarbaar, suggereer hierdie bevinding dat fenol 'n goeie substraat vir formilering in hierdie medium is; veral indien die ontwikkeling van 'n nuwe katalitiese sisteem met betrekking tot HF/BF₃ in gedagte gehou word.
CHAPTER 1
AROMATIC ALDEHYDE SYNTHESSES

1. INTRODUCTION

The synthetic routes to aromatic aldehydes are as numerous as they are diverse, indicating not only the intrinsic value of aldehydes as synthetic intermediates, but also the scarcity of truly general routes towards aldehydes themselves. This resulted in the realization of a number of relatively specific syntheses that often relies on partial oxidation and reduction where the danger of over-reaction is always present. Although carbonylation chemistry offers a limited number of general synthetic routes to aldehydes that are both selective and high yielding, these routes often use readily available starting materials. The two most generally useful substrates for carbonylative aldehyde synthesis are halo-carbons and alkenes.\(^1\) This study will however focus primarily on the synthesis of aldehydes from arenes.

1.1 Comparison of Ketone and Aldehyde Syntheses

Acylation of both aromatic and aliphatic compounds can be carried out with relative ease using acyl halides, acid anhydrides, ketenes, nitriles, amides, acids and esters in the presence of Friedel-Craft catalysts to give ketones.\(^2\) Similar substitution reactions with formic acid derivatives are therefore expected to yield the appropriate aldehydes. However, since the anhydride and acyl halides of formic acid, with the exception of formyl fluoride,\(^3\) are either not known or are not sufficiently stable to be used in Friedel-Crafts type acylation reactions, this objective cannot be fully realized. Table 1.1 compares the main ketone syntheses (based on acylating reagents) with the corresponding aldehyde syntheses (based on formylating reagents).

Table 1.1: Comparison of aldehyde and ketone synthesis.

<table>
<thead>
<tr>
<th>KETONE SYNTHESIS</th>
<th>Acyl halides</th>
<th>Acid</th>
<th>Ketenes</th>
<th>Nitriles</th>
<th>Amides</th>
<th>Acids</th>
<th>Esters</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALDEHYDE SYNTHESIS</td>
<td>CO + HCl (Gattermann-Koch)</td>
<td>Acetic-formic anhydride</td>
<td>CO</td>
<td>HCN (Gattermann) BrCN (Karrer)</td>
<td>Formamides (Vilsmeier)</td>
<td>Formic acid</td>
<td>Ortho-formates</td>
</tr>
</tbody>
</table>
2. FORMYLATING AGENTS

2.1 Formic acid and Derivatives

With the exception of formyl fluoride, which is the only known stable halide of formic acid and used as an electrophilic aromatic formylating agent in the presence of mainly boron trifluoride, no other formyl halides have been isolated.\(^4\) Although the preparation of formyl chloride by high-temperature photo-chlorination of formaldehyde was reported,\(^5\) isolation of the compound could not be substantiated.\(^6,4\) Staab et al.,\(^7\) however, generated the elusive formyl chloride by passing HCl into a solution of 1-formimidazole in CH\(_3\)Cl at \(-60^\circ\)C (Eq 1.1).

\[
\text{N} - \text{CHO} + \text{HCl} \rightleftharpoons \text{N} - \text{NH} + \text{HCOCl} \xrightarrow{\text{CH}_3\text{OH}} \text{HCOOCH}_3 \quad (1.1)
\]

No physical data of the unstable compound were given as it was immediately trapped by methanol to give methyl formate at \(-60^\circ\)C.

An improved \textit{in situ} preparation of formyl chloride as well as of formyl fluoride and even the bromide and iodide from formic acid and tetramethyl-\(\alpha\)-halogeno enamines at or below room temperature in high yield under neutral conditions was reported by Ghosez et al.\(^8\) (Eq 1.2).

\[
\text{HCOOH} + (\text{CH}_3\text{C}=\text{C}=\text{N}(\text{CH}_3)_2) \rightarrow (\text{CH}_3\text{C}=\text{C}=\text{N}(\text{CH}_3)_2)\xrightarrow{\text{HCOX}} (\text{CH}_3\text{C}=\text{C}=\text{N}(\text{CH}_3)_2) \quad (1.2)
\]

Again, the formyl chloride was detected only by its conversion into methyl formate while the other formyl halides were converted into formanilide.

Dichloromethyl ethers and dichloromethyl amines are able to act as formyl chloride equivalents in the formylation of aromatics and olefins. The reactivity of the formylating agent is determined by the nature of the substituent, which determines the electrophilicity of the formyl carbon. Thus, the reactivity for electrophilic formylation decreases in the order 1>2>3 (Eq 1.3).
α,α-Dichlorodimethyl ether is capable of formylating benzene or a slightly activated arene such as toluene in the presence of a Friedel-Crafts catalyst to yield benzaldehyde and tolualdehyde in yields of 37% and 80%, respectively (Eq 1.4).\(^9\)

Nesmejanow et al.\(^{10}\) were the first to prepare formyl fluoride in a yield of 16% from anhydrous formic acid, potassium fluoride and benzoyl chloride (Eq 1.5).

\[ \text{HCOOH} + \text{KF} + \text{PhCOCl} \rightarrow \text{HCOF} + \text{PhCOOH} + \text{KCl} \quad (1.5) \]

Mashentsev\(^{11}\) prepared it from benzoyl fluoride and formic acid in a 36% yield. Olah et al.\(^{12}\) used KHF\(_2\) as alternative reagent to produce formyl fluoride from formic acid and benzoyl chloride. In two improved preparation methods Olah et al.\(^{13}\) prepared formyl fluoride by fluorinating formic acid with cyanuric fluoride in pyridine or by reacting benzoyl fluoride with sodium formate. According to Olah it is possible to achieve a successful formylation reaction by dissolving the generated formyl fluoride in a solution containing the aromatic, followed by the introduction of BF\(_3\) as catalyst. A number of aromatic aldehydes were prepared using this method in yields varying from 56 to 78% (Table 1.2).

**Table 1.2: Formylation of aromatic using formyl fluoride.**\(^a\)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>Benzaldehyde</td>
<td>56</td>
</tr>
<tr>
<td>Toluene</td>
<td>Tolualdehyde</td>
<td>75</td>
</tr>
<tr>
<td>Xylene</td>
<td>Dimethylbenzaldehyde</td>
<td>78</td>
</tr>
<tr>
<td>2,4,6-trimethyl benzene</td>
<td>2,4,6-trimethylbenzaldehyde</td>
<td>70</td>
</tr>
<tr>
<td>2,3,4,6-tetramethyl benzene</td>
<td>2,3,4,6-tetramethyl benzaldehyde</td>
<td>72</td>
</tr>
<tr>
<td>Naphthalene</td>
<td>Naphtaldehyde</td>
<td>20, α-isomer and 67, β-isomer</td>
</tr>
</tbody>
</table>

\(^a\) 0.5mol of the substrate was dissolved in 150ml CS\(_2\) followed by the passing through of a 1:1 formyl fluoride boron trifluoride mixture with stirring while maintaining the reaction temperature between 0 and 10°C for 3hours.
Formyl fluoride reacts with alcohols and phenols in the presence of triethylamine to form the corresponding formates in yields of 73-92% for primary and secondary aliphatic alcohols, while benzyl alcohol and phenol gave the corresponding esters in 69% and 75% yields, respectively (Eq 1.6).

\[
\text{ROH} + \text{HCOF} + \text{Et}_3\text{N} \rightarrow \text{ROC(=O)H} + \text{Et}_3\text{NHF} \quad (1.6)
\]

Olah\textsuperscript{14} prepared the elusive formic anhydride in a reaction of formyl fluoride with sodium formate at -78°C and he extended the preparation of this reagent by three condensation reactions (Eq 1.7).

\[
\begin{align*}
\text{H--C--F} & \quad \text{NaOC--H} & \quad \text{HCOOH} \\
\text{2H--C--OH} & \quad \text{SOCl}_2, \text{pyridine} & \quad \text{Et}_3\text{N, ClSO}_2\text{NCO} & \quad \text{H--C--O--C--H} \\
\text{dicyclohexylcarbodiimide (DCC)}
\end{align*}
\]

(1.7)

Conversion of \(p\)-nitrophenol into \(p\)-nitrophenyl formate in good yield by reaction with this \textit{in situ} generated reagent confirmed that it can act as a formylating agent. However, attempts to formylate aromatics failed due to the instability of the anhydride above -40°C. Also, the presence of acid catalysts leads to the decomposition of the formic anhydride even at low temperatures.

Mixed anhydrides of formic acid with higher homologous acids anhydride are well known and stable. Béhal\textsuperscript{15,16} prepared acetic-formic anhydride from acetic anhydride and formic acid, yielding a suitable formylating agent for the formylation of \(N\)-formyl derivatives from the corresponding amines (Eq 1.8).

\[
\begin{align*}
\text{CH}_3\text{C--O--C--CH}_3 + \text{HCOOH} \rightarrow \text{H--C--O--C--CH}_3 + \text{CH}_3\text{COOH} \\
\end{align*}
\]

(1.8)

Graves\textsuperscript{17} and Roe \textit{et al.}\textsuperscript{18} synthesized acetic-formic anhydride by reaction of ketene with anhydrous formic acid (Eq 1.9).
Olah et al.\textsuperscript{19} attempted to use the acetic formic anhydride as a Friedel-Crafts formylating agent. However, exclusive acetylation of the aromatics was always accompanied by carbon monoxide evolution.

Formic acid in conjunction with appropriate dehydrating agents is also used as formylating agents. Thus, \( N \)-formylation of pyridones is achieved with relative ease using formic acid and dicyclohexylcarbodiimide (DCC) at 0°C (Eq 1.10 and 1.11).\textsuperscript{20}

\[
\begin{align*}
\text{H}_2\text{C} &= \text{C} = \text{O} + \text{HCOOH} \rightarrow \text{H} - \text{C} - \text{O} - \text{C} - \text{CH}_3 \\
(1.9)
\end{align*}
\]

Gross and co-workers\textsuperscript{21} reported an interesting direct aldehyde synthesis using alkyl ortho-formates that is particularly suitable for phenols, as alkyl formates are unable to act as formylating agents under Friedel-Crafts conditions. Aldehydes of phenol are obtained in good yields when phenols react with orthoformates in the presence of aluminum chloride (Eq 1.12).

\[
\begin{align*}
\text{OH} &+ \text{HC(O}_2\text{C}_2\text{H}_5)_3 + \text{AlCl}_3 + \text{H}_2\text{O} \rightarrow \text{OH} + \text{CHO} \\
(1.12)
\end{align*}
\]

Results obtained by formylation of phenolic compounds with orthoformates are summarized in Table 1.3.
Table 1.3: Formylation of phenols by alkyl orthoformates.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>m-cresol</td>
<td>Formyl-m-cresols</td>
<td>66</td>
</tr>
<tr>
<td>2,5-dimethylphenol</td>
<td>4-Hydroxy-2,5-dimethylbenzaldehyde</td>
<td>41</td>
</tr>
<tr>
<td>3,5-dimethylphenol</td>
<td>Formyl-3,5-dimethylphenols</td>
<td>51</td>
</tr>
<tr>
<td>3,4-dimethylphenol</td>
<td>2-Hydroxy-4,5-dimethylbenzaldehyde</td>
<td>44</td>
</tr>
<tr>
<td>Thymol</td>
<td>Formyl-thymols</td>
<td>59</td>
</tr>
<tr>
<td>α-naphthol</td>
<td>Formyl-α-naphthols</td>
<td>97</td>
</tr>
<tr>
<td>β-naphthol</td>
<td>1-Formyl-2-hydroxynaphthalene</td>
<td>41</td>
</tr>
<tr>
<td>Pyrocatechin</td>
<td>3,4-Dihydroxybenzaldehyde</td>
<td>45</td>
</tr>
<tr>
<td>Resorcinol</td>
<td>2,4-Dihydroxybenzaldehyde</td>
<td>64</td>
</tr>
<tr>
<td>Orcinol</td>
<td>2,4,6-Dihydroxy-6-methylbenzaldehyde</td>
<td>66</td>
</tr>
<tr>
<td>Pyrogallol</td>
<td>2,3,4-Trihydroxybenzaldehyde</td>
<td>92</td>
</tr>
<tr>
<td>Hydroxyhydroquinone</td>
<td>2,4,5-Trihydroxybenzaldehyde</td>
<td>89</td>
</tr>
<tr>
<td>Phloroglucinol</td>
<td>2,4,6-Trihydroxybenzaldehyde</td>
<td>96</td>
</tr>
</tbody>
</table>

Formylation of various aromatic substrates can be achieved with fair to good results using methylformate in the presence of HF-BF₃ (Table 1.4).²²,²³

Table 1.4: Formylation of aromatics with HCOOCH₃/HF/BF₃

<table>
<thead>
<tr>
<th>Run</th>
<th>Substrate⁹</th>
<th>HF (eq.)</th>
<th>BF₃ pressure at 0°C (bar)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Conv. (%)</th>
<th>Major Products</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>40</td>
<td>10</td>
<td>50</td>
<td>6</td>
<td>90</td>
<td>CHO</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>40</td>
<td>2.5</td>
<td>40</td>
<td>4</td>
<td>55</td>
<td>Cl-CHO</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>40</td>
<td>10</td>
<td>60</td>
<td>6</td>
<td>15</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>O</td>
<td>40</td>
<td>5</td>
<td>50</td>
<td>5</td>
<td>80</td>
<td>O-CHO</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>30</td>
<td>5</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>OH OCH₃</td>
<td>40</td>
<td>5</td>
<td>50</td>
<td>5</td>
<td>90</td>
<td>OH OCH₃</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>OCH₃</td>
<td>40</td>
<td>2.5</td>
<td>40</td>
<td>4</td>
<td>25</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>40</td>
<td>2.5</td>
<td>40</td>
<td>4</td>
<td>69</td>
<td>CHO</td>
<td>49</td>
</tr>
</tbody>
</table>

¹,³ eq HCOOCH₃ in every case.
Table 1.4 shows that benzene is formylated rather easily while fluorobenzene yields the corresponding aldehyde with total selectivity for the \textit{para} isomer. Chlorobenzenes show poor reactivity while the formation of chloro-toluene, in a competing reaction, indicates the alkylation potential of methyl formate under the reaction conditions.

### 2.2 Gattermann-Koch Reaction

Gattermann and Koch\textsuperscript{24} were not able to prepare formyl chloride but instead discovered that CO and HCl in the presence of AlCl\textsubscript{3} and cuprous chloride behave like the hypothetical formyl chloride and react with toluene in a manner similar to other acid chlorides (Eq 1.13).

\[ \text{CH}_3\text{C}_6\text{H}_5 + \text{CO} + \text{HCl} \xrightarrow{\text{AlCl}_3/\text{Cu}_2\text{Cl}_2} \text{CH}_3\text{C}_6\text{H}_4\text{CHO} \]  

(1.13)

The Gattermann-Koch reaction was the first direct aldehyde synthesis reported and found many industrial applications for the preparation of aldehydes from simple aromatic hydrocarbons such as benzene, alkylbenzenes, naphthalenes etc. In their paper they reported passing a 2CO:1HCl (volume) mixture through toluene containing aluminum chloride and cuprous chloride.\textsuperscript{25} $p$-Tolualdehyde was obtained in a 50\% yield at 20-25°C. The synthesis failed for benzene but when aluminum bromide was used a 90\% yield of benzaldehyde was obtained.\textsuperscript{22,26} The aluminum chloride-benzaldehyde complex was identified as a suitable catalyst for benzaldehyde synthesis \textsuperscript{27} and has been used by Holloway \textit{et al.}\textsuperscript{28} to reduce the induction period in the high-pressure synthesis of benzaldehyde with aluminum chloride. Hardy\textsuperscript{29} found the optimum temperature to be 35°C for the high-pressure synthesis of benzaldehyde with aluminum chloride. He reported that the aluminum chloride complexes with either benzaldehyde or ethyl ether and function as accelerators. Calculations by Eley and Campbell\textsuperscript{30} have shown that the synthesis of benzaldehyde is only rendered thermodynamically favorable by the formation of the benzaldehyde aluminum chloride complex as a stable end-product. This result explained the failure to find a true contact synthesis of benzaldehyde when working at 1atm pressure.\textsuperscript{31}

The Gattermann-Koch reaction can be carried out under two major types of conditions \textit{i.e.} at atmospheric pressure where Cu\textsubscript{2}Cl\textsubscript{2} is necessary as a promoter or complexing agent and secondly at high-pressure where the presence of Cu\textsubscript{2}Cl\textsubscript{2} is not necessary. The Gattermann-Koch aldehyde synthesis is a suitable method for the preparation of simple aromatic aldehydes such as benzaldehyde and tolualdehyde. Formylation of \textit{ortho} and
Para-directing mono-substituted benzenes yield the para-isomer as main product. Examples of mono-substituted benzenes converted to the para-substituted benzaldehydes include toluene, ethylbenzene, isopropylbenzene, t-butylbenzene, t-amylbenzene, cyclohexylbenzene, 3-methylcyclohexylbenzene, di-phenyl, fluoro-benzene and chlorobenzene.32

In the di-substituted benzene series o- and m-xylene give the expected products. However, p-xylene undergoes isomerisation to furnish 2,4-dimethylbenzaldehyde.28 The tri-substituted benzene series i.e. mesitylene and pseudo-cumene yield normal formylation products.28,33 Tetralin and di-isopropyltetralin in the naphthalene series are reported to undergo Gattermann-Koch formylation whereas naphthalene itself is formylated in the modified reaction using HF and BF3 as catalyst.

Carbonylation of halogenated- and alkyl-substituted benzenes in good yield, involving the use of catalytic amounts of aqueous hydrochloric acid, has recently been reported (Table 1.5).34,35,36

Table 1.5: Formylation of aromatics using AlCl3, CO and catalytic amounts of aqueous HCl (0.01mol/mol AlCl3)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (mmol)</th>
<th>AlCl3 (mmol)</th>
<th>Solvent</th>
<th>CO Press. (psi)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Aldehyde</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>o-Xylene (625)</td>
<td>750</td>
<td>Chlorotoluene</td>
<td>110</td>
<td>5</td>
<td>18</td>
<td>3,4-dimethyl-benzaldehyde</td>
<td>88.7</td>
</tr>
<tr>
<td>2</td>
<td>Tetralin (640)</td>
<td>770</td>
<td>Chlorotoluene</td>
<td>200</td>
<td>-4 to 0</td>
<td>14</td>
<td>Tetralin-aldehyde</td>
<td>89.4</td>
</tr>
<tr>
<td>3</td>
<td>2-fluoro-toluene (4540)</td>
<td>1719.7</td>
<td>4-Me-anisole</td>
<td>550</td>
<td>30</td>
<td>66</td>
<td>4-fluoro-3-me-benzaldehyde</td>
<td>86.7</td>
</tr>
<tr>
<td>4</td>
<td>3-fluoro-toluene (4572)</td>
<td>756.6</td>
<td>None</td>
<td>200</td>
<td>60</td>
<td>17</td>
<td>4-fluoro-2-me-benzaldehyde (88.4%)</td>
<td>76.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2-fluoro-4-me-benzaldehyde (11.6%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2-fluoro-m-xylene (386)</td>
<td>468</td>
<td>1,2-dichlorobenzene</td>
<td>200</td>
<td>50</td>
<td>16</td>
<td>4-fluoro-3,5-dimethylbenzaldehyde (73.8%)</td>
<td>68.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3-fluoro-2,4-dimethyl benzaldehyde (26.2%)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3-fluoro-o-xylene (789)</td>
<td>468</td>
<td>1,2-dichlorobenzene</td>
<td>200</td>
<td>50</td>
<td>28</td>
<td>4-fluoro-2,3-dimethyl-benzaldehyde (89.1%)</td>
<td>79.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2-fluoro-3,4-dimethyl-benzaldehyde (10.9%)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Fluorobenzene (5203)</td>
<td>1654.9</td>
<td>4-Me-anisole</td>
<td>550</td>
<td>30</td>
<td>89</td>
<td>4-fluorobenzaldehyde</td>
<td>64.3</td>
</tr>
</tbody>
</table>

Few examples of the reaction in the heterocyclic series have been reported. Thiophene yields only traces of thiophene aldehyde, probably as a result of substrate decomposition and polymerization during the reaction. Formylation of dibenzo-p-dioxane gives 2-
formyldibenzo-p-dioxane, whereas dialkylaminobenzenes cannot be formylated this way as the resultant dialkylaminobenzaldehydes undergo subsequent condensation reactions. Similarly, deactivated aromatics with meta-directing substituents can generally not be formylated using the Gattermann-Koch reaction.

Gresham et al.\textsuperscript{37} effected an interesting modification to the original Gattermann-Koch reaction and by replacing AlCl\textsubscript{3} and HCl with anhydrous HF and BF\textsubscript{3}. Using a mole ratio of HF:BF\textsubscript{3} equal to 1:1, a CO pressure of 50 bar and a reaction temperature of around 0°C, naphthalene, benzene, toluene, \textit{p}-xylene and diphenyl were formylated to the corresponding aldehydes (Table 1.6).

**Table 1.6: CO formylation of aromatics using HF and BF\textsubscript{3} as catalyst.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Mols of substrate</th>
<th>Mols of HF-BF\textsubscript{3}</th>
<th>Temp. (°C)</th>
<th>Time (min)</th>
<th>Press. (bar)</th>
<th>Product</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>0.75</td>
<td>0.75</td>
<td>-32 to -12</td>
<td>24</td>
<td>14 to 37</td>
<td>\textit{p}-Tolualdehyde</td>
<td>40.6</td>
</tr>
<tr>
<td>2</td>
<td>Benzene</td>
<td>0.5</td>
<td>1</td>
<td>-21 to -7</td>
<td>13</td>
<td>8 to 50</td>
<td>Benzaldehyde</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>\textit{m}-Xylene</td>
<td>0.5</td>
<td>1</td>
<td>-38 to -14</td>
<td>13</td>
<td>8 to 50</td>
<td>2,4-Dimethyl-benzaldehyde</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>\textit{p}-Xylene</td>
<td>0.5</td>
<td>1</td>
<td>-10 to 6</td>
<td>22</td>
<td>8 to 50</td>
<td>2,5-Dimethyl-benzaldehyde</td>
<td>70</td>
</tr>
<tr>
<td>5*</td>
<td>Naphthalene</td>
<td>0.5</td>
<td>1</td>
<td>-30 to 20</td>
<td>10</td>
<td>8 to 50</td>
<td>(\alpha)-Naphthaldehyde</td>
<td>74</td>
</tr>
</tbody>
</table>

* Cyclopentane as solvent

Takezaki et al.\textsuperscript{38,39,40,41} carried out kinetic studies on the formylation of aromatics, including toluene, \textit{m}-xylene, anisole and phenol with CO in a HF/BF\textsubscript{3} medium under pressurized conditions. Kudo et al.\textsuperscript{42} investigated the formylation of naphthalene compounds, including 1- and 2-methyl-naphthalene, 1,2,3,4-tetrahydro-2-methyl-naphthalene and 5,6,7,8-tetrahydro-2-methyl-naphthalene with pressurized CO in a HF-BF\textsubscript{3} medium at ambient temperature (Table 1.7).

**Table 1.7: CO formylation of methyl-naphthalene compounds.\textsuperscript{a}**

<table>
<thead>
<tr>
<th>Run</th>
<th>Substrate</th>
<th>Temp. (°C)</th>
<th>Conv. (%)</th>
<th>Total Yield (%)</th>
<th>Aldehyde isomer distribution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>1\textit{a}</td>
<td>25</td>
<td>93</td>
<td>72</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>1\textit{b}</td>
<td>25</td>
<td>100</td>
<td>70</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>1\textit{c}</td>
<td>25</td>
<td>100</td>
<td>98</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>1\textit{d}</td>
<td>0</td>
<td>100</td>
<td>84</td>
<td>100</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Conditions: Substrate (16mmol), HF(2mol), BF\textsubscript{3}(6atm), CO(50atm), 2h.
In contrast to 1a the reaction of 1b proceeded with high positional selectivity affording the 4-formylated product 6 (96%) together with a small amount of by-product 2-formyl-1-methyl-naphthalene 7 (4%) (Table 6 Run 2). The formylation of 1d under similar conditions produced the 3-formylated compound 10 exclusively in high yield (Table 1.6 Run 4).

Fujiyama et al.\textsuperscript{43,44} invented a continuous process for producing alkylbenzaldehydes through alkylbenzene-HF-BF\textsubscript{3} complexation and formylation with CO in the same reactor.

An improved process for the formylation of phenol and phenol derivatives using the HF/BF\textsubscript{3}/CO system is described by Weisse et al.\textsuperscript{45} in a patent to Hoechst Aktiengesellschaft (Table 1.8).

### Table 1.8: Formylation of hydroxy aromatic compounds using the HF/BF\textsubscript{3}/CO system.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Run</th>
<th>Substrate (mmol)</th>
<th>BF\textsubscript{3} (mmol)</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Press. (bar)</th>
<th>Aldehyde isomer</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phenol (100)</td>
<td>206</td>
<td>40</td>
<td>1</td>
<td>50</td>
<td>p-hydroxybenzaldehyde</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>o-hydroxybenzaldehyde</td>
<td>0.1</td>
</tr>
<tr>
<td>2</td>
<td>o-Cresol (100)</td>
<td>203</td>
<td>40</td>
<td>14</td>
<td>100</td>
<td>4-hydroxy-3-methyl-benzaldehyde</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>o-Cresol (100)</td>
<td>206</td>
<td>40</td>
<td>22</td>
<td>100</td>
<td>4-hydroxy-3-methyl-benzaldehyde</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2-hydroxy-3-methylbenzaldehyde</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>2,6-dimethylphenol (100)</td>
<td>213</td>
<td>22</td>
<td>1</td>
<td>110</td>
<td>4-hydroxy-3,5-dimethylbenzaldehyde</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>3,4-dimethylphenol (100)</td>
<td>208</td>
<td>40</td>
<td>22</td>
<td>110</td>
<td>2-hydroxy-4,5-dimethylbenzaldehyde</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>3,4-dimethylphenol (100)</td>
<td>206</td>
<td>40</td>
<td>22</td>
<td>100</td>
<td>2-hydroxy-4,5-dimethylbenzaldehyde</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5,6-dimethyl-2-hydroxybenzaldehyde</td>
<td>4.5</td>
</tr>
<tr>
<td>7</td>
<td>5,6,7,8-tetrahydro-2-naphtol (33.7)</td>
<td>73</td>
<td>40</td>
<td>18</td>
<td>150</td>
<td>3-hydroxy-5,6,7,8-tetrahydro-2-naphthaldehyde</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>2-ethylphenol (100)</td>
<td>202</td>
<td>40</td>
<td>1</td>
<td>50</td>
<td>4-hydroxy-3-ethylbenzaldehyde</td>
<td>95</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Anhydrous hydrofluoric acid (5mol) except Run 7 used 2.5mol HF.

Other catalysts such as HF-SbF\textsubscript{5},\textsuperscript{46,47,48,49,50,51,52} CF\textsubscript{3}SO\textsubscript{3}H-SbF\textsubscript{5}\textsuperscript{47,48,53,54} and HSO\textsubscript{3}F-SbF\textsubscript{5}\textsuperscript{55,56,57} have also been used in the formylation of alkyl benzenes with carbon...
monoxide. Mono and di-formylation of aromatic compounds were studied by Tanaka et al.\textsuperscript{47,48} in a HF-SbF\textsubscript{5} system in a one-pot reaction (Table 1.9).

### Table 1.9: Formylation of aromatics using the HF/SbF\textsubscript{5}/CO system.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Run</th>
<th>Substrate</th>
<th>SbF\textsubscript{5}:substrate Molar ratio</th>
<th>Time (h)</th>
<th>Yields (%) for Mono-Aldehyde\textsuperscript{b}</th>
<th>Regioselectivity (%) for Di-aldehyde\textsuperscript{c}</th>
<th>Ortho meta para</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>0.5</td>
<td>1</td>
<td>34</td>
<td>2.9</td>
<td>0.3</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>20</td>
<td>1</td>
<td>96</td>
<td>22.2</td>
<td>0.5</td>
</tr>
<tr>
<td>3</td>
<td>Diphenyl</td>
<td>1</td>
<td>2</td>
<td>97 (0:0:100)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Diphenyl</td>
<td>2.5</td>
<td>2</td>
<td>18 (0:0:100)</td>
<td>77 (6:8:86)</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>Diphenylmethane</td>
<td>1</td>
<td>2</td>
<td>15 (2:0:98)</td>
<td>2 (0:0:100)</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>Dibenzyl</td>
<td>1</td>
<td>2</td>
<td>38 (48:2:50)</td>
<td>26 (15:9:76)</td>
<td>32</td>
</tr>
<tr>
<td>7</td>
<td>1,3-Diphenylpropane</td>
<td>1</td>
<td>2</td>
<td>50 (2:2:96)</td>
<td>24 (3:6:91)</td>
<td>4</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Conditions: HF (500mmol), SbF\textsubscript{5} (10mmol), substrate (10mmol), under 20atm CO pressure at 0°C unless otherwise stated. \textsuperscript{b} Isomer ratio of o-m-p-formyldibenzyl. \textsuperscript{c} Isomer ratio of o,o'-o,p'-p,p'-diformyldibenzyl.

Dibenzyl formylation was carried out by Tanaka et al.\textsuperscript{48} Various Lewis acids in HF were used to investigate the influence of acidity on regioselectivity. The order of acidity\textsuperscript{58} are SbF\textsubscript{5}>TaF\textsubscript{5}>BF\textsubscript{3}>NbF\textsubscript{5} and the results displayed in Table 1.10 indicate that both the ortho regioselectivity and aldehyde yield decreased with a decrease in Lewis acidity.

### Table 1.10: Influence of Lewis acidity on formylation regioselectivity.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Run</th>
<th>Lewis acid</th>
<th>Yields (%) for Mono-aldehyde\textsuperscript{b}</th>
<th>Di-aldehyde\textsuperscript{c}</th>
<th>Regioselectivity (%) for ortho meta para</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SbF\textsubscript{5}</td>
<td>38 (48:2:50)</td>
<td>26 (15:9:76)</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>TaF\textsubscript{5}</td>
<td>45 (48:1:51)</td>
<td>26 (12:6:82)</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>BF\textsubscript{3}</td>
<td>34 (41:1:58)</td>
<td>18 (9:6:85)</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>NbF\textsubscript{5}</td>
<td>28 (23:2:75)</td>
<td>7 (6:6:88)</td>
<td>18</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Conditions: HF (500mmol), Lewis acid (10mmol), dibenzyl (10mmol) under 20atm CO pressure at 0°C for 2h. Regioselectivity\% presents the total mono- and dialdehyde regioselectivity. \textsuperscript{b} Isomer ratio of o-m-p-formyldibenzyl. \textsuperscript{c} Isomer ratio of o,o'-o,p'-p,p'-diformyldibenzyl.

In an interesting patent of Exxon Chemicals, formylation of alkyl aromatic compounds using Lewis acids (GaBr\textsubscript{3}, GaCl\textsubscript{3}, TaF\textsubscript{5}, NbF\textsubscript{5} and NbBr\textsubscript{5}) and CO in the absence of added HF is claimed.\textsuperscript{59} Toluene (17% conversion) is formylated to the aldehydes (89% para-, 10% ortho-, 1% meta-toluualdehyde) using a GaCl\textsubscript{3}:toluene molar ratio of 0.16 and a CO pressure of 74bar at room temperature for 7 hours.

Formylation of aromatic compounds such as benzene, toluene, xylene, mesitylene, indan, tetralin, fluoro-, chloro- and bromobenzene in HSO\textsubscript{3}F-SbF\textsubscript{5} under atmospheric CO pressure at 0°C was achieved in high yields (Substrate:HSO\textsubscript{3}F:SbF\textsubscript{5} mol ratio of 20:174:138).\textsuperscript{56} Under reduced molar ratios of SbF\textsubscript{5}:HSO\textsubscript{3}F both formylation and sulfonation take place.
Regioselective formylation of toluene, \textit{m}- and \textit{p}-xylene and mesitylene has been achieved using trifluoromethanesulfonic acid and CO as reagents.\textsuperscript{60,61,54} The formation rate of \textit{p}-tolualdehyde increases with increasing amounts of acid to such an extend that a 99.1\% yield is obtained with a acid:substrate ratio of 20mol/mol at 25°C and 138bar CO pressure for 30 minutes.\textsuperscript{62}

In one of a few examples of aromatic formylation using a solid acid catalyst, toluene was carbonylated to \textit{p}-tolualdehyde in low yield (1.7\%) using a calcined mixture of Zr(OH)$_4$, Cr(NO$_3$)$_3$ and (NH$_4$)SO$_4$ at 50°C.\textsuperscript{63,64}

### 2.3 Chloromethylene Dibenzoate and Dichloro Alkyl Ethers

Wenzel\textsuperscript{65} reported the formation of mesitylaldehyde on the addition of chloromethylene dibenzoate and anhydrous aluminum chloride to a benzene solution of mesitylene followed by a hydrolytic work-up (Eq 1.14). Anisole reacts in a similar manner with chloromethylene dibenzoate to give anisaldehyde (80\% yield) while reaction with benzene produces only diphenylcarbinol benzoate

\begin{equation}
(C_6H_5COO)\text{Cl} \rightarrow (C_6H_5COO)\text{H} \rightarrow RCO\text{C}_6\text{H}_4\text{CHO} + 2C_6\text{H}_5\text{COOH}
\end{equation}

Rieche, Gross and Höft\textsuperscript{66} found that dichloromethyl alkyl ethers interact with aromatics and some heterocyclic compounds in the presence of Friedel-Crafts catalysts to give aldehydes in good yields. The intermediates in these reactions are relatively unstable \(\alpha\)-alkoxybenzyl chlorides that decompose thermally or on the addition of water to yield aldehydes (Eq 1.15).\textsuperscript{67}

\begin{equation}
\text{Friedel-Crafts catalyst} \rightarrow \text{CHO} \rightarrow \text{CHO} \rightarrow \text{ROH} + \text{HCl}
\end{equation}

The dichloromethyl alkyl ether is generally added to a solution or suspension of the aromatic substrate and the catalyst (TiCl$_4$, SnCl$_4$, SnBr$_4$, FeCl$_3$ or AlCl$_3$) in methylene chloride, \textit{n}-hexane or carbon disulfide.\textsuperscript{68,69} Gross, Rieche and Matthey\textsuperscript{70} prepared phenolic aldehydes in good yields using this method.
Gross and Mirsch\textsuperscript{71} found that reaction of aromatics with dichloromethyl methyl sulfide and aluminum chloride yield aromatic aldehydes. However, the yields were lower compared to using dichloromethyl ethers as formylating agent. Cumene aldehyde was obtained in a 41%, mesityl aldehyde in 49% and 2-naphthyl aldehyde in 52% yield (Eq 1.16).

\[
\text{ArH} + \text{CH}_3\text{SCH}_2\text{Cl} \xrightarrow{\text{HCl} / \text{AlCl}_3} \text{ArSCH}_3 \xrightarrow{\text{H}_2\text{O}} \text{ArCHO}
\] (1.16)

2.4 Gattermann Synthesis\textsuperscript{72}

As the Gattermann-Koch reaction fails to produce aldehydes from phenol and phenolic ethers, Gattermann and co-workers\textsuperscript{73,74} developed an alternative method that produces aldehydes from phenols, phenol ethers and heterocyclic compounds successfully.\textsuperscript{75} The method involves the addition of HCN and HCl to the aromatic substrate, with or without the presence of an acidic halide catalyst (Eq 1.17)

\[
\text{HO}OH + \text{HCN} + \text{HCl} \xrightarrow{\text{AlCl}_3, \text{ZnCl}_2} \text{HO}OH\text{CHO}
\] (1.17)

Benzene can be used as solvent as it is un-reactive under the reaction conditions.

Gattermann’s reaction was successfully applied by Hinkel \textit{et al.}\textsuperscript{76,77,78} to include the formylation of benzene, toluene, acenaphthene, anthracene, diphenyl, naphthalene and hydridene.

Limitations of the reaction include de-halogenation and halogen exchange in substituted pyrroles,\textsuperscript{79} while condensation products are obtained from the formylation of aniline, dimethylaniline and diphenylamine.\textsuperscript{80}

Adams\textsuperscript{81,82} introduced the relatively safer Zn(CN)\textsubscript{2} to replace anhydrous hydrogen cyanide as catalyst in 1923. By passing HCl through a mixture of aromatic substrate and Zn(CN)\textsubscript{2} the required HCN was produced \textit{in situ} with ZnCl\textsubscript{2} as catalyst. Zinc cyanide is prepared conveniently by mixing an aqueous solution of sodium cyanide and an alcoholic solution of zinc chloride. Niedzielsky \textit{et al.}\textsuperscript{83} replaced HCN with the inexpensive and
easy to handle NaCN and KCN in most cases where the corresponding HCN + HCl + AlCl₃ system is effective.

Karrer⁸⁴ introduced cyanogen bromide in place of HCN in the Gattermann reaction in 1919 and prepared resorcinol- and phloroglucinaldehyde in unspecified yields. The excess aromatic substrate acts as a bromine acceptor in the reaction (Eq 1.18).⁸⁵

\[
\text{CNBr} + \text{HCl} \xrightarrow{\text{ZnCl}_2} \text{Br}^\oplus \left[ \begin{array}{c}
\text{C} = \text{NH} \cdot \text{ZnCl}_2
\end{array} \right]^\ominus
\]

\[
\text{Br}^\oplus \left[ \begin{array}{c}
\text{C} = \text{NH} \cdot \text{ZnCl}_2
\end{array} \right]^\ominus + \text{HO} \overset{\text{OH}}{\overset{\text{OH}}{\overset{\text{OH}}{\text{HO}}}} \rightarrow \text{HO} \overset{\text{OH}}{\overset{\text{OH}}{\overset{\text{OH}}{\text{HO}}}} + \text{H}^\oplus \left[ \begin{array}{c}
\text{C} = \text{NH} \cdot \text{ZnCl}_2
\end{array} \right]^\ominus
\]

(1.18)

The intermediate complex (1) reacts with another aromatic molecule to give the aldehyde upon hydrolysis. Apart from the higher boiling point of BrCN compared to HCN allowing easier handling, the advantage of this method over the conventional Gattermann or Adams technique has not been proved conclusively.

Rahm et al.⁸⁶ describes the formylation of anisole (50% isolated yield) and alkylated benzenes in fair yield using acetone cyanohydrin (Eq 1.19). Similar to the Gattermann reaction no formylation is obtained with pyrrole and only traces of aldehydes were observed with phenol and furane as substrates.

\[
\begin{array}{c}
\text{OCH}_3
\end{array} \xrightarrow{(\text{CH}_3)\text{C(OH)CN}} \begin{array}{c}
\text{OCH}_3
\end{array} + \begin{array}{c}
\text{OCH}_3
\end{array} \xrightarrow{(\text{CH}_3)\text{C(OH)CN}} \begin{array}{c}
\text{CHO}
\end{array} \xrightarrow{(\text{CH}_3)\text{C(OH)CN}} \begin{array}{c}
\text{CHO}
\end{array}
\]

(1.19)

2.5 Formyl Chloride Oxime and Ethoxalyl Chloride

Scholl and co-workers⁸⁷ reported that mercury cyanate (fulminate) and HCl reacts with benzene in the presence of AlCl₃ to give benzaldoxime and benzonitrile, whereas the aldoxime of resorcinol and by-product dioxybenzonitrile is produced from the same reagents but in the absence of AlCl₃ (Eq 1.20).

Scholl discovered that if sublimed aluminum chloride is used as catalyst substituted benzonitriles are the main product, but by using a mixture of sublimed aluminum
chloride, crystallized aluminum chloride hexahydrate and dried aluminum hydroxide yields of 65-70% oxime is obtained.

\[
\text{Hg(ONC)}_2 + 4\text{HCl} \rightarrow 2\text{ClCH} = \text{NOH} + \text{HgCl}_2
\]

\[
2\text{C}_6\text{H}_6 + \text{Hg(OCN)}_2 + 4\text{HCl} \xrightarrow{\text{AlCl}_3} 2\text{C}_6\text{H}_6\text{CH} = \text{NOH} \xrightarrow{\text{H}_2\text{O}} 2\text{C}_6\text{H}_6\text{CHO}
\] (1.20)

According to Böeseken, Nef’s oxime is formed as an intermediate in the condensation between mercury fulminate and benzene. The oxime is easily dehydrated by AlCl₃ to produce cyanogen chloride, which would then react with benzene to form benzonitrile, the by-product in Scholl’s reaction (Eq 1.21).

\[
\text{ClCH} = \text{NOH} + \text{AlCl}_3 \xrightarrow{\text{H}_2\text{O}} \text{ClCN}
\]

(1.21)

Should the catalyst not be active enough or present in sufficient amounts to effect dehydration of the primarily formed oxime the reaction would proceed to yield the aldoximes obtained by Scholl (Eq 1.22).

\[
\text{C}_6\text{H}_6 + \text{ClCH} = \text{NOH} \xrightarrow{\text{AlCl}_3} \text{C}_6\text{H}_6\text{CH} = \text{NOH}
\] (1.22)

Olah supports this theory but points out that the formation of benzonitrile could also be possible via benzaldoxime dehydration by AlCl₃ (Eq 1.23).

\[
\text{C}_6\text{H}_6\text{CH} = \text{NOH} \xrightarrow{\text{AlCl}_3} \text{C}_6\text{H}_6\text{CN} + \text{H}_2\text{O}
\] (1.23)

Bouveault found that ethoxalyl chloride condenses with benzene and alkylbenzenes in the presence of anhydrous aluminum chloride to give esters of phenylglyoxalic acids in yields generally in excess of 70%. These could be hydrolyzed and de-carboxylated to the corresponding aldehydes (Eq 1.24).

\[
\text{C}_6\text{H}_6 + \text{ClCOCOOC}_2\text{H}_5 \xrightarrow{\text{AlCl}_3} \text{C}_6\text{H}_6\text{COCOOC}_2\text{H}_5 \xrightarrow{\text{H}_2\text{O}} \text{C}_6\text{H}_6\text{CHO}
\] (1.24)
2.6 Vilsmeier-Haack reaction

The Vilsmeier-Haack synthesis involves the preparation of aldehydes from formamides, \((N\text{-methylformanilide, dimethylformamide, etc.})\) as formylating agents in the presence of phosphorus oxytrichloride \((\text{POCl}_3)\). It is a special application of the acylation reaction that uses carboxylic acid amides and \text{POCl}_3 for the preparation of ketones.\(^9\) The first acylation of aromatic compounds using carboxylic acid amides and \text{POCl}_3 was carried out in 1887 in a reaction of benzanilide with \(N,N\)-dialkylanilines to give the corresponding ketones (Eq 1.25).\(^9\)

\[
\text{C} = \text{O} \quad \text{N} \quad \text{H} 
\begin{array}{c}
+ \\
\text{N} \quad \text{RR} \quad \text{POCl}_3 \\
\text{C} \quad \text{O} \\
\end{array} 
\text{R} \quad \text{R} 
\quad \text{H}_2 \text{N} 
\quad \text{CHO} 
(1.25)
\]

Dimroth and Zoepritz\(^9\) attempted to extend the acylation reaction to aldehyde preparation using formanilide to replace other acid amides in 1902. However, the formylation reaction failed for \(N,N\)-dialkylanilines, but good yields were obtained in the case of poly-hydroxy aromatics (Eq 1.26).

\[
\text{CHO} 
\begin{array}{c}
\quad + \\
\text{OH} \quad \text{OH} \\
\text{OH} \\
\text{OH} \\
\end{array} 
\quad \text{H}_2 \text{N} 
\quad \text{CHO} 
\quad \text{N} \quad \text{R} \quad \text{R} 
\quad \text{POCl}_3 
\quad \text{N} \quad \text{H} 
\quad \text{CH} = \text{N} 
\quad \text{N} \quad \text{R} 
(1.26)
\]

Vilsmeier and Haack\(^9\) found that \(N\text{-methylformanilide}\) reacts with alkylanilines in the presence of \text{POCl}_3 to give the corresponding alkyl-aminobenzaldehydes (Eq 1.27).

\[
\begin{array}{c}
\text{CHO} \\
\text{N} \quad \text{CH}_3 \\
\end{array} 
\quad \text{R} \quad \text{NH} 
\quad \text{POCl}_3 
\quad \text{CH}_3 \quad \text{NH} 
\quad \text{R} \quad \text{NH} 
\quad \text{CHO} 
(1.27)
\]

The Vilsmeier and related reactions are amongst the most widely used reactions in organic chemistry. Although the first application of the reaction was for the preparation
of poly-oxybenzaldehydes, it was not only extended later to \(N\)-alkyl- and \(N\),\(N\)-dialkylaminobenzaldehydes, but also to aldehydes of alkyl- and di-alkylanilines, phenols, naphthols, phenol ethers, naphthol ethers, anthracene, alkylanthracenes, benzanthracene, acenaphthene, azulene and derivatives, pyrene, pyrrole and derivatives, thiophene and derivatives, indole and derivatives and many other compounds.

New formamide derivatives have also been introduced into the reaction and as such dimethylformamide became one of the most frequently used formylating agents of this type. Lambooy\(^94\) found similar activity of dimethylformamide and methylformanilide in the Vilsmeier reaction (POCl\(_3\) catalyst).

In some special cases the usual method involving the use of POCl\(_3\) has to be modified, as halogen exchange takes place in some instances, for example 2-bromothiophene is converted into 5-chloro-thiophene-aldehyde under the standard reaction conditions (Eq 1.28).\(^95\)

\[
\text{S Br} \quad \text{S CHOCl} \quad \text{POCl}_3 \quad \text{NC}_6\text{H}_5 \quad \text{CHO} \quad \text{CH}_3 \quad \text{++} \quad \text{CH}_3\text{NH} \quad \text{C}_6\text{H}_5
\]

King and Nord\(^96\) found that bromothiophene aldehyde can be obtained in good yield if POCl\(_3\) is replaced by POBr\(_3\).

Generally, the Vilsmeier reaction fails for benzene, alkylbenzenes and naphthalene.\(^97\) The reaction gives low yields in the case of phenol ethers if the \textit{para}-position is already occupied and fails for highly substituted benzofurans,\(^98\) indicating that the presence of a sufficiently reactive (labile) hydrogen atom on the aromatic ring is necessary for successful application. However, Martinez \textit{et al}.\(^99\) reported the formylation of 1,3,5-trimethylbenzene, naphthalene, acenaphthene, anthracene and phenanthrene in fair yield using the trifluoromethanesulphonic anhydride/dimethylformamide complex (Eq 1.29).

\[
\text{(CF}_3\text{SO}_2\text{)}_2\text{O} \quad \text{+} \quad \text{(CH}_3\text{)}_2\text{NCHO} \quad \text{CF}_3\text{SO}_2\text{O} \quad \text{CF}_3\text{SO}_2\text{O} \quad \text{CH}_3 \quad \text{CH}_3
\]

It was established that other reactive halides such as thionyl chloride (SOCl\(_2\)) and phosgene (COCl\(_2\)) also react with formamide derivatives and it has been shown that the
active formylating species (chloroiminium salts) is similar in each case.\textsuperscript{100} The chloroiminium salts react with electron rich aromatics (e.g. hydroxy- and alkoxybenzenes) to afford both ortho and para aldehydes on hydrolysis (Eq 1.30).\textsuperscript{101}

\[
\text{OH} \quad \text{OH} \quad \text{OH} \quad \text{OH}
\begin{align*}
\text{Me}_2\text{NCHCl} & \quad \text{Me}_2\text{NCHO + SOCl}_2 \\
\text{Me}_2\text{NCHO} & \quad \text{Me}_2\text{NCHO} + \text{SOCl}_2
\end{align*}
\]

\[
\text{(1.30)}
\]

2.7 Formylation of Organometallic Compounds

Aryl- and heteroaryl halides can be converted to organolithium reagents which on reaction with iron pentacarbonyl to give adducts [ArCOFe(CO)\textsubscript{4}]\textsuperscript{+}. These generate aldehydes in moderate yields on acidification of the reaction mixture (Eq 1.31).\textsuperscript{102}

\[
\text{ArX Li} \quad \text{Fe(CO)}_5 \quad \text{Li [ArCOFe(CO)_4]} \quad \text{H} \quad \text{ArCHO}
\]

\[
\text{(1.31)}
\]

In the presence of palladium-phosphine complexes such as Pd(PPh\textsubscript{3})\textsubscript{2}X\textsubscript{2} (X=Cl, Br or I), aryl, heteroaryl and vinylic halides are catalytically converted to aldehydes on treatment with synthesis gas (CO/H\textsubscript{2}). Although a stoichiometric amount of tertiary amine is necessary to remove the hydrogen halide formed in the reaction, the yields are generally good, given the somewhat forced conditions (50-100bar at 100-150°C) (Eq 1.32).\textsuperscript{103}

\[
\text{ArX} + \text{R}_3\text{N} + \text{CO} + \text{H}_2 \quad \text{R}_3\text{NHX} + \text{ArCHO}
\]

\[
\text{(1.32)}
\]

Interestingly the formylation of o-dibromobenzene yields only benzaldehyde due to reductive removal of the second bromine group. The reactivity of the iodides and bromides are comparable.

With iodo compounds yields are particularly high as they carbonylate more rapidly compared to the chloride and bromide derivatives. This can be ascribed to the greater ease of oxidative addition of the C–I bond to the zero-valent palladium complex. Activation to oxidative addition of the C–Cl bond in chloroarene may be achieved by the formation of the corresponding arenetricarbonyl derivative, after which palladium-catalyzed formylation of the complex proceeds in fair yield at 30 bar CO/H\textsubscript{2} pressure at 130°C (Eq 1.33).\textsuperscript{104}
The results obtained for various chloroarenes show that coordination of the tricarbonylchromium group to the chloroarenes enables their carbonylation even in the presence of moderately electron donating groups. The reaction fails in the absence of the tricarbonylchromium group.

Another communication\textsuperscript{105} indicates that palladium catalysis can allow low-pressure carbonylation of free chloroarenes to the aldehydes in the presence of the bulky chelating ligand 1,3-\textit{bis}(di-isopropylphosphino)propane (dippp). Very high yields of aromatic aldehydes can be obtained from the corresponding chloroarenes under relatively mild conditions (6 bar, 150°C) by using formate ion as the hydrogen source and Pd(dippp)\textsubscript{2} as catalyst (Eq (1.34)). The Pd(0) complex can be conveniently generated \textit{in situ} under reducing reaction conditions by the use of Pd(OAc)\textsubscript{2} and dippp.

\begin{equation}
\text{ArCl} + \text{CO} + \text{HCO}_2\text{Na} \xrightarrow{\text{Pd(dippp)}_2, 6 \text{ bar, 150°C}} \text{ArCHO} + \text{CO}_2 + \text{NaCl} \quad (1.34)
\end{equation}

Results of the aryl chloride formylation experiments show that the formylation reaction is specific to the dippp ligand. It is interesting to note that complexes of smaller or larger chelate sizes catalyze de-halogenation rather than formylation and that \textit{ortho} substituents significantly reduce the reaction rate.

Poly(methylhydrosiloxane) (PMHS) as hydrogen donor in the presence of Pd(PPh\textsubscript{3})\textsubscript{4} have been successfully employed to formylate aryl and benzyl halides at low carbon monoxide pressure (Eq 1.35).\textsuperscript{106}

\begin{equation}
\text{ArI} + \text{CO} + \text{PMHS} \xrightarrow{\text{Pd(PPh}_3\text{)}_4} \text{ArCHO} \quad (1.35)
\end{equation}

A similar type of reaction uses tributyltin hydride as hydrogen donor in the formylation of a wide variety of substrates including aryl and vinyl iodides, benzylic halides, vinyl triflates and allylic halides under mild reaction conditions (1-3 bar CO pressure at 50°C for 2.5-3.5 hours) (Eq 1.36).\textsuperscript{107,108}

\begin{equation}
\text{RI} + \text{CO} + \text{Bu}_3\text{SnH} \xrightarrow{\text{Pd(PPh}_3\text{)}_4} \text{RCHO} \quad (1.36)
\end{equation}
Arenediazonium tetrafluoroborates (ArN$_2$BF$_4$ where Ar=X-C$_6$H$_4$; X=H, 2-Me, 3-Me, 4-Me, 4-MeO, 4-MeCO, 2-Ph, 2-Cl, 3-Cl, 4-Cl, 4-Br, 4-I, 3-NO$_2$ and 4-NO$_2$), like iodoarenes are converted into aldehydes in good yield by palladium-catalyzed carbyonation in the presence of poly-methylhydrosiloxane (PMHS) at room temperature. The rather slow reaction rate is remarkably enhanced by replacing the polymeric silane with Et$_3$SiH (Eq 1.37).

\[
\text{ArN}_2\text{BF}_4 + \text{CO} + \text{Et}_3\text{SiH} \xrightarrow{\text{Pd(OAc)$_2$}} \text{ArCHO} \tag{1.37}
\]

The formylation of various ArN$_2$BF$_4$ compounds were carried out with Et$_3$SiH or PMHS as reducing agents. Good yields of ArCHO were obtained for all the substituted benzenes, except the 2-NO$_2$. Reactions with PMHS were slow at room temperature and required 4 to 12 hours for completion.

Halo-naphthalenes, and more particularly 1,6-dibromo-2-methoxynaphthalene (10mmol) are converted into 2-formyl-6-methoxynaphthalene in good yield (80%) with Ph$_3$P (0.5mmol), Pd(OAc)$_2$ (0.1mmol) and Et$_3$N (22mmol) in toluene with a 1:1 CO/H$_2$ molar ratio at 150°C and 40bar pressure.

A recent Japanese patent reported the formylation of 3,5-bis(trifluoromethyl)iodo-benzene in DMF with CO:H$_2$ (1:1) at 1.5MPa in the presence of palladium acetate, tri-o-tolylphosphine and triethylamine to furnish 3,5-bis(trifluoromethyl)benzaldehyde in 42% isolated yield.

### 2.8 Selective ortho formylation of phenols

Gassman and Amick introduced two methods, both similar to 2,4-rearrangement to effect ortho formylation of phenols. Although products were obtained in only moderate (20-45%) yields, the reactions are attractive in effecting exclusive ortho substitution (Eq 1.38).

#### Table 1.11: Formylation of phenolic substrates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate with X</th>
<th>% yield of 5$^b$</th>
<th>%yield of 6 from 5</th>
<th>Overall %yield of 6 from 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl</td>
<td>42</td>
<td>79</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>30</td>
<td>67</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>CH$_3$</td>
<td>46</td>
<td>76</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>OCH$_3$</td>
<td>39</td>
<td>78</td>
<td>30</td>
</tr>
</tbody>
</table>

$^a$ 1.7eq of substrate was reacted with 1eq of reagent (7) for 15 min at -70°C followed by the addition of Et$_3$N. This was followed by a water wash, organic phase separation and drying. $^b$ %yield of 5 was based on un-recovered phenol. The % conversion ranged from 64-74%.
Another ortho formylation method that is useful since it is also applicable to phenols containing bulky substituents, involves three stages and furnish products in yields as high as 65%, even with di-tert-butyl-phenols (Eq 1.40).\(^{114}\)

Reaction of phenoxy-magnesium halides with orthoformates is an older method for regioselective ortho formylation and gives moderate yields (30-55%) with simple alkyl phenols, however yields are very low when bulky groups, halo, nitro or carboxy substituents are present (Eq 1.40).\(^{115}\) Contrary to this the formylation of free phenol with aluminum chloride-triethylorthoformate yields the para-isomer (Eq 1.40).\(^{116}\)
2.9 Duff Reaction

The Duff reaction\textsuperscript{117,118} is a formylation method normally used for electron-rich aromatics such as phenols and aromatic amines with the formylating agent being hexamethylenetetramine in the presence of glycerol or acetic acid. Conditions are rigorous and the yields are generally low, but the main value is the occurrence of mainly ortho substitution.\textsuperscript{119}

Kreutzberger \textit{et al.}\textsuperscript{120,121} used the HCl/AlCl\textsubscript{3} system to produce aldehydes in good yield from alkylbenzenes, phenols and phenol ethers (Eq 1.41).

\[
\begin{align*}
\text{OCH}_3 & \quad \text{HCl/AlCl}_3 \\
\text{OCH}_3 & \quad \text{H}_2\text{O} \\
\text{CHO} & \quad \text{NH}_4\text{Cl}
\end{align*}
\]

(1.41)

Using this method for substituting aluminum trichloride with hydrofluoric acid, trifluoromethoxy benzene (C\textsubscript{6}H\textsubscript{5}OCF\textsubscript{3}) is formylated in excellent yield and \textit{para}-selectivity at 80°C for 5 hours.\textsuperscript{122}

A modern adaptation uses trifluoroacetic acid as catalyst. That allows for formylation of aromatics such as toluene and xylene and even electron deficient phenols such as 2,4-difluorophenol under mild conditions in good yields.\textsuperscript{123} A high order of \textit{para} regioselectivity is exhibited even for phenols.\textsuperscript{124} The mechanism involves fast aminomethylation followed by a rate-determining dehydrogenation step to the imine similar to that observed in the Sommelet reaction; hydrolysis then gives the aldehyde (Eq 1.42).\textsuperscript{125}

\[
\begin{align*}
\text{OH} & \quad \text{CF}_3\text{COOH} \\
\text{OH} & \quad \text{H}_2\text{O} \\
\text{OH} & \quad \text{CHO}
\end{align*}
\]

(1.42)
2.10 Glyoxylic Acid

Condensation of phenols with glyoxylic acid in basic media to furnish substituted mandelic acids, which yield the corresponding aldehyde on homogeneous catalytic oxidative de-carbonylation. Information regarding the process is mostly confined to patent literature (Eq 1.43). The conversion of phenol to \( p \)-hydroxybenzaldehyde was achieved in an overall yield of 66%.

\[
\begin{align*}
\text{C}_6\text{H}_5\text{OH} + \text{CHO} + \text{H}_2\text{O} + \text{NaOH} & \xrightarrow{\text{O}_2, \text{catalyst}} \text{C}_6\text{H}_4\text{OH} + \text{CHO} + \text{Na}_2\text{CO}_3 \\
\text{R} & = \text{H, OMe, OEt}
\end{align*}
\]

A negative aspect of this reaction is the formation of unwanted di-mandelic acid side-products due to the higher reactivity of the 2- and 4-hydroxymandelic acid compared to phenol. Formation of these side-products is minimized by the addition of excess phenol, generally two or more equivalents.

2.11 Saligenin Reaction

A widely used industrial process for the production of salicylaldehyde is the Saligenin process that produces hydroxybenzyl alcohols (o- and \( p \)-isomers) from the base-catalyzed reaction of formaldehyde with phenol, followed by oxidation using a palladium or platinum catalyst to produce the hydroxybenzaldehyde (Eq 1.44).

\[
\text{OH} + \text{HCHO} + \text{KOH} \xrightarrow{\text{Oxidation, Pt or Pd}} \text{OH} + \text{CHO} \]

In a refinement of the process the reaction of phenyl metaborate with formaldehyde followed by catalytic oxidation under atmospheric pressure has been reported to give salicylaldehyde directly from phenol without isolation of any intermediary products with aldehyde yields as high as 93% (Eq 1.45).
Casiraghi et al.\textsuperscript{133} reported that the reaction of paraformaldehyde and magnesium phenoxides, produced from phenol and ethylmagnesium bromide in benzene as solvent in the presence of stoichiometric amounts of hexamethyolphosphoric triamide (HMPTA) resulted in formylation exclusively at the ortho position. In an improved method by Skattebøll et al.\textsuperscript{134}, phenolic derivatives are formylated selectively ortho to the hydroxy group by paraformaldehyde with magnesium dichloride-triethylamine as base in the absence of HMPTA, which is being regarded as a potent carcinogen.

Sartori et al.\textsuperscript{135} recently synthesised substituted salicylic aldehydes in good yields and excellent selectivities from alkyl substituted phenols with formaldehyde and montmorillonite KSF-Et\textsubscript{3}N as heterogeneous catalyst (Eq 1.46 and Table 1.12). Unfortunately recycling of the montmorillonite was problematic, as only one additional cycle yielding 36% of product was possible.

\begin{equation}
\text{OH} \begin{array}{c}
\text{R} \\
\text{R'}
\end{array} + 4\text{CH}_2\text{O} \xrightarrow{\text{KSF-Et}_3\text{N}} \begin{array}{c}
\text{OH} \\
\text{R} \\
\text{R'}
\end{array}
\text{Toluene, 100°C, 4h}
\end{equation}

\textbf{Table 1.12: Synthesis of various salicylic aldehydes.}

<table>
<thead>
<tr>
<th>Run</th>
<th>R</th>
<th>R'</th>
<th>Yield (%)</th>
<th>Conversion (%)</th>
<th>Selectivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(CH\textsubscript{3})\textsubscript{3}C</td>
<td>CH\textsubscript{3}</td>
<td>67</td>
<td>74</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>(CH\textsubscript{3})\textsubscript{3}C</td>
<td>(CH\textsubscript{3})\textsubscript{3}C</td>
<td>70</td>
<td>79</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>CH\textsubscript{3}</td>
<td>H</td>
<td>60</td>
<td>65</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>(CH\textsubscript{3})\textsubscript{3}C</td>
<td>H</td>
<td>63</td>
<td>70</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>CH\textsubscript{3}</td>
<td>C\textsubscript{10}H\textsubscript{21}</td>
<td>65</td>
<td>71</td>
<td>91</td>
</tr>
</tbody>
</table>

\textbf{2.12 Reimer Tiemann Reaction}

Formylation of phenol with chloroform in a basic medium was first proposed in 1876 by Reimer and Tiemann.\textsuperscript{136} Treatment of phenol with aqueous chloroform and aqueous
sodium hydroxide results in the formation of benzal chlorides that are rapidly hydrolyzed by the alkaline medium to produce the ortho aldehyde predominantly (Eq 1.47).\textsuperscript{137,138,139,140}

\begin{align*}
\text{C}_{6}\text{H}_{5} & \xrightarrow{\text{CCl}_2} \text{C}_{6}\text{H}_{4}\text{C}(-\text{Cl})\text{CHO} + \text{C}_{6}\text{H}_{4}\text{C}(-\text{Cl})\text{OH} \\
\end{align*}

\text{(1.47)}

Several attempts were made to shift the regioselectivity towards the para-product. Phenols irradiated in chloroform are converted in the corresponding 2- and 4-substituted benzaldehydes by a mechanism involving attack by the dichloromethyl radical to produce the para and ortho-aldehyde in 46% and 19% yield respectively.\textsuperscript{141,142}

Increased para selectivity has been reported by using potassium, cesium and ammonium hydroxide as bases instead of sodium hydroxide.\textsuperscript{143} The addition of B-cyclodextrin (BCD) afforded 100% para selectivity due to formation of a preferentially para ternary molecular complex between the phenolate ion, BCD and the dichlorocarbene intermediate.\textsuperscript{144,145,146,147} Although the presence of BCD does not enhance the total aldehyde production, it reduces the proportion of other isomeric aldehydes formed in favour of the para-product. Recently Zhang et. al.\textsuperscript{148} reported the synthesis of \textit{p}-hydroxybenzaldehyde from phenol and chloroform in NaOH solution using BCD as catalyst in excellent yield and selectivity (98.6% and 100% respectively).

A modified Reimer-Tiemann reaction was performed using tertiary amines to give the para-aldehyde as main product. A total phenol conversion of 74% together with 66% and 7% para- and ortho-aldehyde yield respectively, were obtained.\textsuperscript{149} Similarly, reaction of phenol and CHCl\textsubscript{3} in an aqueous alkali solution in the presence of polyethylene glycol (PEG) gave after acid hydrolysis the para- and ortho-aldehyde in 75% and 16% yield respectively.\textsuperscript{150}
2.13 Alternative Reactions

Periasamy et al. obtained aldehydes in good yield from poly-cyclic aromatic hydrocarbon radical anions prepared by the addition of sodium to the aromatic hydrocarbon in THF, followed by formylation with carboxylic acid esters or \(N,N\)-dialkyformamides. Reactions of sodium naphthalenide, \(-\)anthracenide and \(-\)phenanthrenide with ethyl formate yielded the corresponding aldehydes. Substituted naphthalenes e.g. acenaphthene and 2-methylnaphthalene are also formylated using \(N,N\)-dialkylformamides, but in low yields (20% and 26% respectively).

Kantlehner et al. reported the formylation of (hetero)aromatic compounds including unsubstituted and alkyl-substituted aromatics, aromatic ethers, tertiary aromatic amines, fused aromatic rings and thiophenes using new formylating agents (Scheme 1.1) based on formamide derivatives in the presence of Lewis acids.

![Scheme 1.1: New formylating agents based on formamide derivatives](image)

Anisaldehyde (96% \(p\)-isomer, 4% \(o\)-isomer) was prepared in good yield (62%) from anisole (187mmol) using \(\text{ZnCl}_2\) (31.6mmol) and tris(dichloromethyl)amine (15.8mmol) under mild conditions (3hours at 60°C). Although excellent selectivities for the \(p\)-aldehyde were achieved, stoichiometric amounts of the formamide derivative and two equivalents of Lewis acid per formyl group transferred are required, resulting in an \(E\)-factor (kg of waste per kg product) ranging from 4 to 11.

Methoxy- and methyl substituted naphthalenes are rapidly formylated in moderate yield in the presence of malonic acid and manganese(III) acetate at 70°C. Using the same oxidation conditions, anisole, 1,3-dimethoxybenzene and 1,2,3-trimethoxybenzene were inactive and afforded only small amounts of benzaldehydes and benzoic acids.

The reaction of trichloro-acetaldehyde (chloral) with phenols under base catalysis leads to \(p\)-hydroxyaryltrichloroethanols together with some \(o\)-isomer. The corresponding aromatic hydroxy aldehydes are produced after reaction with aqueous alkali or boiling in water (Eq 1.48).
OH + CCl₃CHO → K₂CO₃ → 50% NaOH/H₂O →

HO-—COCHO

H₂O 100°C

HO—CHCCl₃

HO—CHO

+ OH

CHO

(1.48)
2.14 REFERENCES


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CHAPTER 2
CO as reagent in the formylation of aromatic compounds

1. INTRODUCTION

Sasol, through its various divisions endeavours to expand its current business in a number of ways. One such strategy concentrates on the beneficiation of current commodity feedstreams having marginal value into high-value chemicals via cost-effective processes.

Hydroxy- and alkoxy aldehydes are important products that are primarily used in the flavour and fragrance market and as intermediates in the manufacturing of agrochemicals, pharmaceuticals, cosmetics and the electroplating industry.\textsuperscript{155} Para-anisaldehyde or PAA (1), ortho- and para-hydroxybenzaldehyde, vanillin (2), ethyl vanillin (3), protocatechuic aldehyde (4), veratraldehyde (5) and piperonal (6) are the most important products. Merisol, a division of Sasol having excess to phenolic and cresylic feedstreams, expressed interest in the possible production of PAA as a high-value fine chemical. However, as a new aldehyde producer, market penetration could be extremely difficult and a competitive advantage is required over the rest of the producers. This can be realised in a number of ways, one of which includes a reduced product price. However, this will necessitate amongst others, cheaper feedstock and reagent costs as well as an economically feasible process compared to the competitor’s.

PAA is an important precursor in the manufacture of OMC [2-ethylhexyl-p-methoxy- cinnamate (7), a UV adsorber in sunscreens] as well as of various pharmaceuticals, e.g., the coronary therapeutic Diltiazem (8) and chemotherapeutics like trimethoprimg (9).\textsuperscript{156}
PAA is mainly produced in a two-step process involving O-methylation of \( p \)-cresol to \( p \)-methylanisole followed by benzylic oxidation to the corresponding aldehyde using manganese dioxide and sulphuric acid (Scheme 2.1).\(^{157}\) Other industrial processes employ liquid-phase oxidation in the presence of cobalt catalysts\(^{158}\) and electrochemical oxidation in the presence of lower aliphatic alcohols via the corresponding anisaldehyde dialkyl acetal.\(^{159}\) These processes suffer from the drawback of either producing a large amount of salt effluent that needs to be disposed of and/or making use of expensive feedstock as starting material. In a patent by Hoechst Aktiengesellschaft, phenol was claimed to be converted to \( p \)-hydroxybenzaldehyde in high yield (80\%) by formylation using anhydrous hydrofluoric acid, boron trifluoride and carbon monoxide under mild temperature.\(^{160}\) Although this process employs reagents, especially hydrogen fluoride and boron trifluoride in stoichiometric amounts that are considered harmful to human health and the environment, the one-step nature and relatively cheap feedstock utilised in the process appears to be economically beneficial.

![Scheme 2.1: Comparison of the current industrial PAA process from \( p \)-cresol against possible cheaper alternative processes from phenol or anisole.](image)

If this technology could be applied to the production of PAA from anisole, having a selling price of almost half that of \( p \)-cresol, in a catalytic way, this would give Merisol the competitive advantage required to enter into the market (Scheme 2.1).
Furthermore, carbon monoxide is produced in abundance as side-product in Sasol’s Fischer-Tropsch water-gas shift reaction, making it a cheap and subsequently attractive formylating agent. Thus, using CO as reagent in the formylation process will result in further reduced production costs.

2. FORMYLATION UTILIZING HF/BF₃ AS CATALYST

Although many processes using a variety of reagents other than CO exist for formylation of aromatic compounds, hydrogen fluoride and boron trifluoride are the only catalyst system claimed to produce hydroxy aldehydes effectively from phenol derivatives in conjunction with CO as formylating agent. In spite of the fact that HF and BF₃ are regarded as environmentally unfriendly gasses, their catalytic usage could be beneficial with minimal effect on the environment.

2.1 The Carbon Monoxide Molecule

The carbon monoxide molecule can be described in conventional valence bond terms as having two canonical forms; one having the carbene-like structure in which divalent carbon is linked to oxygen by a double bond and the other a dinitrogen-like form, in which both atoms carry a lone pair and are linked by a triple bond [Eq (2.1)].

\[
\begin{align*}
\text{:C} & \equiv \text{O} & \text{Major contribution} \\
\text{:C} & \equiv \hat{\text{O}} & \text{Minor contribution}
\end{align*}
\]

(2.1)

The chemistry of carbon monoxide is, however, more often rationalised on a qualitative molecular orbital (MO) basis rather than in terms of its valence bond description. Figure 2.1 depicts the energy level MO diagram for carbon monoxide with occupied orbital energies determined by photoelectron spectroscopy. An approximate correlation can be made between valence bond and MO descriptions through assignment of the filled orbitals 4σ and 5σ* to lone pairs on oxygen and carbon respectively and orbitals 3σ and 1π to the triple bond.¹⁶¹

Thus, carbon monoxide is a metastable molecule that is almost inert under mild conditions, but becomes very reactive when subjected to high pressure or elevated temperature and can be easily activated by catalysts.
2.2 Properties of hydrogen fluoride

The unique physical properties of hydrogen fluoride allow it to be an excellent solvent for a variety of organic and inorganic solutes. Being a liquid at convenient temperature and pressure (bp 19.5°C at 1atm) allows for greater ease of handling compared to other gasses e.g., hydrogen chloride. It has a lower vapour pressure (363.8 mmHg at 0°C), longer liquid range (102.9 atm°C) and a higher dielectric constant (175 at −73°C and 84 at 0°C) that is characteristic of hydrogen-bonded liquids when compared to the other hydrogen halides.\textsuperscript{162} Although a monomeric structure is formed above 80°C, equilibrium between HF and its hexamer, (HF)\textsubscript{6}, with a puckered ring structure is obtained at lower temperatures. The crystal structure consists of planar zigzag chain polymers with an F–H–F distance of 2.55Å and an H–F–H angle of 120° (Figure 2.2).\textsuperscript{163}

\[ \text{Figure 2.2: Structure of crystalline hydrogen fluoride.} \]

The self-ionisation equilibria or auto-protolysis of liquid HF are demonstrated in Eq (2.2). The high Hammett acidity function\textsuperscript{164} of the anhydrous acid (−H\textsubscript{0}=11)\textsuperscript{165} compared to HCl can be partly attributed to the formation of stable hydrogen-bonded anions e.g., HF\textsubscript{2}−, H\textsubscript{2}F\textsubscript{3}− etc.
2HF $\rightleftharpoons$ H$_2$F$^+$ + F$^-$ $K \approx 10^{-10}$

$\mathrm{F}^- + \mathrm{HF} \rightleftharpoons \mathrm{HF}_2 \rightleftharpoons \mathrm{HF} \rightleftharpoons \mathrm{H}_2\mathrm{F}_3$ etc. \hspace{1cm} (2.2)

The acidity of anhydrous hydrofluoric acid can be adjusted conveniently over a wide range: On addition of alkali metal fluorides the acidity is reduced; while the inverse effect is obtained on addition of BF$_3$. In the latter case acidity is enhanced by removal of fluoride ions [Eq (2.3)]$^{166}$

$$\mathrm{BF}_3 + \mathrm{F}^- \rightarrow \mathrm{BF}_4^-$ \hspace{1cm} (2.3)

Hydrogen fluoride is not only known to be a pollutant harmful to plants having the strongest phytotoxic action of all gases, but also for causing bony fluorosis, a human disease associated with extended periods of exposure. Finally, it is incompatible with glass with which it reacts to form the highly stable SiF$_4$.\footnote{167}

### 2.3 Properties of boron trifluoride

Boron trifluoride (bp $-99^\circ\mathrm{C}$) is one of the most powerful acceptor molecules known and has a strong tendency to combine with atoms having unshared electron pairs to increase its six outer shell electrons to a stable electronic configuration of eight, thus forming a coordinate covalent bond.\footnote{168} It is a gas at room temperature and has trigonal symmetry with X–B–X angles of 120°. Mootz et al.\footnote{169} reported a crystal structure for the metastable phase of BF$_3$ at $-131^\circ\mathrm{C}$ in which the boron atoms are trigonal prismatic with B–X$_{eq}$ bond lengths of 126 - 131Å and B–X$_{ax}$ bond lengths of 268 - 271Å.

The chemistry of trivalent boron halides is dominated by the unfilled boron $p_z$-orbital allowing the ready forming of adducts with a variety of electron donors, thus functioning as Lewis acids. The relative strengths of boron halides as Lewis acids are in the order BBr$_3$ > BCl$_3$ $\geq$ BF$_3$, which is opposite to that expected on either steric grounds or on the basis of electronegativity. This can partially be explained in terms of boron-halogen $\pi$-bonding. Overlap of the un-filled boron $p_z$-orbital with the non-bonding filled orbitals on the halides reduces the electron acceptor ability of the molecule, but increases the strength of the B–X bonds. The boron-halide $p_z$ overlap decreases with increasing size of the halide resulting in the B–F bond in BF$_3$ being one of the strongest single bonds known. Boron trifluoride chemistry is dominated by Lewis acid-base reactions whereas halide displacement reactions predominate in BBr$_3$ and BI$_3$ adducts, which is the cause of this relative instability.\footnote{170,171,172}
The formation of coordination compounds between boron trifluoride and organic oxy-compounds are well known and a rule announced by Landolph states that boron trifluoride combines in a definite mole to mole ratio with aldehydes and ketones.

### 2.4 Properties of the active HF/BF₃ catalyst

Solutions of BF₃ in hydrogen fluoride are commonly known as superacids as their acidity are higher compared to conventional strong acids such as sulphuric acid. Industrial applications of this system include hydro depolymerisation of coal to liquid hydrocarbons, the preparation of carbon fibre and isomerisation of saturated straight chain hydrocarbons to highly branched hydrocarbons which can be added to fuel to increase the octane number. HF/BF₃ is also frequently used in Friedel-Crafts alkylation reactions. The main advantages of the system being the high stability of HF and BF₃ as well as the easy recovery of both gasses due to their gaseous nature at room temperature.

Studies on the interaction between hydrogen fluoride and boron trifluoride have been documented. According to Sharp, reaction to produce HBF₄ is unlikely unless an electron donor is present to solvate the proton. McCaulay et al. investigated the HF/BF₃ system and did not find any sign of interaction in the absence of a base. Vapour pressure measurements involving individual xylene isomers indicated all the isomers react rapidly and reversibly with HF/BF₃ to form a complex in which the mol ratio of boron trifluoride to hydrocarbon is one. They postulated that the reaction of complex formation is the sum of two reaction steps [Eq (2.4)].

\[
\begin{align*}
\text{Ar} + \text{HF} & \rightleftharpoons \text{ArH}^+ \text{ + F}^- \\
\text{F}^- + \text{BF}_3 & \rightleftharpoons \text{BF}_4^- \\
\text{Ar} + \text{HF} + \text{BF}_3 & \rightarrow \text{ArH}^+\text{BF}_4^-
\end{align*}
\]

Hughes et al. investigated the solubility of boron trifluoride (bp –99°C) in hydrogen fluoride over a wide temperature range (Table 2.1). The rapid increase in solubility with decreasing temperature below the critical temperature (between 4.4 and –26°C) suggests possible HF/BF₃ coordination.

**Table 2.1: Solubility of gaseous boron trifluoride in liquid hydrogen fluoride**

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>Partial Pressure BF₃ (psi)</th>
<th>Mole % BF₃ in solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>-81</td>
<td>14.7</td>
<td>8.76</td>
</tr>
<tr>
<td>-74</td>
<td>14.7</td>
<td>7.46</td>
</tr>
</tbody>
</table>
Kilpatrick et al.\textsuperscript{184} postulated the equilibrium reaction (Eq 2.5) from the addition of BF\textsubscript{3} to HF.

\[
\text{BF}_3 + 2\text{HF} \rightleftharpoons \text{BF}_4^- + \text{H}_2\text{F}^+ \tag{2.5}
\]

This follows from the auto-protolysis reaction equilibrium of hydrofluoric acid [(Eq2.6)], which is displaced to the right by boron trifluoride by the reaction (Eq 2.7).

\[
2\text{HF} \rightleftharpoons \text{H}_2\text{F}^+ + \text{F}^- \tag{2.6}
\]

\[
\text{BF}_3 + \text{F}^- \rightleftharpoons \text{BF}_4^- \tag{2.7}
\]

According to Olah et al.,\textsuperscript{185} boron trifluoride ionises in anhydrous HF and the stoichiometric compound exists only in excess HF or in the presence of suitable proton acceptors e.g. NaF [Eq (2.8)].

\[
\text{BF}_3 + 2\text{HF} \rightleftharpoons \text{BF}_4^- + \text{H}_2\text{F}^+ \tag{2.8}
\]

Olah et al.\textsuperscript{186,187} was successful also in isolating the boron trifluoride-hydrogen fluoride complexes of the methylbenzenes: toluene, m-xylene, mesitylene and isoduene and determined their respective melting points and specific conductivities [Eq (2.9)].

\[
\begin{array}{c}
\text{CH}_3 \\
\text{C} \\
\text{H} \\
\text{H} \\
\text{H}
\end{array} + \text{HF} + \text{BF}_3 \rightleftharpoons \begin{array}{c}
\text{CH}_3 \\
\text{C} \\
\text{H} \\
\text{H} \\
\text{H}
\end{array}^+ \text{BF}_4^- \tag{2.9}
\]

Kim et al.\textsuperscript{188} studied BF\textsubscript{3} + (HF)\textsubscript{1-7} clusters using density functional theory calculations to elucidate the superacidity associated with HF/BF\textsubscript{3} systems. They found that BF\textsubscript{3} + (HF)\textsubscript{1-3} are essentially weakly bound Van der Waals complexes due to long intermolecular B-F bond distances. In BF\textsubscript{3} + (HF)\textsubscript{4} and BF\textsubscript{3} + (HF)\textsubscript{5} the B-F bond distance is significantly
shortened so that ring structures are adopted that are stabilised by multiple hydrogen bonding between hydrogen and fluorine. The B-F bond distance is further shortened when two additional HF molecules are bound to BF$_3$ through hydrogen bonding, indicating both increased stability and acidity of the system through the addition of excess HF. Although gas phase interaction between BF$_3$ and HF is weak, the fluorine atom transfer reaction can occur in a BF$_3$/HF solution to produce the solvated BF$_4^-$ ion and an H$_2$F$^+$ ion, provided that a sufficient number of HF ligands are available.

Acidity measurements of a 7mol% BF$_3$ solution in hydrogen fluoride using electrochemical determinations indicated a Hammett acidity ($-H_0$) of 16.6, classifying it as a super acid (Fig 2.3).\textsuperscript{189}

**Figure 2.3: Acidity ranges for the most common superacids.** The solid and open bars have been measured using indicators, while the broken bars are estimated by kinetic measurements.

The highest acidity level measured according to the $H_0$ acidity scale is around -27 for 90% SbF$_5$ in HSO$_3$F. However, based on rate measurements in superacidic reactions the fluoroantimonic acid system is predicted to be even stronger [Fig 2.3]. Similar to BF$_3$ in HF, SbF$_5$ also ionises in dilute solutions to produce the H$_2$F$^+$ cation. The lower Hammett acidity of the HF/BF$_3$ system compared to SbF$_5$ and TaF$_5$, can be attributed to the lower concentration of the H$_2$F$^+$ cation produced in the HF/BF$_3$ system. The HF/BF$_3$
system is however strong enough to protonate many weak bases and is an efficient and widely used catalyst.\textsuperscript{190,191}

Although tetrafluoroboric acid (HBF\textsubscript{4}) is believed to be the superacid responsible for CO formylation, it has never been isolated.\textsuperscript{192} Gay-Lussac \textit{et al}.\textsuperscript{193} prepared it by passing an excess of boron trifluoride into cold water with crystallisation of boric acid upon cooling [Eq (2.10)].

\begin{equation}
4\text{BF}_3 + 3\text{H}_2\text{O} \rightarrow 3\text{HBF}_4 + \text{H}_3\text{BO}_3 \tag{2.10}
\end{equation}

Fischer \textit{et al}.\textsuperscript{194} prepared HBF\textsubscript{4} from boric acid and a 50\% aqueous solution of hydrofluoric acid, while Berzelius\textsuperscript{166} used concentrated hydrofluoric acid. Wamser\textsuperscript{195} has shown that the reaction proceeds in at least two steps, the first being the rapid formation of the hydroxy moiety [Eq (2.11)], followed by the slow formation of HBF\textsubscript{4} [Eq (2.12)].

\begin{equation}
4\text{HF} + \text{H}_3\text{BO}_3 + \text{HBF}_3\text{OH} \rightarrow 3\text{HBF}_4 + \text{HF} + 2\text{H}_2\text{O} \tag{2.11}
\end{equation}

\begin{equation}
\text{HBF}_3\text{OH} + \text{HF} \rightleftharpoons \text{HBF}_4 + \text{H}_2\text{O} \tag{2.12}
\end{equation}

Concentrated aqueous- and diethyl ether solutions of HBF\textsubscript{4} are well known and commercially available. Our attempts to isolate the superacid from these solutions via reduced pressure distillation were not successful and is indicative of the strong complex formation between the acid and the oxygen moiety of ether and water.

\section*{3. SUBSTRATE AND CATALYST EVALUATION}

\subsection*{3.1 Phenol and Anisole}

Although a plethora of reagents does exist for the formylation of aromatic hydrocarbons with CO as reagent, this reaction generally fails with phenolic substrates. However, only a single patent\textsuperscript{196} by Hoechst Aktiengesellschaft and two papers by Takezaki,\textsuperscript{197,198} which utilise HF/ BF\textsubscript{3} as catalyst, describe the formation of phenolic aldehydes by formylation with CO. In order to compare this HF/ BF\textsubscript{3} promoted formylation of phenolics to that of aromatic hydrocarbons, a study was initiated with phenol and anisole as substrates (Table 2.2). A reaction temperature of 45°C was used and is in accordance with that reported in literature.\textsuperscript{199} The progress of the reactions was followed by GC analysis of samples taken at regular intervals.
Table 2.2: CO formylation of various aromatic substrates using anhydrous HF (50eq) and BF₃ (2eq) as catalysts.

<table>
<thead>
<tr>
<th>Run</th>
<th>Substrate</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Products (mass%)</th>
<th>Secondary Products*</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p-Aldehyde</td>
<td>o-Aldehyde</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Toluene</td>
<td>45</td>
<td>1</td>
<td>91</td>
<td>5</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>Phenol</td>
<td>45</td>
<td>1</td>
<td>43</td>
<td>1</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>Phenol</td>
<td>45</td>
<td>4.5</td>
<td>80</td>
<td>6</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>Anisole</td>
<td>45</td>
<td>1</td>
<td>38</td>
<td>6</td>
<td>51</td>
</tr>
<tr>
<td>5</td>
<td>Anisole</td>
<td>45</td>
<td>4.5</td>
<td>50</td>
<td>13</td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>Anisole</td>
<td>45</td>
<td>4.5</td>
<td>13</td>
<td>5</td>
<td>23</td>
</tr>
</tbody>
</table>

* See figure 2.4

With toluene as substrate formylation proceeded in a high yield (99%) with respect to aldehyde formation and with good para-selectivity (90%) in a reaction time of only 1 hour. The reaction was carried out on phenol under the same reaction conditions. Surprisingly, the reactivity of phenol proved to be much lower than that of toluene and a reaction time of more than 4 hours was required to obtain acceptable yields, albeit with reduced para-selectivity. When the reaction was extended to anisole, only small differences compared to phenol were observed within the first hour of the reaction, but at extended reaction times phenol proved to give better conversions. The results indicate that the reaction is sustained for a longer time with phenol than with anisole.

Although unreacted substrate can be separated from the reaction mixture and recycled back to the reactor, this adds to the capital costs since reactor size needs to be increased for a given supply market demand. Thus, maximising product yield is one of the factors imperative to minimisation of production costs.

In an attempt to increase product yields through increased mass transfer, a modified gas-entrainment stirrer was tested, using anisole as substrate. This resulted in decreased yields and conversions (Table 2.2 Run 6), indicating that mass transfer of CO is not a limiting factor in the reaction.

Aldehydes of 4-nonylphenol are used as precursors for foaming agents in the mining chemical industry, thus presenting an opportunity to utilise the HF/BF₃/CO technology. However, the formylation of 4-nonylphenol at 45°C furnished mainly dealkylated
secondary products including phenol together with its formylation product, \( p \)-hydroxy-benzaldehyde.

The main aldehyde isomer produced in the HF/BF\(_3\)/CO formylations of all of the ortho-para directing mono-substituted benzenes tested in our laboratories is in accordance with published results\(^{200,201,202,203}\). We also found that extending the reaction times from 1 hour to 4.5 hours lead towards a decrease in the para-ortho ratio in the case of both phenol and anisole. This may suggest gradual change from a product of kinetic control to a product of thermodynamic control indicative of the reversibility of the formylation process.

The high acidity level in the reaction mixture provides ample opportunity for side reactions to occur. The amounts of side product generated by these acidic conditions were generally on the low side (<10%). However, these amounts increased dramatically with increased reaction times. On increasing the reaction time of anisole from 1 to 4.5 hours the side product amount increased four-fold while the aldehyde product increased by only half during the same period. Although anisole de-alkylation may occur under the reaction conditions, only low amounts of phenol (<1%) were detected.

The MS fragmentation patterns of by-products detected by GC indicated that majority of secondary products (10 - 14) most probably arose from acid catalysed reactions between the substrate and the corresponding formylation products.

\[
\begin{align*}
10 & \quad (0-1\%) \\
11 & \quad (3-7\%) \\
12 & \quad (0.5-6\%) \\
13 & \quad (1-15\%) \\
14 & \quad (0.5-2\%)
\end{align*}
\]

\[R = \text{OH or CH}_3 \text{ or OCH}_3 \quad R' = \text{CH}_3 \quad R'' = \text{OCH}_3\]

**Figure 2.4:** Secondary products obtained during CO formylation reactions of toluene, anisole and phenol using HF/BF\(_3\) as catalyst. (Yield ranges in brackets)
3.2 Evaluation of Other Catalyst/Reaction Systems

In an effort to obtain augmented yields and selectivities in the CO formylation of phenol, anisole and toluene, a few reactions were initiated during which the type and amount of Lewis- and Brønsted acid were varied.

Although literature states that phenolic compounds are not responsive to CO formylation in the presence of AlCl₃ and hydrogen chloride, the possibility of some aldehyde formation using excess aluminum trichloride was investigated.

Attempted phenol formylation with excess aluminum trichloride did not yield any aldehyde products, even at elevated CO pressures and extended reaction times (Table 2.3 Run 1 and 2). Superacid H⁺AlCl₄⁻ may be on the lower end of the acidity scale compared to H⁺BF₄⁻ resulting in reduced protonation ability which may be an essential requirement for the formylation reaction.

Nitrobenzene was used as solvent in an investigation as it is frequently used in Friedel-Crafts reactions and facilitates the solubility of aluminum chloride. However, nitrobenzene may inhibit the formylation reaction as the polar NO₂ group competes with CO in the protonation reaction (CHO⁺), resulting in low or no reactivity. Another possible reason for the apparent unreactivity of phenol under these conditions was proposed by Olah and involves the formation of phenyl formate (O-formylation of phenol). These compounds decarbonylate easily, instead of undergoing acid catalysed Fries rearrangement to the aldehyde [Eq (2.13)].

\[
\begin{array}{c}
\text{C}_6\text{H}_5\text{OH} + \text{CO} \xrightarrow{\text{H}^+} \text{AlCl}_3 \rightarrow \text{C}_6\text{H}_5\text{OOCH} \\
(2.13)
\end{array}
\]

<table>
<thead>
<tr>
<th>Run</th>
<th>Substrate (mmol)</th>
<th>Reactants</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Conv. (%)</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phenol (106)</td>
<td>AlCl₃ (212) CO 50bar</td>
<td>33-55</td>
<td>12</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Phenol (19)</td>
<td>AlCl₃ (64) CO 72bar</td>
<td>28-50</td>
<td>60</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Anisole (93)</td>
<td>AlCl₃ (196) CO 50bar</td>
<td>33</td>
<td>12</td>
<td>&gt;95</td>
<td>Only phenol and tarry material</td>
</tr>
<tr>
<td>4</td>
<td>Anisole (50)</td>
<td>AlCl₃ (100) HF (2500) CO 50bar</td>
<td>5-30</td>
<td>22</td>
<td>3</td>
<td>Phenol 1% PAA 1% Secondary Products 1%</td>
</tr>
<tr>
<td>5</td>
<td>Toluene (25)</td>
<td>HF (1250) CO 50bar</td>
<td>45</td>
<td>1</td>
<td>21</td>
<td>p-Tolualdehyde 12%</td>
</tr>
<tr>
<td>6</td>
<td>Toluene (185)</td>
<td>BF₃ (80) CO 50bar</td>
<td>45</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Anisole (100)</td>
<td>HF (1400) BF₃ (217)</td>
<td>40</td>
<td>4.5</td>
<td>92</td>
<td>PAA 20% OAA 11%</td>
</tr>
</tbody>
</table>
Extending this reaction to anisole as substrate, no aldehyde product was observed, while extensive de-alkylation of anisole to phenol occurred (Run 3). The important role of an added Brønsted acid (hydrogen fluoride) was confirmed as some aldehyde product was obtained from anisole in the presence of aluminium trichloride together with HF (Run 4).

In order to gain a better understanding of their individual roles, hydrogen fluoride and boron trifluoride were used separately as catalysts in the formylation of toluene. The fact that no aldehyde products were obtained from BF₃ as catalyst and only a minor amount from HF, accentuates the effect of their combined potential. This effect is evident when results of Run 5 and 6 in Table 2.3 are compared with Run 1 in Table 2.2.

Minimising reagent volumes from an industrial perspective makes economic sense, hence the effect of less hydrogen fluoride and boron trifluoride respectively with regard to the anisole reaction was investigated. However, decreasing the hydrogen fluoride from 50 to 14 equivalents not only reduces the yield and selectivity towards the 𝑝-aldehyde, but a substantial increase in secondary product formation was observed. (Table 2.3 Run 7 vs Table 2.2 Run 5) The dramatic effect of less boron trifluoride (0.14 eq) is evident from the drop in the 𝑝-aldehyde yield to 3%. This result confirmed the important facilitating role of the Lewis acid. (Table 2.3 Run 8 vs Table 2.2 Run 4)

Since near-supercritical water may act as an acid₂⁰⁵, it offers an environmentally benevolent alternative for the replacement of undesirable solvents and catalysts and may potentially assist in the formylation of aromatic aldehydes using carbon monoxide. As toluene is the most likely to formylate under these conditions, it was the obvious choice of substrate. However, no reaction occurred at 275°C under CO pressure of 60bar in near-supercritical water, which may be ascribed to the non-supercriticality of the solvent (Table 2.3 Run 9).
Carbon dioxide in its liquid or supercritical state has prodigious potential as an environmentally benign reaction medium or reactant for sustainable chemical synthesis. The possibility of using carbon dioxide as carboxylation agent of anisole in the presence of hydrogen fluoride and boron trifluoride to \( p \)-anisic acid, followed by reduction to the corresponding aldehyde was briefly investigated. Carbon dioxide should technically be easier to protonate than carbon monoxide. \([\text{cf the four resonance structures (Eq 2.14) of protonated carbon dioxide that increases the stability of the cation to a much higher degree when compared to only two resonance structures of CO (paragraph 2.1).}]\] However HF/BF\(_3\) promoted carboxylation of anisole in supercritical CO\(_2\) was not observed (Table 2.3, Run 10).

\[
\begin{align*}
\text{HBF}_4 & \quad \overset{\text{O}}{\text{O}} \quad \overset{\text{H}}{\text{O}} \\
\text{HBF}_4 \cdot \text{OEt}_2 & \quad \overset{\text{O}}{\text{O}} \quad \overset{\text{H}}{\text{O}} \\
\text{HBF}_4 \cdot \text{OEt}_2 & \quad \overset{\text{O}}{\text{O}} \quad \overset{\text{H}}{\text{O}} \\
\text{HBF}_4 \cdot \text{OEt}_2 & \quad \overset{\text{O}}{\text{O}} \quad \overset{\text{H}}{\text{O}} \\
\end{align*}
\] (2.14)

The possible interaction of HF and BF\(_3\) to obtain HBF\(_4\) as active catalyst in CO formylation reactions was noted in literature\(^{206,207}\) and raised the expectation of HBF\(_4\) in diethyl ether being an appropriate acid catalyst. The use of HBF\(_4\)OEt\(_2\) from an industrial and environment perspective is advantageous as it enables easy handling and excludes the need for mixing HF and BF\(_3\) gasses that are harmful to the environment and infrastructure.

HBF\(_4\)OEt\(_2\) was subsequently used in an attempt to formylate both phenol and toluene in the presence of CO (Table 2.4). However, no reaction was observed probably due to the stability of the complex between HBF\(_4\) and diethyl ether.

<table>
<thead>
<tr>
<th>Run</th>
<th>Substrate</th>
<th>Reagents</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phenol (32mmol)</td>
<td>HBF(_4)OEt(_2)(160mmol); CO 83bar</td>
<td>25</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Toluene (13mmol)</td>
<td>HBF(_4)OEt(_2)(156mmol); CO 83bar</td>
<td>30</td>
<td>24</td>
<td>-</td>
</tr>
</tbody>
</table>

The successful utilisation of strong solid acids and superacids in Friedel-Crafts acylation described in the literature\(^{208}\) suggests its application in the CO formylation of aromatic substrates. Advantages regarding the replacement of homogeneous liquid acids by heterogeneous solid acids as catalysts in the chemical industry would not only bring about ease of separation from the reaction mixture allowing continuous operation,
regeneration and re-utilisation of the catalyst, but also include corrosion-free operation and less impact on the environment.

The acidity values reported for sulphated metal oxides is highest in the case of sulphated zirconia (SO$_4^{2-}$/ZrO$_2$) and is comparable to that of HF/BF$_3$. Another attractive feature of this catalyst is its dual Lewis- and Brønsted acidity that might be beneficial to our specific application.

Toluene, due to its high reactivity in HF/BF$_3$/CO formylation reactions was initially used as formylation substrate with un-activated sulphated zirconium oxide as acid catalyst. No reaction occurred even after extended reaction times and increased temperatures (Table 2.5, Run 1 and 2).

**Table 2.5: Attempted CO formylation and acylation of aromatics using sulphated zirconiumoxide as catalyst.**

<table>
<thead>
<tr>
<th>Run</th>
<th>Substrate (mmol)</th>
<th>SO$_4$ZrO$_2$ (g)</th>
<th>CO (bar)</th>
<th>Acylating Agent (mmol)</th>
<th>BF$_3$ (mmol)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene (386)</td>
<td>31$^a$</td>
<td>80</td>
<td>-</td>
<td>60</td>
<td>2.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Toluene (336)</td>
<td>20$^a$</td>
<td>80</td>
<td>-</td>
<td>100</td>
<td>15</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Toluene (333)</td>
<td>20$^b$</td>
<td>80</td>
<td>-</td>
<td>100</td>
<td>20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Toluene (292)</td>
<td>2$^a$</td>
<td>-</td>
<td>Acetic-anhydride (25)</td>
<td>-</td>
<td>100</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Toluene (141)</td>
<td>1$^c$</td>
<td>-</td>
<td>Benzoic-anhydride (4)</td>
<td>-</td>
<td>100</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Toluene (141)</td>
<td>1$^c$</td>
<td>-</td>
<td>Benzoic-anhydride (4)</td>
<td>-</td>
<td>100</td>
<td>3</td>
<td>o-, m-, p-Me-benzophenone, benzoic acid</td>
</tr>
<tr>
<td>7</td>
<td>Toluene (271)</td>
<td>3$^c$</td>
<td>50</td>
<td>-</td>
<td>45</td>
<td>12</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Anisole (231)</td>
<td>5$^c$</td>
<td>50</td>
<td>-</td>
<td>45</td>
<td>12</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>Toluene (271)</td>
<td>5$^c$</td>
<td>50</td>
<td>44</td>
<td>45</td>
<td>12</td>
<td>p-Toluald. 0.1%</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Anisole (231)</td>
<td>5$^c$</td>
<td>50</td>
<td>263</td>
<td>45</td>
<td>12</td>
<td>Phenol, no ald.</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Phenol (266)</td>
<td>5$^c$</td>
<td>50</td>
<td>208</td>
<td>45</td>
<td>12</td>
<td>p-Hydroxybenz-ald. 0.1%</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ un-activated, $^b$ activated at 150°C for 2h in argon, $^c$ calcined at 500°C for 50h in air

In an effort to reduce the Brønsted acidity and increase the Lewis acidity, water was removed from the catalyst at 150°C. This catalyst also did not promote formylation (Run 3). These results raised the question whether the material used showed any catalytic activity. A literature procedure for acylation using benzoic acid anhydride failed (Run 5), which suggests that it may still contain small amounts of moisture, not removed during the activation step. Since good acylation yields with calcined sulphated zirconium oxide were reported the same activating conditions were applied to the
catalyst. With this catalyst 2-, 3-, and 4-methyl-benzophenone, benzoic acid and phenyl benzoate were obtained identified by GC-MS analysis as acylation products using benzoic acid anhydride (Run 6) [Eq (2.15)].

\[
\begin{align*}
  &\text{Ph} + \text{Ph} \text{O} \text{O} \text{Ph} \xrightarrow{\text{SO}_4 \text{ZrO}_2, 100^\circ\text{C}, 3\text{h}} \text{Ph} \text{O} \text{H} + \text{Ph} \text{O} \text{O} \text{Ph}, \\
  &\quad \quad o, m, p
\end{align*}
\] (2.15)

The formation of phenyl benzoate was both unexpected and inexplicable. GC-MS fragmentation patterns of pure benzoic acid anhydride dissolved in dried toluene indicated the presence of phenyl benzoate. It is possible that due to the high split-inlet temperature (250°) in the gas chromatograph, the anhydride decomposes to the ester with the loss of CO.

Freshly calcined catalyst was then utilised in CO formylation reactions using toluene and anisole as substrates respectively. However, no aldehyde products were observed (Runs 7 and 8).

BF$_3$ is known to form complexes with aldehydes and according to calculations done by Eley et al.\textsuperscript{214}, synthesis of benzaldehyde is rendered thermodynamically more favourable by the formation of the benzaldehyde-aluminum-chloride-complex as a stable product. Thus, the addition of BF$_3$ to the reaction mixture using calcined sulphated zirconium oxide could possibly facilitate aldehyde formation.

On addition of BF$_3$, para-aldehyde isomers were obtained \textit{albeit} in very low yield (0.1%) from toluene and phenol as substrates using the same conditions whereas only de-alkylation occurred in the case of anisole (Runs 9, 10, 11). The formation of aldehyde product is at least in line with the predicted enhancing effect of boron trifluoride on the reaction thermodynamics.

In a final effort to establish CO formylation with heterogeneous catalysts, fluoridised silica-alumina (used effectively as an hydrofluoric acid alternative in the liquid phase alkylation of benzene\textsuperscript{215}), was activated and investigated for catalytic anisole formylation (Table 2.6). As in the case of the other heterogeneous catalysts, no formylation was observed.
Table 2.6: Attempted CO formylation of anisole using fluoridised silica-alumina\(^a\) as acid catalyst

<table>
<thead>
<tr>
<th>Run</th>
<th>Substrate (mmol)</th>
<th>Engelhard 483-11 (g)</th>
<th>CO (bar)</th>
<th>BF(_3) (mmol)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anisole (231)</td>
<td>5</td>
<td>50</td>
<td>264</td>
<td>45</td>
<td>14</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\) Activated at 350°C for 2 hours under argon

Although the super acidity of sulphated zirconium oxide is widely accepted, Fărcașiu\(^{216}\) indicated that traditional acidity measurements, *i.e.* Hammett type, can not be applied to solid acids. He showed that the exceptional catalytic activity of sulphated zirconia and other sulphated metal oxides (SMO) is not justified by their acid strength and that they are in fact not superacidic at all. He argues that sulphated zirconium exhibits a bifunctional character in which oxidation in the initiation step is combined with acid catalysed reaction of the intermediates formed. Oxidation is normally achieved through the reduction of the sulphate or added redox promotors, which increases the catalytic activity but not the acid strength.

3.3 Mechanism Studies

3.3.1 Formylation Mechanisms

Understanding the CO/HF/BF\(_3\) formylation mechanism would be beneficial to the extend that it would facilitate reaction optimisation, minimisation of side-product formation and provide an indication of whether the reaction can be performed under catalytic conditions. As little is known in the literature of the reaction mechanism in the case of anisole, efforts were focused on this aspect.

The mechanism of the conventional electrophilic aromatic substitution reaction is expected to consist of four steps: (i) formation of an electrophile (E\(^+\)) by activation with a Lewis- or Brønsted acid (A), (ii) attack of the electrophile on the aromatic compound (ArH) resulting in a \(\pi\)-complex (iii) conversion of the \(\pi\)-complex into a \(\sigma\)-complex, (iv) followed by the loss of a proton from the \(\sigma\)-complex to give the product (Eq 2.16). The formation and attack of the electrophile are separate steps *i.e.* the electrophile is formed and dispersed in the reaction medium before attack on the aromatic compound takes place.

\[
P + A \rightleftharpoons E^+ \quad \text{ArH} \quad [\text{ArH} \cdot E^+] \quad [\text{ArHE}^+] \quad \text{ArE} + H^+ \quad (2.16)
\]

\( P = \) pro-electrophile \quad \( A = \) Lewis- or Brønsted acid
The active acid involved in the initiation of the formylation reaction following HF and BF$_3$ addition to the substrate, is believed to be the super acidic HBF$_4$, since excess amounts of hydrofluoric acid are used (Eq 2.17). Although the active acid is indicated as being HBF$_4$, it must be taken into account that the existence of this super acid has only been demonstrated in the presence of nucleophilic/basic reagents (cf paragraph 2.4). The probability of the active electrophile being a species similar to that indicated in eq 2.18 can therefore not be excluded.

$$\text{BF}_3 + \text{HF} \rightleftharpoons \text{HBF}_4 \quad (2.17)$$

$$\text{BF}_3 + \text{HF} + \text{CO} \rightleftharpoons \text{HCO}^+\text{BF}_3^- \quad (2.18)$$

Since both CO and toluene (or anisole or phenol) are nucleophilic/basic compounds and the reaction is performed in a super acidic medium (with excess acid), the formation of the initial electrophile and corresponding nucleophile are by no means trivial and needs careful consideration. Furthermore, the protonation of toluene by the HF/BF$_3$ system has been reported by Olah et al.$^{217}$ (Eq 2.19), while the existence of an HCO$^+$ containing ion pair has recently been demonstrated by Gladysz et al.$^{218}$

$$+ \text{HF} \quad (2.19)$$

During their investigation on the behaviour of CO in the super acid system, HF-SbF$_5$ (1:1), by high pressure NMR, the existence of equilibria as indicated in Scheme 2.2 could also be identified by the Gladysz group.

Scheme 2.2: Proposed equilibria in the superacid HF-SbF$_5$ under CO pressure
For the reaction to proceed via the conventional electrophilic aromatic substitution mechanism, CO must be protonated, while the aromatic substrate acts as nucleophile. On the other hand, if the aromatic substrate is assumed to be the more basic, the reaction should proceed by a nucleophilic aromatic substitution pathway, with CO being the nucleophile. Since no products originating from nucleophilic displacement of the halogen could be detected during the reaction of halogenated benzenes with CO under the same conditions (cf paragraph 3.4), it must be assumed that CO acts as the more basic reagent during the reaction between CO and toluene and is being protonated to form the active electrophile ($E^+$ in Eq 2.16). If however, the basicity of both reagents is assumed to fall in close proximity of each other and excess acid is used, the protonation of both CO and the aromatic substrate is a definite probability and the reaction should be governed by the presence and position of protonation equilibria. In this instance where CO is the more basic component it should be protonated to a higher degree than the aromatic substrate, with the protonation equilibrium of the aromatic reactant more to the left (Eq 2.20 or 2.21), i.e. some un-protonated molecules are available to act as nucleophiles and thus allowing the reaction to proceed. The higher reactivity of toluene vs phenol and anisole could therefore be attributed to the latter substrates being protonated to a higher degree than toluene (due to higher basicity) thus leading to lower concentrations of unprotonated and, therefore, reactive substrate (Eq 2.20).

\[
\begin{align*}
\text{OCH}_3 + 2\text{H}^+ & \rightleftharpoons \text{CH}_3^+ \cdot \text{O}^- \cdot \text{H} + \cdot \text{OCH}_3
\end{align*}
\]  (2.20)

\[
\begin{align*}
\text{CH}_3 & \rightleftharpoons \text{CH}_3^+ \cdot \text{H}^+
\end{align*}
\]  (2.21)

Although the conventional mechanism, as indicated above (Eq 2.16), might prevail during these reactions, it only holds true if it is assumed that CO is the more basic of all reactants employed. In order to validate this assumption it was decided to perform some reactions with only one equivalent of super acid (relative to toluene) on mixtures (1:1) of toluene and phenol or anisole respectively. If CO is the more basic reagent, the
presence of the other aromatic compound would have limited effect on the toluene formylation reaction rate. The presence of phenol or anisole during the reaction of toluene, however, had a profound inhibiting effect on the formylation of the toluene (Table 2.7), while very little formylation of the added phenol or anisole took place under these conditions. A plausible explanation for these results could be that these compounds are more basic than toluene while their susceptibility to protonation under the prevailing conditions is better or at least comparable to that of CO. Indirect evidence that anisole and phenol are more basic than toluene is provided by the relative stability of the cations of toluene and anisole. In this regard Takezaki et al.\textsuperscript{219} reported a melting point (with some decomposition\textsuperscript{217}) of -65°C for the 1:1:1 complex of toluene, HF and BF$_3$ while -60°C was reported for the anisole-HF-BF$_3$ complex, both at atmospheric pressure.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Time (min)</th>
<th>Toluene (%)</th>
<th>p-Toluald. (%)</th>
<th>o-Toluald. (%)</th>
<th>Phenol (%)</th>
<th>PHBAld. (%)</th>
<th>Anisole (%)</th>
<th>PAA (%)</th>
<th>Sec. Prod. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>15</td>
<td>4</td>
<td>81</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>2</td>
<td>80</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>&lt;0.1</td>
<td>83</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>1:1 Toluene-Phenol</td>
<td>15</td>
<td>44</td>
<td>6</td>
<td>-</td>
<td>46</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>40</td>
<td>10</td>
<td>-</td>
<td>44</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>36</td>
<td>14</td>
<td>-</td>
<td>43</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>1:1 Toluene-Anisole</td>
<td>15</td>
<td>45</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>48</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>44</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>46</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>43</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>44</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

Although the formation of the aldehydes from toluene, phenol and anisole could be explained by the conventional mechanism, as discussed above, this mechanism is based on the assumption that the protonation of CO is at least as feasible as that of the aromatic substrates. According to Gladysz \textit{et al.}\textsuperscript{218} the protonated species of CO (at room temperature under 28bar CO pressure) could only be detected while employing HF-SbF$_5$, the strongest super acid known, and not even with HSO$_3$F-SbF$_5$ (a weaker acid by a factor 1000), the second member in the series of super acids (\textit{cf} paragraph 2.4).
Therefore, it is justifiable to assume that the protonation of CO is extremely difficult compared to that of the aromatic substrates involved in the formylation reactions (vide supra) and that the equilibria involved should rather be to the left for equation 2.18* and right for equation 2.20. This would render the concentration of reacting species in the proposed electrophilic aromatic substitution extremely low and be expected to result in almost no reaction; a result in direct contrast to experimental observations.

Cacace\textsuperscript{220} and Tanaka\textsuperscript{221}, however, proposed an alternative mechanism for the formation of products and the difference in reactivity observed for the different substrates in this study. In the Cacace-Tanaka mechanism (Eq 2.22) it is proposed that the protonated aromatic compound act as an acid to protonate the pro-electrophile (CO in this case) with the formation of a so-called intracomplex. The formation of the intracomplex is followed by attack of the liberated aromatic nucleophile on the newly formed electrophile leading to a π-complex, which is then transformed into a σ-complex before releasing a hydrogen ion and formation of the final product (Eq 2.23).

\[
P + \text{ArH}_2^+ \rightarrow [\text{ArH}_2^+ \cdot P] \xrightarrow{\pi\text{-complex}} [\text{ArH}\cdot\text{E}^+] \xrightarrow{\sigma\text{-complex}} \text{ArE} + H^+ \quad (2.22)
\]

\[
P = \text{pro-electrophile}
\]

\[
\text{R} + \text{HCO}^+ \xrightarrow{\text{[Intracomplex]}} \text{R} + \text{HCO}^+ \xrightarrow{\text{para-oriented \pi-complex}} \text{R} + \text{H}^+ \quad (2.23)
\]

The increased reactivity of toluene compared to anisole (and phenol) could probably be explained in terms of the former reacting at least partially through the conventional mechanism, while for the more basic anisole and phenol the reaction would proceed through the intracomplex mechanism. In this instance the aromatic substrate can be protonated to a large extent and still allow the reaction to proceed by an electrophilic aromatic substitution pathway. Only limited quantities of unprotonated CO would also be

\[
* \text{Low conversion of CO into HCO}^+ \text{ was also indicated by Tanaka et al. (Trends Org. Chem., 7, 1998, 45)}
\]
required to act as pro-electrophile during the reaction. The higher reactivity of phenol vs anisole is probably explicable in terms of the fact that phenol is less basic than anisole and would therefore be more prone to protonate CO after formation of the intracomplex.

Although it has been reported in a Molecular Modelling study that the formation of a formyl dication (HCOH\(^{++}\)) by the action of HF/SbF\(_5\) on CO is associated with extremely high activation energy\(^{222}\), this species has been proposed by several authors\(^{223}\) as the active electrophile in formylation reactions utilising CO and HF/SbF\(_5\). The formation of a formyl dication could, therefore, also be invoked as plausible explanation for electrophilic aromatic substitution reactions in case of full protonation of both CO and the aromatic substrate by the HF/BF\(_3\) super acid (Eq 2.24).

\[
\begin{align*}
\text{C}=\text{O}+\text{H}^+ & \rightleftharpoons \text{HCOH}^{++} \\
\text{HCOH}^{++} & \rightarrow \text{R} \quad \text{para-oriented } \pi\text{-complex} \\
\text{R} & \rightarrow \text{R}^+ \quad \text{a-complex}
\end{align*}
\]

The dication concept can also be extended to the formation of the anisole- and phenol dication as reported by Takezaki\(^{224}\) who isolated an anisole/HF/BF\(_3\) complex containing a 1:1:2 ratio of reactants (Scheme 2.3). Protonation of the pro-electrophile CO via the intracomplex mechanism is followed by electrophilic aromatic substitution with formation of the \(\pi\)- and \(\sigma\)-complex respectively followed by aldehyde formation through the loss of a proton and X. The corresponding rate of formylation is expected to be slower than in the case of toluene due to the lower nucleophilicity of the protonated anisole.
Scheme 2.3: Dication formation with resulting intracomplex formylation to the aldehyde.

A third possible explanation for the reduced reactivity of anisole and phenol compared to that of toluene could be that the former two substrates are deactivated towards electrophilic aromatic substitution by reaction of the alcohol or ether moiety with either the Lewis (BF$_3$) or Brønsted (HBF$_4$') acid. In this instance the first equivalent of acid would be consumed by reaction with the oxygen (Scheme 2.4), and the second equivalent effecting protonation of CO. Inductive deactivation of the aromatic ring by the cationic oxygen will result in reduced reactivity of the aromatic system. Since the positive charge resulting from complexation of phenol with BF$_3$ on the phenolic entity could be neutralised by proton loss to the reaction medium, phenol is expected to be more reactive than anisole under the reaction conditions (Scheme 2.4). Additional support for this explanation is provided by the reported isolation of an anisole/HF/BF$_3$ complex containing a 1:1:2 ratio of reactants.$^{226}$
Scheme 2.4: Protonated anisole/phenol.

Yet another possible formylation mechanism that needs to be considered, involve direct nucleophilic attack of CO on the protonated aromatic system. However, this mechanism (Scheme 2.5) can be discounted since it will result in meta-substituted aldehydes in the case of toluene, phenol and anisole as substrates.

Scheme 2.5: Meta-aldehyde formation through nucleophilic aromatic substitution of groups that contain an unshared pair of electrons on the atom connected to the ring.

The different substrates studied showed big differences in reactivity but little variation in product selectivity. While meta-substitution is not expected in the reactions of activated aromatic substrates, i.e. toluene, phenol, and anisole, the virtual absence of ortho substituted products can only be explained in terms of the mechanistic pathway of the reactions. Since early intermediates could be associated with the π-complex and thus low regioselectivity, it must be concluded that the important intermediates in these reactions have a σ-complex nature resulting in high para-selectivity\textsuperscript{225}. According to Tanaka et al.\textsuperscript{226} the intracomplex mechanism could be associated with high para regioselectivity in the formylation of methylnaphthalene when the Lewis acid to substrate molar ratio was less than 1. In contrast, lower regioselectivity, indicative of the conventional mechanism, was observed when the molar ratio exceeded 1. Even though the Lewis acid to substrate molar ratio exceeded 1 during the present study, relatively high para selectivity was still observed for all substrates. No conclusive deductions as to
the prevailing mechanism, *i.e.* intracomplex or conventional, could therefore be made from the regio-isomer distribution of products either.

### 3.3.2 Deuterium Labelling Experiments

The uncertainty about the mechanism(s) of the formylation reaction of anisole and phenol, on the one hand, and toluene on the other, presented a challenging investigative opportunity. Deuterium labelling as a tool to probe reaction mechanisms is widely used and in this regard the use of deuterium fluoride could indicate whether protonation in the initial stages of the reaction occurs preferentially on the aromatic ring or on the carbon monoxide molecule.

Deuterium fluoride (50eq), prepared from sodium fluoride and concentrated deuterated sulphuric acid, was used in the formylation of anisole (1eq) with BF$_3$ (2eq) for 2 hours at 45°C. The $^1$H-NMR spectrum of the $p$-aldehyde product (Plate 17, experimental section) indicated singlets in both the aldehyde and methyl regions as well as two singlets in the aromatic region. Integrals of 1 for the formyl group (inert to exchange with DF) and both sets of aromatic protons respectively and 14 for the methyl protons could be explained in terms of the presence of at least two deuterated $p$-anisaldehyde isomers (Fig 2.5).

![Deuterated $p$-anisaldehyde isomers obtained from DF/BF$_3$/CO formylation.](image)

**Figure 2.5:** Deuterated $p$-anisaldehyde isomers obtained from DF/BF$_3$/CO formylation.

The position of the *ortho*-proton in 15 was identified using NOESY (Plates 19 and 20) experiments. The $^{13}$C-NMR spectrum also supported the conclusion. The isomers are present in a 1:3 ratio. Although H-D exchange occurred freely, the appearance of the proton in the aldehyde moiety of (15), points strongly to the presence of the intracomplex reaction mechanism where the hydrogen or deuterium originates from the aromatic ring as opposed to from CDO$^+$. The existence of the D-atom on the aldehyde moiety of (16) may result from H-D exchange prior to formylation or CO protonation. The extensive exchange of other aromatic hydrogen atoms may be a consequence of the long reaction times.
In an effort to minimise H-D exchange, the reaction time with toluene was reduced to 20 minutes. $^1$H-NMR (Plate 21) analysis, after isolation and purification of the aldehyde product, indicated singlets in both the aldehyde and methyl regions in addition to two singlets in the aromatic region. Integrals in the $^1$H-NMR spectrum varied from 1 for the aldehyde- to two for the aromatic- and 15 for the methyl protons and only partial structures could be allocated (Fig 2.6). The excess in methyl protons compared to aldehyde and aromatic protons are indicative of the existence of partial structure 17, while the two 2H singlets suggests the existence of 18 or both 19 and 20. $^1$H-NMR integral calculations indicated the deuterated aldehyde moiety to be present in 80% with the remainder being CHO. $^{13}$C-NMR integrals show at least two isomers containing the CHO and CDO moieties in 37% and 67% respectively (Plate 22). As in the previous case, the appearance of the proton in the aldehyde moiety points strongly to the presence of the intracomplex mechanism where the hydrogen originates from the aromatic ring as opposed to CDO$^+$. Again, the deuterated aldehyde moiety may originate from CDO or D-transfer after exchange.

![Diagram of isomers](image)

**Figure 2.6: Deuterated $p$-tolualdehyde isomers obtained from DF/BF$_3$/CO formylation.**

Since the isotope effect would render D-transfer less facile compared to H-transfer, an attempt was made to show that protonation do not occur preferentially on the carbon monoxide molecule in the case of toluene. The hydrogen containing substrate was replaced with d$_5$-toluene and formylated under similar conditions using hydrogen fluoride while the reaction time was reduced even further to 10 minutes to minimise H-D exchange.
The $^1$H-NMR of the aldehyde product displayed an AA'$BB'$-system ($J=8.75$) in addition to singlet's corresponding to CHO (Plate 23). Integrals ranged from one for CHO- to two for aromatic-H and four for the methyl protons. The spectrum is indicative of two isomers $21$ and $22$ in a ratio of 4:1 (Fig 2.7). This interpretation was in line with the $^{13}$C-NMR spectrum that indicated a CHO to CDO ratio of 10:1 (Plates 24 and 25). The occurrence of deuterium in the aldehyde moiety ($22$) again strongly supports the intracomplex reaction where the deuterium originates from the aromatic ring as opposed to CHO$^+$. 

![Deuterated p-tolualdehyde isomers obtained from HF/BF$_3$/CO formylation.](image)

In all of the deuterium labelling experiments proton and deuterium exchange occurred freely on the aromatic ring, which complicated structure elucidation and therefore mechanistic conclusions tremendously. Despite this, compounds that could have originated only from the intracomplex mechanism were obtained in all reactions.

### 3.3.3 Mechanism of Secondary Product Formation

GC-MS-fragmentation patterns indicated the following secondary products isomers resulting from the formylation of toluene: dimethylbenzophenone ($30$), di(methylphenyl)methane ($31$), tri(methylphenyl)methane ($29$) and di(methylphenyl)-methanol ($26$). The formation of the various side-products is explicable in terms of a two-step mechanism.

In the first step acid catalysed addition of toluene to the aldehyde product leads to the key-intermediate in the reaction, the alcohol ($26$) (Scheme 2.6). If this reaction is followed by an acid catalysed substitution of the OH by another toluene molecule the “trimer” ($29$) is formed.
Scheme 2.6: Nucleophilic addition of toluene to p-tolualdehyde.

An acid catalyzed oxidation/reduction process could be suggested for the formation of 4,4’-dimethylbenzophenone (30) and di(4-methylphenyl)methane (31) (Scheme 2.7).

Scheme 2.7: Proposed redox disproportionation reaction

Formation of (29) and (31) in the CO formylation of toluene in HF/BF$_3$\textsuperscript{227} as well as in trifluorosulphonic acid\textsuperscript{228} were reported in the literature.

Secondary products of the anisole reaction were similar to those obtained for the toluene reaction with the exception that di(4-methoxyphenyl)methanol was not found. The absence of this alcohol can probably be ascribed to its higher reactivity leading to further reactions more readily than in the case of the toluene equivalent (Scheme 2.8).
Scheme 2.8: Nucleophilic addition of anisole to PAA

In an effort to confirm the proposed mechanism for by-product formation in the anisole reaction, anisole and PAA was added to hydrogen fluoride and BF$_3$ in the absence of carbon monoxide under typical reaction conditions (Table 2.8, Run 1). Isomers of the products (38), (39) and (40) were obtained in a 7:1:1 ratio and again none of the alcohol (35) was detected. The remaining question, i.e. whether (39) and (40) are formed from the proposed intermediate (35) was addressed by subjecting the separately prepared alcohol (35) to the reaction conditions in the absence of a nucleophile (Scheme 2.9).

Scheme 2.9: Proposed redox disproportionation reaction

Although care should be taken in the handling of the highly reactive alcohol (35), it could easily be prepared in almost quantitative yield by NaBH$_4$ reduction of the ketone (39). Normal neutralisation of the excess NaBH$_4$ and decomposition of the resultant alcohol borate complex with hydrochloric acid however could not be applied and the alcohol was isolated through an acetone/water work-up. The pure white di(4-methoxyphenyl)-
methanol crystals were subsequently added to HF/BF₃ under typical reaction conditions (Table 2.8, Run 2). This resulted in the formation of benzophenone, diphenylmethane as well as the “trimer”. These products were however accompanied by smaller amounts of anisole and p-methoxyacetophenone. Anisole probably arises by an acid catalysed decomposition reaction (Scheme 2.10).

![Scheme 2.10: Formation of anisole via acid catalysed decomposition](image)

**Table 2.8: Reactions in HF/BF₃ in the absence of CO**

<table>
<thead>
<tr>
<th>Run</th>
<th>Substrate</th>
<th>Reagents</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anisole (25mmol)</td>
<td>PAA (25mmol)</td>
<td>45</td>
<td>3.5</td>
<td>Di(4-methoxyphenyl)methane (2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HF (2500mmol)</td>
<td></td>
<td></td>
<td>4,4’-dimethoxybenzophenone (2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BF₃ (111mmol)</td>
<td></td>
<td></td>
<td>Tri(4-methoxyphenyl)methane (14%)</td>
</tr>
<tr>
<td>2</td>
<td>Di(4-methoxy-phenyl)methanol (20mmol)</td>
<td>HF (1025mmol)</td>
<td>45</td>
<td>3.5</td>
<td>Anisole (10%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BF₃ (41mmol)</td>
<td></td>
<td></td>
<td>p-methoxyacetophenone (2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Di(4-methoxyphenyl)methane (22%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4,4’-dimethoxybenzophenone (30%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tri(4-methoxyphenyl)methane (23%)</td>
</tr>
</tbody>
</table>

The occurrence of p-methoxyacetophenone (46) as secondary product in both of the mechanistic studies as well as with anisole formylation reaction was rather surprising. The same product was however reported by Saint-Jalmes et al.²⁰ during the HCO₂Me/HF/BF₃ formylation of anisole. These workers postulated the acid catalysed decomposition of methyl formate into methanol and CO as first step in the reaction. This is followed by dehydration of the liberated methanol with the formation of the methyl cation (43), which is then carbonylated to produce the acylium ion (44). Subsequent nucleophilic attack of anisole on 44 then produces the observed acetophenone (45) (Scheme 2.11).
Scheme 2.11: Acetophenone formation during HCO₂Me/HF/BF₃ formylation of anisole

In a similar way, anisole (32) may be dealkylated to phenol and the methyl cation, which in turn is converted into the acylium ion, which reacts with anisole to produce 46 (Scheme 2.12).

Scheme 2.12: Acetophenone formation during CO/HF/BF₃ formylation of anisole

The investigations into the secondary product mechanisms lead to some insight regarding the overall picture. The formation of addition- and other secondary products resulting from reaction between the substrate and the aldehyde product has a profound impact on a number of important issues. Firstly, secondary products are produced right from the start of the reaction i.e. as soon as the first molecule of aldehyde is produced. Thus, extended reaction times to increase the p-aldehyde yield will exacerbate secondary product formation and decrease expensive feed capacity. Although shorter reaction times should minimise this problem, it will result in additional production- and capital costs, as larger amounts of feed will have to be recycled. Furthermore, increased reactor size will be necessary due to the lower product yield.

3.4 Formylation of other substrates

A better understanding of the formylation reaction is important and warranted the evaluation of the effect of other ring substituents on the reaction. Chlorobenzene was used to provide information on the influence of deactivating groups on the aromatic ring, while the effect of steric hindrance and increased activation was assessed using diphenyl ether and p-methyl anisole as substrate respectively. Although not important from a
mechanistic point of view, the aldehyde from 4-nonylphenol has industrial applications and was therefore included in the study. The results are summarised in table 2.9.

Table 2.9: CO formylation of various aromatic substrates using anhydrous HF (50eq) and BF$_3$ (2eq) as catalysts.

<table>
<thead>
<tr>
<th>Run</th>
<th>Substrate</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Products (mass%)</th>
<th>Secondary Products</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nonylphenol</td>
<td>45</td>
<td>0.5</td>
<td>-</td>
<td>-</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>Chlorobenzene</td>
<td>45</td>
<td>4.5</td>
<td>31</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>3</td>
<td>Diphenyl ether</td>
<td>45</td>
<td>1</td>
<td>85</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>4-Me-anisole</td>
<td>45</td>
<td>2</td>
<td>-</td>
<td>85</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>45</td>
<td>1</td>
<td>91</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>Phenol</td>
<td>45</td>
<td>1</td>
<td>43</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>Anisole</td>
<td>45</td>
<td>1</td>
<td>38</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

The formylation of nonylphenol yielded a myriad of products of which only phenol and $p$-hydroxybenzaldehyde could be identified unambiguously. Since no 4-nonylsalicylaldehyde was found, it is clear that de-alkylation of the substrate prevailed under the super acidic conditions of the reaction. (Table 2.9).

As expected, the reactivity of chlorobenzene turned out to be low with only 32% conversion even after extended reaction times of 4.5 hours. The activated substrates, diphenyl ether and 4-methylanisole, on the other hand, showed reactivities comparable to that of toluene (97 and 99% conversions respectively under the same conditions), albeit with a higher degree of secondary product formation (12 and 14% respectively vs 3% for toluene). Although the high reactivity of 4-methylanisole was expected in the presence of two activating groups, that of DPE was somewhat surprising and can probably be ascribed to the sterically hindered oxygen being less available for complexation with BF$_3$. Booth et al.$^{166}$ also reported a lack of evidence for the formation of coordination complexes between DPE and BF$_3$.

The relative bulky substituents on the benzene rings of chlorobenzene and diphenyl ether probably inhibited ortho substitution ($\leq$1%) contributing to an observed extremely high para-selectivity. Another contributing factor to the apparent high para-selectivity in the use of DPE is that the ortho-aldehyde rapidly converts into components (48) and (49) by a known reaction mechanism demonstrated earlier (cf paragraph 3.3.3).
In the case of 4-methylanisole, the question arose as to which of the ortho positions would be preferred in the substitution process. A strong NOE between the methyl groups and hydrogens 3 and 5 confirms the assigned structure (47) of the product.

The aldehyde product in the DPE reaction was accompanied by two major secondary products, i.e. 9H-xanthene (48) and the xanthone (49), probably originating in a way similar to that of the benzophenone (39) and diphenyl methane (40) during the anisole reaction (cf paragraph 3.3.3) (Scheme 2.13).

\[ 
\begin{align*}
47 & \quad \text{CHO} \\
48 & \quad \text{O} \\
49 & \quad \text{O}
\end{align*}
\]

**Scheme 2.13: Mechanism of 9H-xanthene and xanthone formation**

In order to establish relative rates between different substrates, the effect of different substituent groups on \( p \)-aldehyde formation was compared over time. All reactions (2eq BF\(_3\) and 50eq HF) were conducted in the presence of \( n \)-decane as internal standard (20 mass% with respect to the substrate) under 50bar CO pressure. From the results represented in Graph 2.1 it is clear that the formylation rate of toluene and benzene are significantly higher compared to the other substrates and maximum aldehyde yield was achieved after only ten minutes. Thereafter a gradual drop in aldehyde yield was observed, indicating that the rate of secondary product formation now becomes faster than aldehyde formation. Of the non-alkyl substituted benzenes, fluorobenzene shows the fastest rate of formylation with little evidence of further reaction of the resulting
aldehyde. The formylation of chlorobenzene is extremely slow and it appears that the rate of aldehyde formation is soon overtaken by further reactions of the aldehyde. It is clear that anisole has not reached maximum aldehyde yield after one hour and that extended reaction time is necessary to determine the point of maximum aldehyde yield. Although the reactivity of bromobenzene appears to be high under the reaction conditions, debromonation mainly occurred under the conditions resulting in the production of mainly benzaldehyde with little bromobenzaldehyde (<1%). It is further evident that the concentration of aldehyde product from toluene, anisole and chlorobenzene at one hour is somewhat less compared to previous results (cf. Table 2.9). This may be due to the effect of dilution resulting from the addition of the internal standard and the reduced solubility of carbon monoxide in n-decane. The reaction rates decreases from toluene> benzene> fluorobenzene> anisole> chlorobenzene emphasising the fact that for electrophilic aromatic substitution reactions, methyl groups are activating while halogens are deactivating relative to benzene as substrate. The decrease in reactivity from fluorobenzene> chlorobenzene> bromobenzene is in accordance with formylation trends observed in HSO₃F-SbF₅ and HCO₂CH₃-HF-BF₃ catalyst systems. The higher reactivity of fluorobenzene compared to chlorobenzene is probably explicable in terms of the intracomplex reaction mechanism. Protonation of chlorobenzene should be accomplished easier (stronger base) compared to fluorobenzene due to the lower electronegativity of the chlorine. Protonated chlorobenzene, however will be a weaker acid compared to protonated fluorobenzene and as a result would not be able to activate the pro-electrophile to the same extend as the latter, effecting lower formylation reactivity. The increased reactivity of toluene over benzene originates in the better nucleophilicity associated with toluene and suggests that both toluene and benzene are formylated via the conventional mechanism.
Graph 2.1: Aromatic $p$-aldehyde product and substrate distributions over time during the CO formylation of aromatic hydrocarbons in HF/BF$_3$ at 45°C

Different substituents in the vicinity of a reaction centre may influence a given system (e.g. benzene ring) to react in different ways. Studying the effects of substituents on reaction rates of polar reactions in particular may provide valuable mechanistic information.$^{230}$

Polar reactions involve interactions between a nucleophile and electrophile and factors that will facilitate the process are supply of electrons to the nucleophilic centre and withdrawal of electrons from the electrophilic centre. Common substituents used to bring about these electronic perturbations are OH, Me, Cl, F, NO$_2$, CN.

Hammett showed that a plot of log $K_A$ for benzoic acid ionization against a plot of log $k$ for ester hydrolysis over many substituents is reasonably linear. All the meta- or para-substituents are exerting a similar effect in each of these quite dissimilar reactions.
Hammett made the first attempt to describe the effects of substituents on such reaction rates in a numerical way. For \( m \)- and \( p \)-XC\(_6\)H\(_4\)Y, he set up the equation

\[
\log \frac{k}{k_0} = \sigma \rho
\]

where \( k_0 \) is the rate- or equilibrium constant for \( X = H \), \( k \) is the constant for the group \( X \), \( \rho \) is the constant for a given reaction under a given set of conditions and \( \sigma \) is a constant characteristic of the group \( X \). The \( \sigma \) values are numbers that sum up the resonance plus field effects of a group \( X \) attached to a benzene ring, but fails for groups in the ortho-position due to additional steric effect.

With the \( \rho \) values calculated from an experimental set of reactions and the known \( \sigma \) values for other groups, rates may be predicted for reactions that have not been run.

Some reactions do not fit the treatment and for those, two new sets of \( \sigma \) values have been devised: \( \sigma^+ \) values for cases in which an electron donating group interacts with a developing positive charge in the transition state (including electrophilic aromatic substitutions) and \( \sigma^- \) values for where electron withdrawing groups interact with developing negative charge.

As in all linear free-energy relationships, the Hammett equation expresses the similarity of behaviour among two or more sets of reactions. Various types of non-linear behaviour between rates and \( \sigma \)-values may be encountered and include: random deviations due to experimental error, mechanistic change, enhanced resonance and variable resonance interactions.

Sporadic change in the energetically-preferred mechanism may take place after altering a substituent due to the availability of two pathways of similar energy with very different electronic demands. This will result in a sudden change in the slope of the Hammett plot. Changes in the rate-determining step of a multi-step reaction or a unique reaction pathway will also result in discontinuity.

In graph 2.2, the relative reactivities compared to benzene of toluene, fluoro-, chlorobenzene and anisole are plotted as a function of their respective \( \sigma^+ \)-values. A linear plot starting from chlorobenzene through fluorobenzene and toluene down to anisole is expected in line with decreasing \( \sigma^+ \)-values. The slope of the plot however
deviates drastically with anisole, indicative of a different reaction pathway or intermediate involved in this case e.g. competitive protonation on the methoxy substituent.

Graph 2.2: Hammett plot* for CO/HF/BF₃ formylation reactions

* rates were equated with conversion at a given reaction time

3.5 Conclusion

From this study it seems that oxygenated aromatic compounds are less reactive towards acidic CO formylation in comparison to alkylated ones and this effect can be explained by the relative acid-base properties of the substrate and carbon monoxide. More than stoichiometric amounts of acid are required for acceptable rates and yields. Various acids apart from the HF/BF₃ system were investigated without success in an attempt to facilitate formylation of anisole. Deuterium labelling experiments as a tool to probe the possible reaction mechanism provided interesting but inconclusive results in support of the intra-complex mechanism. Secondary product formation was shown to result mainly from acid catalysed reactions between the substrate and the aldehyde product. Preliminary economic evaluations indicated boron trifluoride to be the major cost driver in these reactions, necessitating its quantitative recovery. A successful HF/BF₃ retrieval process is described by Fujiyama et al.²³¹,²³² and involves the decomposition of the p-tolualdehyde complex in the presence of fluorine substituted aromatic compounds with recovery of the aldehyde, HF and BF₃ in excess of 99%. Such a process could be applicable to PAA production. However, it may require prior removal of the unreacted substrate in order to prevent secondary product formation. A typical approach would be
to remove anisole selectively from the product stream without the application of heat e.g. liquid-liquid extraction followed by the acid recovery process.

In the light of the difficult economic application of formylation with CO, the development of new catalysts or methodology will be required to allow the use of HF/BF₃ in a catalytic way. One such an alternative may be found in the exploration of a new and ecological-friendly field, i.e. ionic liquids.

4. IONIC LIQUIDS AS SOLVENT FOR HF/BF₃ CATALYSED REACTIONS

4.1 Introduction

Ionic liquids are non-volatile liquid salts at room temperature with physical and chemical properties that can be tailored to facilitate not only the reactivity of specific reactions, but also the regioselectivity.

The first CO formylation reaction of aromatic compounds using an ionic liquid was described by Kniften et al. who carbonylated toluene in N-butylpyridinium-aluminum-tetrachloride under drastic conditions (100°C, 4h, 207bar CO pressure) to obtain the para-aldehyde in low yield of 6.6%. Excellent yields and selectivities were however obtained by Exxon Mobil Chemical Co. when an ionic liquid consisting of alkyl imidazolium- and AlCl₄⁻ ions were used (Eq 2.25). Recovery of the temperature labile aldehyde was conveniently achieved by using a wiped film evaporator separating the ionic liquid from the aldehyde. Since literature precedent for formylation of aromatic compounds exist, it was therefore decided to investigate this possibility as method for the production of PAA using HF/BF₃ in a catalytic way.

\[
\text{CO, 80 bar, rt} \quad \text{[EMIM]AlCl₄} \quad \text{CHO} + \text{CHO} + \text{CHO} \quad \text{(2.25)}
\]

89% p- + 10% o- +1% m-
conversion = 24 - 66%

4.2 General definitions and characteristics of ionic liquids

Although the discovery of ionic liquids can be dated back to 1914 when Walden reported the formation of ethyl ammonium nitrate (m.p. 12°C) from the reaction of ethylamine with concentrated nitric acid, no interest in these compounds was shown at the time. Over the last few years however, ionic liquids are emerging as an attractive
“green” alternative technology in organic and organometallic chemistry. This “green” technology involves the reduction of waste from industrial processes. Sheldon\textsuperscript{236} defines the \( E \)-factor, environmental efficiency, of a process as the weight ratio of by-products to that of the desired product(s) (Table 2.10).

**Table 2.10: Sheldon \( E \)-factor for different industries**

<table>
<thead>
<tr>
<th>Industry</th>
<th>Production (tons pa)</th>
<th>( E )-factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil Refining</td>
<td>( 10^3-10^8 )</td>
<td>0.1</td>
</tr>
<tr>
<td>Bulk Chemicals</td>
<td>( 10^5-10^6 )</td>
<td>1-5</td>
</tr>
<tr>
<td>Fine Chemicals</td>
<td>( 10^2-10^4 )</td>
<td>5-50</td>
</tr>
<tr>
<td>Pharmaceuticals</td>
<td>( 10^1-10^3 )</td>
<td>25-100</td>
</tr>
</tbody>
</table>

The exact definition of an ionic liquid pertaining to the melting point is not clear-cut as some variations are found in literature. Wasserscheid et al.\textsuperscript{237} defines an ionic liquid as a liquid consisting of mainly ions having a liquid range below 100°C. Gordon\textsuperscript{238} describes ionic liquids as a liquid which is composed entirely of ions with melting points of below 100–150°C, while Hagiwara et al.\textsuperscript{239} exclude ionic species having a melting point higher than 25°C.

Ionic liquids exhibit interesting physical properties that could lead to the substitution of volatile organic solvents\textsuperscript{240} by these compounds. These properties can be summarised as follows:

- No measurable vapour pressure.
- Good solubility properties over a wide range of both organic and inorganic materials.
- The potential to be highly polar yet non-coordinating solvents.
- Provide a non-aqueous, polar alternative for two-phase systems.

**4.3 Synthesis of ionic liquids**

Ionic liquids typically consist of a bulky hetero-carbon cation \( e.g. \) alkyl imidazolium or – pyridinium in combination with an anion \( e.g. \) \( \text{BF}_4^- \) or \( \text{PF}_6^- \).

The first step in ionic liquid synthesis involves quaternization or alkylation of 1-methylimidazole using chlorobutane for example to obtain the cation (Eq 2.26).\textsuperscript{241,242,243}
Some of the most important cations are shown in Scheme 2.14:

\[
\begin{align*}
\text{Imidazolium ion} & \quad \text{Pyridinium ion} & \quad \text{Ammonium ion} & \quad \text{Phosphonium ion}
\end{align*}
\]

Scheme 2.14: Important types of cations in ionic liquids

Salts having melting points of less than 100°C with altered anions are obtained by quaternization reactions with different alkylation reagents (Table 2.11)

**Table 2.11: Examples of ionic liquids that can be formed by direct quaternization**

<table>
<thead>
<tr>
<th>Ionic Liquid</th>
<th>Alkylation Reagent</th>
<th>M.p. (°C)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>([\text{EMIM}]\text{CF}_3\text{SO}_3)  (^a)</td>
<td>Methyl triflate</td>
<td>-9</td>
<td>244</td>
</tr>
<tr>
<td>([\text{BMIM}]\text{CF}_3\text{SO}_3)  (^b)</td>
<td>Methyl triflate</td>
<td>16</td>
<td>249</td>
</tr>
<tr>
<td>([\text{Ph}_3\text{POc}]\text{OTs})  (^c)</td>
<td>OcOTs</td>
<td>70-71</td>
<td>245</td>
</tr>
<tr>
<td>([\text{Bu}_3\text{NMe}]\text{OTs})</td>
<td>MeOTs</td>
<td>62</td>
<td>246</td>
</tr>
<tr>
<td>([\text{BMIM}]\text{Cl})</td>
<td>Chlorobutane</td>
<td>65-69</td>
<td>247</td>
</tr>
</tbody>
</table>

\(^a\) EMIM = 1-ethyl-3-methylimidazolium; \(\text{CF}_3\text{SO}_3\) = triflate anion  \(^b\) BMIM = 1-\(n\)-butyl-3-methylimidazolium  \(^c\) Oc = octyl; Ts = \(\text{H}_3\text{CC}_6\text{H}_4\text{SO}_2\) (tosyl)

When it is not possible to produce the desired anion directly from the quaternization reaction (Step I), two other different routes are possible (Scheme 2.15). An ammonium halide \([\text{R}'\text{R}_3\text{N}]^+\text{X}^-\) can for example be treated with a Lewis acid \(\text{MX}_y\) to give the ionic liquid \([\text{R}'\text{R}_3\text{N}]^+\text{[MX}_{y+1}^-\) (Step IIa). The halide ion \(\text{X}^-\) can alternatively, (Step IIb) be exchanged with the desired anion by either addition of a metal salt \(\text{M}^+\text{[A]}^-\) over an ion exchanger, or removal of the halide ion using a strong acid \(\text{H}^+\text{[A]}^-\) (Scheme 2.15).
Scheme 2.15: Example of the synthesis paths for the preparation of ionic liquid from an ammonium salt

When excess Lewis acid MX is added to the ammonium salt, additional anionic species are formed from further acid-base reactions by the already present anion. This is observed with chloroaluminate melts, e.g. Eq 2.27 and 2.28.

\[
[R'NR_3]^+ \text{AlCl}_4^- + \text{AlCl}_3 \rightleftharpoons [R'NR_3]^+ \text{Al}_2\text{Cl}_7^- \quad (2.27)
\]

\[
[R'NR_3]^+ \text{Al}_2\text{Cl}_7^- + \text{AlCl}_3 \rightleftharpoons [R'NR_3]^+ \text{Al}_3\text{Cl}_{10}^- \quad (2.28)
\]

The formation of different anions is dependent on the chloride/AlCl₃ ratio. The addition of aluminum trichloride to the chloride initially results in the formation of the AlCl₄⁻ ion and this is essentially the only anion present at an aluminum trichloride mole-fraction of exactly 0.5. At x(AlCl₃)>0.5, multi-nuclear chloroaluminate anions are formed which are in equilibrium with one another, the AlCl₄⁻ ion and at very high AlCl₃ mole fractions with dimeric aluminum trichloride (Eq 2.27 and 2.28). Chloroaluminates are well known, however other ionic liquids may also be prepared from a halide and Lewis acid (Table 2.12).

**Table 2.12: Examples of ionic liquids that can be generated by the reaction of a halide with a Lewis acid**

<table>
<thead>
<tr>
<th>Ionic Liquid a</th>
<th>Established anion</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>[cation]Cl/AlCl₃</td>
<td>Cl⁻, AlCl₄⁻, Al₂Cl₇⁻, Al₃Cl₁₀⁻</td>
<td>250, 251</td>
</tr>
<tr>
<td>[cation]Cl/AlEtCl₂</td>
<td>AlEtCl₃⁻, Al₂Et₂Cl₅⁻</td>
<td>252</td>
</tr>
<tr>
<td>[cation]Cl/BCl₃</td>
<td>Cl⁻, BCl₄⁻</td>
<td>253</td>
</tr>
<tr>
<td>[cation]Cl/CuCl</td>
<td>CuCl₂⁻, Cu₂Cl₅⁻, Cu₃Cl₄⁻</td>
<td>254</td>
</tr>
<tr>
<td>[cation]Cl/SnCl₂</td>
<td>SnCl₃⁻, Sn₂Cl₅⁻</td>
<td>255</td>
</tr>
</tbody>
</table>

a cation = pyridinium or imidazolium ion.
Ionic liquids of the type [cation][A] are formed using Step IIb, (Scheme 2.10) and contain only one anion species once the exchange reaction reaches completion (Table 2.13).

Table 2.13: Examples of ionic liquids prepared by anion exchange

<table>
<thead>
<tr>
<th>Ionic Liquid a</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>[cation]BF₄</td>
<td>256,257</td>
</tr>
<tr>
<td>[cation]PF₆</td>
<td>258</td>
</tr>
<tr>
<td>[cation]SbF₆</td>
<td>259</td>
</tr>
<tr>
<td>[cation]NO₃</td>
<td>260</td>
</tr>
<tr>
<td>[cation]CH₃CO₂</td>
<td>261</td>
</tr>
<tr>
<td>[cation]HSO₄</td>
<td>262</td>
</tr>
<tr>
<td>[cation]B(Et₃Hex)</td>
<td>263</td>
</tr>
</tbody>
</table>

a cation = pyridinium, imidazolium, ammonium ion.

The above-mentioned methods can also be used to prepare previously unknown combinations of cations and anions that may result in low-melting salts with the possibility to obtain ionic liquids with new properties.²⁶⁴

4.4 Acidity and coordination ability of ionic liquids

The acidity and coordination properties of an ionic liquid are dependant on the nature of its anion. Different anions realise many intermediate levels between “strongly basic/strongly coordinating” and “strongly acidic/practically non-coordinating” (Table 2.14).²⁶⁵

Table 2.14: Coordinative characteristics of various anions

<table>
<thead>
<tr>
<th>Basic/strongly coordinating</th>
<th>Acidity/coordination</th>
<th>Acidic/non-coordinating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl⁻</td>
<td>AlCl₄⁻</td>
<td>Al₂Cl₇⁻</td>
</tr>
<tr>
<td>NO₃⁻</td>
<td>CuCl₂⁻</td>
<td>Al₃Cl₁₀⁻</td>
</tr>
<tr>
<td>SO₄²⁻</td>
<td>SbF₆⁻</td>
<td>Cu₂Cl₅⁻</td>
</tr>
<tr>
<td></td>
<td>BF₄⁻</td>
<td>Cu₃Cl₄⁻</td>
</tr>
</tbody>
</table>

Scheme 2.16 illustrates the ionic liquids that produce a neutral anion (e.g. AlCl₄⁻) or an acidic anion (e.g. Al₂Cl₇⁻) from a basic anion (e.g. Cl⁻) by addition of a Lewis acid (e.g. AlCl₃).
Scheme 2.16: Acidity control of ionic liquids by the ratio of halide to Lewis acid exemplified for 1-ethyl-3-methylimidazolium (EMIM) chloroaluminate melt

Chloroaluminate melts qualify as basic when the molar ratio of AlCl\textsubscript{3} is smaller than 0.5. A neutral melt has an AlCl\textsubscript{3} ratio of exactly 0.5, and essentially only the anion AlCl\textsubscript{4}\textsuperscript{-} is present.\textsuperscript{266} Finally, an acidic chloroaluminate melt is one in which the AlCl\textsubscript{3} ratio is larger than 0.5 and consists of the anions Al\textsubscript{2}Cl\textsubscript{7}\textsuperscript{-} and Al\textsubscript{3}Cl\textsubscript{10}\textsuperscript{-} which act as very strong Lewis acids.\textsuperscript{267,268}

“Latent acidity” and “super acidity” are two interesting phenomena in the field of acid base chemistry in ionic liquids.

Latent acidity of ionic liquid arises when weak bases are added to buffered neutral chloroaluminate ionic liquid. These neutral ionic liquids are formed when excess alkali metal chloride (MCl) is added to an acidic chloroaluminate ionic liquid (Equation 2.28).\textsuperscript{269,270} The alkali metal chloride (MCl) reacts with the acidic chloroaluminate dimers until the ionic liquid becomes neutral.

\[
\text{Al}_{2}\text{Cl}_{7}^{\ominus} + \text{MCl} \rightleftharpoons 2\text{AlCl}_{4}^{\ominus} + \text{M}^{\oplus}
\] (2.28)

A buffered ionic liquid is one in which the neutrality is maintained by reaction of excess alkali metal chloride when acid AlCl\textsubscript{3} is added. The latent acidity of this neutral system becomes observable when a weak base (B) such as N,N-dimethylaniline, pyrrole, or acetylferrrocene is added.\textsuperscript{271,272} Reaction between the added base and the AlCl\textsubscript{3} results in adduct formation with precipitation of the alkali chloride MCl (Eq 2.29).

\[
\text{B} + \text{AlCl}_{4}^{\ominus} + \text{M} \rightleftharpoons \text{B-AlCl}_{3}^{\ominus} + \text{MCl}_{(s)}
\] (2.29)

The reaction is not detected in the absence of excess alkali metal cations. The latent acidity of different ionic liquids have been quantitatively measured by Osteryoung et al.\textsuperscript{273}

Superacidity have been observed when strong mineral acids were dissolved in acidic chloroaluminate ionic liquids.\textsuperscript{274,275} Smith\textsuperscript{276} and co-workers investigated the acidity of
ionic liquids by the protonation of aryl compounds with a solution of HCl gas in acidic [EMIM]Cl/AlCl₃ ionic liquids and the acidity were measured quantitatively by UV spectroscopy. Acid strength was obtained as a function of the ionic liquid’s acidity, which was clearly above that of 100% sulphuric acid (Fig 2.8).²⁷⁷

The superacidity of chloroaluminate ionic liquids is explained by the reaction of the dissolved hydrogen chloride and the acidic species in the melt, which releases protons with extremely low solvation and thus very high reactivity (Eq 2.30).

\[
\text{HCl} + \text{Al}_2\text{Cl}_7^- \rightleftharpoons [\text{H}]^{+}\text{ nonsolvated} + 2\text{AlCl}_4^- \quad (2.30)
\]

![Figure 2.8: Acid strength of super acid ionic liquids compared to conventional super acids](image)

Superacidic ionic liquids are much safer and easier to handle compared to normal super acid systems and could therefore represent promising alternatives to the conventional super acids.²⁷⁸

The cation of an ionic liquid can also influence the acidity of a system and a weak Lewis acidity is attributed by the imidazolium ion itself. The catalytic effect of imidazolium bromide melts in Diels-Alder reactions is reported to be related to this weak acidity of the imidazolium ion.²⁷⁹ Moreover, the H atom in the α-position of an imidazolium ion possesses significant Brønsted acidity which could be beneficial for reactions involving transition metal complexes as in situ carbene complexes can be formed in the presence of base.²⁸⁰
4.5 Ionic Liquids as Solvents for Transition Metal Catalyzed Reactions

Ionic liquids are being researched extensively in the fields of hydrogenation,\textsuperscript{281} oxidation,\textsuperscript{282} oligomerization,\textsuperscript{283} hydroformylation,\textsuperscript{284} Heck and Suzuki reactions,\textsuperscript{285} Trost-Tsuji couplings,\textsuperscript{286} Friedel-Crafts reactions,\textsuperscript{287} Diels-Alder reactions,\textsuperscript{288} electrophilic nitrations,\textsuperscript{289} and palladium catalysed carbonylation of aryl halides.\textsuperscript{290}

4.6 Formylation Reactions in Ionic Liquids

The unique properties of ionic liquids in general, allow these compounds to be versatile reagents and solvent for many reactions. The enhanced reactivity and isomer selectivity brought about by ionic liquids in many reactions may also be applicable to phenolic derivatives used in CO formylation, hence the interest to explore these possibilities.

The superacidity of chloro-aluminate melts, (\textit{cf} paragraph 4.4) allows them to be ideal candidates for CO formylations. In order to compare the formylation of phenolics to that of aromatic hydrocarbons in ionic liquids, a study of formylation using CO in an ionic liquid was started with toluene as substrate and acidic chloro-aluminate melts (Table 2.15). A 1:1 mol ratio of toluene to ionic liquid with mol fraction AlCl\textsubscript{3} = 0.67 gave moderate yields of the aldehyde derivative at mild temperature (Runs 1 and 2). When the ethyl-derivative of the melt was used, a slight increase in the conversion was observed which may be attributed to the higher solubility of CO in this specific melt.

Table 2.15: Formylation of aromatic substrates in chloro-aluminate ionic liquids at 83bar CO pressure*

<table>
<thead>
<tr>
<th>Run</th>
<th>Substrate (mmol)</th>
<th>Ionic Liquid (mmol)</th>
<th>Conditions</th>
<th>Products (%)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene (41)</td>
<td>BmimAlCl\textsubscript{4} (44)</td>
<td>rt 1h</td>
<td>p-Tolualdehyde (22)</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>o-Tolualdehyde (2.7)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Toluene (42)</td>
<td>EmimAlCl\textsubscript{4} (50)</td>
<td>rt 1h</td>
<td>p-Tolualdehyde (37)</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>o-Tolualdehyde (1)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Anisole (37)</td>
<td>BmimAlCl\textsubscript{4} (37)</td>
<td>rt 1h</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Anisole (39)</td>
<td>BmimAlCl\textsubscript{4} (38)</td>
<td>rt 1h AlCl\textsubscript{3} complexation followed by substrate addition</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Anisole (14)</td>
<td>BmimAlCl\textsubscript{4} (129)</td>
<td>70°C 1.5h</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Phenol (42)</td>
<td>EmimAlCl\textsubscript{4} (108)</td>
<td>60°C 4.5h</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Phenol (42)</td>
<td>BmimAlCl\textsubscript{4} (128) Cu\textsubscript{2}O 0.03g</td>
<td>45°C 0.5h</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*All reactions mol fraction(x) AlCl\textsubscript{3} in alkylmimCl = 0.67 except run 7 x(AlCl\textsubscript{3}) = 0.75
Subjecting anisole to similar reaction conditions however, led to no detectable formylation. Since Al-complexation to anisole could have effected a reduction in the acidity of the ionic liquid, it was decided to minimise this possibility by CO-Al pre-complexation. The ionic liquid was therefore pressurised with CO for a short period at room temperature before anisole addition at atmospheric pressure (Run 4). Apart from de-alkylation to phenol (<1%) together with alkylation of anisole to methoxy-2-methyl benzene, the bulk of the substrate remained unchanged. The lack of any formylation activity could arise from inadequate amounts of uncomplexed Al-ions, thus leading to lower acidity. The substrate was therefore treated with excess chloro-aluminate melt (3:1) and the substrate was introduced at 83bar CO pressure (Run 5). Although a slight increase in anisole dealkylation (compared to the previous run) was observed, the bulk of substrate remained unchanged. Addition of toluene to the reaction mixture and subsequent formation of tolualdehyde confirmed reaction conditions conducive to formylation.

Although it is known, that phenol cannot be formylated under ordinary Gattermann-Koch conditions,\textsuperscript{291} it was decided to evaluate acidic ionic liquids in this regard. Phenol was subjected to a chloro-aluminate ionic liquid containing (mol fraction AlCl\textsubscript{3} 0.67 vs. 0.75) an excess of AlCl\textsubscript{3}. The substrate however remained unchanged with no detectable aldehyde generation. Since it is also known that Gattermann-Koch formylations should either be performed at elevated pressures (100-250bar) or with addition of CuCl\textsuperscript{292} or Cu\textsubscript{2}O\textsuperscript{293} to enhance CO solubility through formation of Cu(CO)\textsubscript{4}\textsuperscript{+} species, the reaction was repeated in the presence of Cu\textsubscript{2}O. Again no aldehyde product could be detected. Although this result points towards the inadequate acidity of chloro-aluminate ionic liquids with regard to CO formylation of phenols, the solubility of CO and the unknown effect of the addition of the copper salts to IL’s on the solubility of CO in the IL’s may be a contributing factor. From these results, it is clear that chloro-aluminate ionic liquids are able to formylate methyl activated benzene derivatives, but not oxygen-containing aromatics.

The potential super acid capability of excess aqueous HBF\textsubscript{4} and HPF\textsubscript{6} in ionic liquid may facilitate formylation reactions of aromatics and were subsequently investigated. Toluene, being highly susceptible to CO formylation under acidic conditions, was therefore subjected to treatment with excess HPF\textsubscript{6} and HBF\textsubscript{4} in BmimPF\textsubscript{6} and BmimBF\textsubscript{4} respectively (Table 2.16, Runs 1 and 2). No formylation products were obtained which
may be explained in terms of the HBF$_4^-$ and HPF$_6^-$-water complexes being exceptionally stable and thus not acidic enough to facilitate the formylation reaction.

Table 2.16: Formylation of aromatic substrates in acidified neutral ionic liquids at 50bar CO pressure

<table>
<thead>
<tr>
<th>Run</th>
<th>Substrate (mmol)</th>
<th>Ionic Liquid (mmol)</th>
<th>Reagents (mmol)</th>
<th>Conditions</th>
<th>Products (%)</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene (37)</td>
<td>BmimPF$_6$ (18g)</td>
<td>aqHPF$_6$ (88)</td>
<td>rt 1h</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Toluene (40)</td>
<td>BmimBF$_4$ (17g)</td>
<td>aqHBF$_4$ (111)</td>
<td>rt 1h</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Phenol (21)</td>
<td>BmimBF$_4$ (14g)</td>
<td>CF$_3$SO$_3$H (106)</td>
<td>rt 1h</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Anisole (11)</td>
<td>OmimBTA (20g)</td>
<td>CF$_3$SO$_3$H (154)</td>
<td>45°C 4.5h</td>
<td>PAA (0.6) OAA (0) 10</td>
<td>Phenol (5)</td>
</tr>
</tbody>
</table>

Triflic acid is known as one of the strongest monoprotic organic acids (-H$_o$ = 14) and it is used in processes for production of aldehydes from alkyl benzenes have been described. It was decided to investigate whether this acid in IL’s can promote anisole formylation, despite the fact that this acid was not successfully used in this way even at high CO pressure. Anisole dissolved in omimBF$_4$ containing excess (5-14eq) triflic acid under CO was reacted at 45°C or at room temperature. Phenol in bmimBF$_4$ was treated in the same way. No formylation products were however obtained. Since BF$_3$ is known to form stable complexes with aldehydes thus rendering the reaction thermodynamically more favourable, subsequent reactions with triflic acid were carried out in the presence of excess BF$_3$ (8eq). PAA was obtained in only minute quantities while some de-alkylation of the substrate occurred (Run 4). Although triflic acid is in the range of low super acidity, it must therefore be concluded that its acidity is insufficient for formylation of oxygen containing aromatics.

It was now decided to revert to the use of HF/BF$_3$ and evaluate its efficacy in ionic liquids. If this super acid could be used in catalytic quantities and remain in the ionic liquid during separation of the product, it could form the basis of a viable industrial process. Toluene, anisole and phenol were successfully formylated in bmimBF$_4$ following HF/BF$_3$ acidification (Table 2.17, Runs 1, 2 and 3). The total aldehyde yield of phenol (32%) was significantly higher compared to both toluene (5%) and anisole (7%) under similar conditions. Although a reaction time of 12hours was allowed, the total aldehyde yield of all three substrates remained inferior to earlier results obtained (Table 2.2). The difference between conversion and aldehyde product obtained in the case of
toluene and anisole are mainly attributed to the formation of the same secondary products observed in the HF/BF₃ system (cf Figure 2.4).

Although these formylations gave some aldehyde product, yields remained poor and had to be improved if the process were to be any way near commercially applicable. While it is known that the physical properties of ionic liquids can be changed by utilizing different cationic- and anionic species, it has also been described that the solubility of gasses such as CO, O₂ and H₂ are influenced by the constituents of a particular ionic liquid. In general, it has been found that imidazolium cations with increased chain length favors high CO solubility while it is also enhanced by anions such as BF₄⁻ and BTA⁻. With this in mind the alkyl chain-length of the cations were changed from 4 to 8 and the anions from BF₄⁻ to PF₆⁻ to BTA⁻. Changing the ionic liquid cation from Bmim to Omim resulted in a dramatic increase in aldehyde yield for phenol (31 to 91%), but only a moderate improvement (7 to 26%) was reached in the case of anisole. Substituting the BF₄⁻ counter anion for PF₆⁻ afforded slightly lower aldehyde yields for anisole (Runs 7 and 8). When the PF₆⁻ counter anion was replaced with trifluoromethanesulfonimide (BTA) however, significantly higher aldehyde yields (45%) were obtained for anisole (Run 9). The increase in alkyl chain-length resulted in further improvement (Runs 9 and 10). The lower yields of PAA can be attributed to the formation of secondary products. The presence of even small amounts of moisture in the ionic liquid was detrimental to the formylation reaction (Run 12 compared to run 10).

Anisole was subjected to formylation with reduced amounts of HF (2eq) and BF₃ (0.5eq) under otherwise similar reaction conditions (Run 11). Although high conversion of anisole to phenol and alkylated phenol were observed, no aldehyde products were produced. It is thus clear that this particular type of ionic liquid is unable to facilitate the catalytic use of HF/BF₃ in formylation reactions.

Table 2.17: Formylation of aromatic substrates in acidified neutral ionic liquids at 50bar CO pressure

<table>
<thead>
<tr>
<th>Run</th>
<th>Substrate (mmol)</th>
<th>Ionic Liquid (mmol)</th>
<th>Reagents (mmol)</th>
<th>Conditions</th>
<th>Products (%)</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene (11)</td>
<td>BmimBF₄ (46g)</td>
<td>HF (555)</td>
<td>45°C 12h</td>
<td>p-Tolualdehyde (5)</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>Anisole (11)</td>
<td>BmimBF₄ (45g)</td>
<td>HF (555)</td>
<td>45°C 12h</td>
<td>PAA (7) OAA (0.2) Phenol (21)</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>Phenol (11)</td>
<td>BmimBF₄ (41g)</td>
<td>HF (550)</td>
<td>45°C 12h</td>
<td>PHBAlddehyde (31) OHBAlddehyde (1)</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>Phenol (11)</td>
<td>OmimBF₄ (20g)</td>
<td>HF (550)</td>
<td>rt 12h</td>
<td>PHBAlddehyde (83)</td>
<td>97</td>
</tr>
<tr>
<td>Run</td>
<td>Substrate (mmol)</td>
<td>Ionic Liquid (mmol)</td>
<td>Reagents (mmol)</td>
<td>Conditions</td>
<td>Products (%)</td>
<td>Conv. (%)</td>
</tr>
<tr>
<td>-----</td>
<td>-----------------</td>
<td>-------------------</td>
<td>----------------</td>
<td>------------</td>
<td>-------------</td>
<td>----------</td>
</tr>
<tr>
<td>5</td>
<td>Anisole (11)</td>
<td>OmimBF₄ (20g)</td>
<td>BF₃ (69)</td>
<td>45°C 6h</td>
<td>OHBAdehyde (8)</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td>Anisole (11)</td>
<td>OmimBF₄ (20g)</td>
<td>HF (550) BF₃ (59)</td>
<td>45°C 12h</td>
<td>PAA (26) OAA (2)</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>Anisole (11)</td>
<td>OmimPF₆ (20g)</td>
<td>HF (550) BF₃ (81)</td>
<td>45°C 4.5h</td>
<td>PAA (26) OAA (2)</td>
<td>84</td>
</tr>
<tr>
<td>8</td>
<td>Anisole (11)</td>
<td>HexmimPF₆ (20g)</td>
<td>HF (550) BF₃ (47)</td>
<td>45°C 4.5h</td>
<td>PAA (15) OAA (1)</td>
<td>67</td>
</tr>
<tr>
<td>9</td>
<td>Anisole (11)</td>
<td>OmimBTA (20g)</td>
<td>HF (550) BF₃ (61)</td>
<td>45°C 4.5h</td>
<td>PAA (45) OAA (2)</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>Anisole (11)</td>
<td>BmimBTA (20g)</td>
<td>HF (550) BF₃ (63)</td>
<td>45°C 1h</td>
<td>PAA (8) OAA (1) Phenol (2)</td>
<td>30</td>
</tr>
<tr>
<td>11</td>
<td>Anisole (300)</td>
<td>OmimBTA (20g)</td>
<td>HF (600) BF₃ (150)</td>
<td>45°C 4.5h</td>
<td>Phenol and alkylated anisole</td>
<td>76</td>
</tr>
<tr>
<td>12</td>
<td>Anisole (11)</td>
<td>BmimBTA (20g) 0.3% H₂O</td>
<td>HF (550) BF₃ (35)</td>
<td>45°C 4.5h</td>
<td>No reaction</td>
<td>-</td>
</tr>
</tbody>
</table>

### 4.7 Conclusions

Chloro-aluminate ionic liquids promote the carbonylation of alkylated aromatic compounds, but fails in the case of oxygenated aromatics. Aldehyde yields of formylation in the acidified neutral ionic liquids were generally similar compared to reactions conducted in HF as solvent/catalyst (cf Table 2.2). The increase in aldehyde yields with the use of extended alkyl chain lengths of the cationic part of the melt, may be due to improved CO solubility. HF/BF₃-acidified neutral ionic liquids showed both increases in para-selectivity compared to HF as solvent and catalyst. Formylation of anisole and toluene, but not of phenol in the neutral ionic liquids resulted in increased secondary product formation in comparison with hydrogen fluoride used as solvent/catalyst. This difference in behaviour is not understood at present, but suggests that phenol is a good substrate for formylation in this medium, particularly with the development of a system catalytic with respect to HF/BF₃ in mind.
4.8 REFERENCES


159 Degner D., Barl M., Siegel H., *DE 2848397* to BASF, **1978**.


Waffenschmidt H., *Dissertation*, RWTH Aachen, Germany, **2000**.


CHAPTER 3

EXPERIMENTAL

1 INTRODUCTION

The synthesis of aromatic aldehydes comprised the use of high pressures and extremely toxic reagents that also required the exclusion of moisture, not only to benefit reaction yields, but also to minimize corrosion of experimental apparatus. Naturally, the safety aspects surrounding the laboratory set-up were of paramount importance and should receive attention prior to commencement of experimental work.

1.1 Personal Protective Equipment

The use of personal protective equipment was essential, as hydrogen fluoride is notorious for inducing bony fluorosis, a condition that weakens the human skeletal structure through continuous inhalation of vapors and skin contact. This safety equipment consisted of special hydrogen fluoride resistant gloves, a long-sleeve suit and a face shield due to the high CO pressures employed.

1.2 Reactor

A 100ml Parr reactor constructed from Hasteloy-C and equipped with a gas entrainment stirrer with variable speed was used during all formylation reactions. Special PTFE seals were used as the normal acid resistant seals were incompatible with the HF/BF₃ combination.

1.3 Reagents

The high toxicity of reagents CO, HF and BF₃ necessitated all reactions to be conducted in a fume-hood.

2 GENERAL EXPERIMENTAL PROCEDURE

2.1 HF Formylation Reactions

Pre-cooled (4°C) substrate (10-300mmol, dried as described in 3.2.7) was added to the reactor positioned in an ice-bath under an inert gas flow (N₂). This was followed by
careful addition of hydrogen fluoride (0.6-2.5mol, 99.95%, Pelchem, 4°C) from a 1litre cylinder.

The reactor lid was sealed and the reactor pressurized with boron trifluoride (20-300mmol, 99.98%, Messer Griesheim) until the required mass was obtained whilst stirring. The required CO pressure (50-80bar, 99.99%) was applied and the resulting exotherm (3-10°C) aided in heating the mixture to the required temperature. On completion of the reaction (10min-24h), the reactor was cooled in ice water and the CO pressure released as reaction mixture reached temperature of 5°C. The reaction mixture was quenched in 500ml ice followed diethyl ether extraction (4x20ml). Neutralization of the acid using aqueous K2CO3 to pH=7 was followed by drying with Na2SO4. The course of the reaction was followed by GC analysis. The 1H, 13C and mass spectra of compounds formed in the formylation reaction are included as an addendum to the experimental section. Compounds formed in the formylation reaction were initially identified by analysis of the MS fragmentation patterns followed by direct comparison with authentic materials.

2.2 HF Formylation Reactions in Ionic Liquid

The same protocol as described in 3.2.1 was used for reactions conducted in ionic liquid which was added prior to the substrate. No extraction of the ionic liquid was done. Diethyl ether was added to reduce the viscosity of the reaction mixture followed by GC analysis.

2.3 Deuterium Fluoride Preparation and DF Formylation Reactions

A 600ml Parr reactor, used to produce the deuterium fluoride, was coupled via a ¼" stainless steel tubing to the 100ml Parr formylation reactor to enable transfer of the produced DF. To NaF (dried at 120°C for 3 days, 120g), D2SO4 (150g) was added drop-wise, whilst maintaining the 100ml reactor at –50°C using a CO2/ acetonitrile/ chloroform mixture. The NaF/D2SO4 mixture temperature was increased to 170°C and maintained for 2hours to distill the yielding 29gram of deuterium fluoride. Keeping the formylation reactor at –50°C, pre-cooled formylation substrate (29mmol) was added using a syringe followed by BF3 (58mmol) addition. The remaining formylation procedure is similar to that described in 3.2.1.
2.4 Preparation of di-(4-methoxyphenyl)methanol

In a round bottom flask 10 gram 4,4'-dimethoxybenzophenone (41.3 mmol) was dissolved in ethanol (200 ml) and THF (200 ml). To the solution 1.6 gram NaBH₄ (42.3 mmol) was added whilst stirring at rt. An additional 2 gram of NaBH₄ (52.9 mmol) was added with continued stirring overnight. The reaction mixture was quenched with 200 ml of acetone and distilled at 35°C and 300 mBar (Repeated 3x). The resultant borate salt was dissolved in water (100 ml) and the alcohol extracted with diethyl ether (50 ml). Vacuum distillation of the diethyl ether solution (40°C at 120 mbar) furnished the white alcohol crystals in quantitative yield. Water from the crystals was removed azeotropically with benzene.

2.5 Ionic Liquid Preparation

The ¹H-NMR spectra of ionic liquids prepared and used in the reactions are collected in an addendum to the experimental section.

2.5.1 1-Butyl-3-methylimidazolium chloride [bmim]Cl, 1-hexyl-3-methylimidazolium chloride [hexmim]Cl and 1-octyl-3-methyl-imidazolium-chloride [omim]Cl

1-methylimidazole (99%) was freshly distilled from CaH₂ and stored under argon and 4Å molecular sieves. A stirred mixture of distilled 1-methylimidazole (246 g, 3 mol), alkylhalide (1.6-3.6 mol, 99.5% anhydrous) was refluxed for 48 hours under argon. Subsequent formation of two layers was followed by separation and the excess chloroalkane was removed in vacuo at 120°C overnight. Quantities of alkylhalides: chlorobutane (3.6 mol), chlorohexane (1.6 mol), chloro-octane (1.6 mol)

2.5.2 1-Butyl-3-methylimidazolium trifluoromethane sulfonimide [bmim]-[N(SO₂CF₃)₂] or [bmim]BTA

To an aqueous solution of N-lithiotrifluoromethanesulfonyl amide (LiBTA) (24.69 g, 0.086 mol in 30 ml) was added an aqueous solution of [bmim]Cl (15.02 g, 0.086 mol in 30 ml) and the mixture was stirred for 2 h at rt. The [bmim]BTA produced was separated from the aqueous layer and washed with distilled water (5 x 100 ml) to remove residual LiCl salt. The ionic liquid was subsequently heated at 120°C under vacuum overnight to remove traces of water.
2.5.3 1-Octyl-3-methylimidazolium trifluoromethane sulfonimide [omim]-[N(SO$_2$CF$_3$)$_2$] or [omim]BTA

To an aqueous solution of $N$-lithiotrifluoromethanesulfonyl amide (LiBTA) (24.69g, 0.086mol in 30ml) was added an aqueous solution of [omim]Cl (19.85g, 0.086mol in 30ml) and the mixture was stirred for 2h at rt. The [omim]BTA produced was separated from the aqueous layer and washed with distilled water (5x100ml) to remove residual LiCl salt. The ionic liquid was subsequently heated at 120°C under vacuum overnight to remove traces of water.

2.5.4 1-Butyl-3-methylimidazolium tetrafluoroborate [bmim]BF$_4$

Fluoroboric acid (89.36g of 48% aqueous solution, 0.44mol) was added to an aqueous solution of [bmim]Cl (77.31g, 0.44mol in 140ml) at 0°C. Addition of the acid was gradually done with continuous stirring. After addition of the fluoroboric acid was completed, the temperature of the reaction medium was increased to 20°C and the mixture left overnight. Portions of dichloromethane (5x80ml) were used to extract the ionic liquid preceded the removal of traces of un-reacted fluoroboric acid with distilled water (10x100ml). Removal of the remaining dichloromethane and water occurred in vacuo at 120°C overnight.

2.5.5 1-Octyl-3-methylimidazolium tetrafluoroborate [omim]BF$_4$

In a similar procedure to 2.5.4, [omim]Cl (101.54g, 0.44mol in 140ml) was used.

2.5.6 1-Butyl-3-methylimidazolium hexafluorophosphate [bmim]PF$_6$

To an aqueous stirred solution of [bmim]Cl (118.19g, 0.6773mol in 150ml) at 0°C was added aqueous 50% excess hexafluorophosphoric acid (200ml of 60% solution). The resulting bi-phasic system was stirred for 4hours followed by dichloromethane extraction (5x80ml) to remove the ionic liquid. A water wash (10x100ml) using distilled water was used to remove un-reacted acid prior to the removal of dichloromethane and water in vacuo overnight at 120°C.

2.5.7 1-Hexyl-3-methylimidazolium hexafluorophosphate [hexmim]PF$_6$

To a stirring solution of [hexmim]Cl (137.31g, 0.6773mol) and water (150ml) at 0°C, 50% excess hexafluorophosphoric acid (200ml of 60% aqueous solution) was slowly added. The resulting bi-phasic system was stirred for 4hours followed by dichloromethane
extraction (5x80ml) to remove the ionic liquid. A water wash (10x100ml) using distilled water remove un-reacted acid. The dichloromethane and water were removed \textit{in vacuo} overnight at 120°C.

2.5.8 1-Octyl-3-methylimidazolium hexafluorophosphate [omim]PF$_6$

Using the same procedure as described in 3.2.4.6, aqueous stirred solution of [omim]Cl (156.30g, 0.6773mol) at 0°C was added to aqueous 50% excess hexafluorophosphoric acid (200ml of 60% solution).

2.5.9 1-Butyl-3-methylimidazolium tetrachloroaluminate [bmim]AlCl$_4$

\[ x(\text{AlCl}_3) = 0.67 \]

Freshly sublimed aluminum trichloride (99.9%, 89.34g, 0.67mol) was carefully added to [bmim]Cl (57.64g, 0.33mol) whilst stirring under an argon atmosphere. The resulting ionic liquid was stored under argon.

2.5.10 1-Butyl-3-methylimidazolium tetrachloroaluminate [bmim]AlCl$_4$

\[ x(\text{AlCl}_3) = 0.75 \]

Freshly sublimed aluminum trichloride (99.9%, 100.0g, 0.75mol) was carefully added to [bmim]Cl (43.67g, 0.25mol) whilst stirring under an argon atmosphere. The resulting ionic liquid was stored under argon.

2.5.11 1-Ethyl-3-methylimidazolium tetrachloroaluminate [emim]AlCl$_4$

\[ x(\text{AlCl}_3) = 0.67 \]

Freshly sublimed aluminum trichloride (99.9%, 89.34g, 0.67mol) was carefully added to [emim]Cl (48.38g, 0.33mol) whilst stirring under an argon atmosphere. The resulting ionic liquid was stored under argon.

2.6 Chromatography

2.6.1 Flash Column Chromatography

A glass column (15x350mm) was filled with silica gel (70-230mesh, 60Å, 100gram for each 1gram of product) mixed with the chosen mobile phase. Slight N$_2$ pressure (50kPa) was applied to force air bubbles out and a thin layer (5mm) of acid washed sand was
added onto the gel. The product was carefully applied on top of the sand and the pure components obtained through the chosen mobile phase in 10ml fractions.

2.6.2 Gas Chromatography

A Hewlett-Packard 4890 Series II equipped with a capillary, non-polar PONA column (50m x 0.25mm id x 0.25µm) and a glass liner split injector was used for quantifying purposes. Plate 26 indicates a typical gas chromatogram obtained of the reaction product after formylation. The following set points were used:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oven Temp</td>
<td>100°C</td>
</tr>
<tr>
<td>Initial Time</td>
<td>10 min</td>
</tr>
<tr>
<td>Rate</td>
<td>5°C/min</td>
</tr>
<tr>
<td>Final Temp</td>
<td>300°C</td>
</tr>
<tr>
<td>Detector</td>
<td>FID</td>
</tr>
<tr>
<td>Column Flow</td>
<td>1 ml/min</td>
</tr>
<tr>
<td>Split Flow</td>
<td>150 ml/min</td>
</tr>
<tr>
<td>Carrier Gas</td>
<td>Helium</td>
</tr>
</tbody>
</table>

Where possible the response factors of the different compounds with regard to the detector were determined using standard samples with known concentrations. Internal standards were used to quantify compounds in reaction mixtures. Retention times (minutes) of important constituents of products of formylation include the following:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retention Time (min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anisole</td>
<td>4.70</td>
</tr>
<tr>
<td>OAA</td>
<td>7.06</td>
</tr>
<tr>
<td>PAA</td>
<td>7.18</td>
</tr>
<tr>
<td>p-Methoxyacetophenone</td>
<td>8.13</td>
</tr>
<tr>
<td>Di(4-methoxydiphenylmethane isomer)</td>
<td>14.55</td>
</tr>
<tr>
<td>Dimethoxybenzophenone isomer</td>
<td>17.70</td>
</tr>
<tr>
<td>Trimethoxy-phenylmethane isomers</td>
<td>25.37 and 29.03</td>
</tr>
<tr>
<td>Toluene</td>
<td>4.41</td>
</tr>
<tr>
<td>o-tolualdehyde</td>
<td>6.42</td>
</tr>
<tr>
<td>p-tolualdehyde</td>
<td>6.59</td>
</tr>
<tr>
<td>Di-(methylphenyl)methane isomers</td>
<td>15.96 and 16.34</td>
</tr>
<tr>
<td>Di-(methylphenol)methanol isomer</td>
<td>20.16</td>
</tr>
<tr>
<td>Dimethylbenzophenone isomers</td>
<td>20.42 and 20.99</td>
</tr>
<tr>
<td>Tri-(methylphenyl)methane isomers</td>
<td>27.90 and 28.69</td>
</tr>
<tr>
<td>Compound</td>
<td>Retension Time (min.)</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Phenol</td>
<td>4.33</td>
</tr>
<tr>
<td>o-Hydroxybenzaldehyde</td>
<td>4.93</td>
</tr>
<tr>
<td>p-Hydroxybenzaldehyde</td>
<td>7.29</td>
</tr>
<tr>
<td>Di-(hydroxyphenyl)methane isomer</td>
<td>14.6</td>
</tr>
<tr>
<td>Dihydroxybenzophenone isomer</td>
<td>18.16</td>
</tr>
<tr>
<td>Tri-(hydroxyphenyl)methane isomer</td>
<td>32.47</td>
</tr>
</tbody>
</table>

### 2.7 Drying of Reagents

Drying of substrates were conducted in a still under inert (Ar) conditions using sodium metal lumps as drying agent and benzophenone as indicator.

### 2.8 Spectrometric and Spectroscopic Methods

#### 2.8.1 Nuclear Magnetic Resonance (NMR)

NMR spectroscopy was conducted on both a Bruker Avance 500 and a Varian Inova 400 instrument. Chemical shift as parts-per-million (ppm) on the $\delta$-scale and coupling constants (J) in Hz were used throughout. Unless stated otherwise, all NMR-spectra were recorded in CDCl$_3$ at 30°C with TMS as internal standard. The following abbreviations were used:

- s = singulet
- br = broad
- d = doublet
- t = triplet
- q = quartet
- i = impurity
- m = multiplet

#### 2.8.2 Mass Spectrometry (MS)

A Hewlett-Packard HP5973 mass spectrometer equipped with a photon multiplier was used for determination of accurate mass and recording of mass spectra. Unless stated otherwise, the molecular ion was generated via Electron Impact (EI). The following abbreviation was used:

- $M^+$ = molecular ion
- M.W. = molar weight
Addendum: NMR-, MS- and GC spectra of key compounds
Plate 1: $^1$H NMR spectrum of $p$-Anisaldehyde

Solvent: CDCl$_3$

<table>
<thead>
<tr>
<th>Proton</th>
<th>PPM</th>
<th>Multiplicity</th>
<th>Coupling Constant, (J)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,5</td>
<td>7.87</td>
<td>d</td>
<td>8.5</td>
</tr>
<tr>
<td>2,6</td>
<td>7.04</td>
<td>d</td>
<td>8.5</td>
</tr>
<tr>
<td>9a</td>
<td>9.92</td>
<td>s</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>3.92</td>
<td>s</td>
<td>-</td>
</tr>
</tbody>
</table>
Plate 2: $^1$H NMR spectrum of o-Anisaldehyde

Solvent: CDCl$_3$

<table>
<thead>
<tr>
<th>Proton</th>
<th>PPM</th>
<th>Multiplicity</th>
<th>Coupling Constant, (J)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4,5</td>
<td>7.00-6.98</td>
<td>m</td>
<td>-</td>
</tr>
<tr>
<td>9a</td>
<td>10.43</td>
<td>s</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>7.78</td>
<td>dd</td>
<td>1.8, 7.5</td>
</tr>
<tr>
<td>5</td>
<td>7.51</td>
<td>ddd</td>
<td>1.9, 7.3, 8</td>
</tr>
<tr>
<td>8</td>
<td>3.88</td>
<td>s</td>
<td>-</td>
</tr>
</tbody>
</table>
Plate 3. $^1$H NMR spectrum of 4,4'-dimetoxybenzophenone

Solvent: CDCl$_3$

<table>
<thead>
<tr>
<th>Proton</th>
<th>PPM</th>
<th>Multiplicity</th>
<th>Coupling Constant, (J)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,5,12,16</td>
<td>7.82</td>
<td>d</td>
<td>8.5</td>
</tr>
<tr>
<td>2,8,13,15</td>
<td>6.99</td>
<td>d</td>
<td>8.5</td>
</tr>
<tr>
<td>6,18</td>
<td>3.92</td>
<td>s</td>
<td>-</td>
</tr>
</tbody>
</table>

H3, 5, 12, 16

H2, 6, 13, 15

H8, 18

7.85 ppm

7.80 ppm

7.00 ppm

3.95 ppm
Plate 4: $^1$H NMR spectrum of Di-(4-metoxyphenyl)methane

Solvent: CDCl$_3$

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<th>Multiplicity</th>
<th>Coupling Constant (J)</th>
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<tbody>
<tr>
<td>3,5,11,15</td>
<td>7.12</td>
<td>d</td>
<td>8.5</td>
</tr>
<tr>
<td>2,6,12,14</td>
<td>6.85</td>
<td>d</td>
<td>8.5</td>
</tr>
<tr>
<td>9</td>
<td>3.90</td>
<td>br.s</td>
<td>-</td>
</tr>
<tr>
<td>8,17</td>
<td>3.81</td>
<td>s</td>
<td>-</td>
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</table>
Plate 5: $^1$H NMR spectrum of Tri(4-methoxyphenyl)methane

Solvent: CDCl$_3$

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<td>8,23,25</td>
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<tr>
<td>3,5,11,15,17,21</td>
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<td>2,6,12,14,18,20</td>
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<td>d</td>
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<tr>
<td>9</td>
<td>5.44</td>
<td>br.s</td>
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Plate 6: $^1$H NMR spectrum of p-Methoxyacetophenone

Solvent: CDCl$_3$
Plate 7: $^1$H NMR spectrum of Di(4-metoxyphenyl)methanol

Solvent: CDCl$_3$

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<tr>
<td>3,5,13,17</td>
<td>7.30</td>
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<tr>
<td>9</td>
<td>2.20</td>
<td>s</td>
<td></td>
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<tr>
<td>8,19</td>
<td>3.82</td>
<td>s</td>
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<tr>
<td>11</td>
<td>5.79</td>
<td>s</td>
<td></td>
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Plate 8: $^1H$ NMR spectrum of 1-Butyl-3-methylimidazolium tetrachloroaluminate [bmim]AlCl$_4$

Solvent: CDCl$_3$

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<th>Coupling Constant (J)</th>
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<tr>
<td>2</td>
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<td>30</td>
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<td>3</td>
<td>1.76</td>
<td>1.68 m</td>
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<td>4</td>
<td>1.26</td>
<td>1.16 m</td>
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<tr>
<td>5</td>
<td>0.76</td>
<td>t</td>
<td>4.2</td>
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<tr>
<td>6</td>
<td>8.24</td>
<td>s</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>7.23</td>
<td>s</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>7.19</td>
<td>s</td>
<td>-</td>
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Plate 9: $^1$H NMR spectrum of 1-Ethyl-3-methylimidazolium tetrachloroaluminate [emim][AlCl$_4$]

Solvent: CDCl$_3$

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<th>Coupling Constant (J)</th>
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<td>4.05-3.95</td>
<td>m</td>
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<tr>
<td>3</td>
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<td>7.8</td>
</tr>
<tr>
<td>6</td>
<td>9.10</td>
<td>s</td>
<td>-</td>
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<td>7</td>
<td>7.47</td>
<td>s</td>
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<td>8</td>
<td>7.41</td>
<td>s</td>
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[Diagram showing NMR peaks and assignments]
Plate 10: $^1$H NMR spectrum of 1-Butyl-3-methylimidazolium tetrafluoroborate [bmim]BF$_4$  

Solvent: CDCl$_3$  

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<th>Coupling Constant (J)</th>
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<td>2</td>
<td>4.21</td>
<td>t</td>
<td>-</td>
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<tr>
<td>3</td>
<td>1.83-1.86</td>
<td>m</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>1.44-1.36</td>
<td>m</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>0.99</td>
<td>t</td>
<td>7.5</td>
</tr>
<tr>
<td>6</td>
<td>8.86</td>
<td>br s</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>7.35</td>
<td>br s</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>7.30</td>
<td>br s</td>
<td>-</td>
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8.84 ppm  

4.20 ppm  

7.35 ppm  

4.00 ppm  

1.90 ppm  

1.45 ppm  

1.00 ppm
Plate 11: $^1$H NMR spectrum of 1-Octyl-3-methylimidazolium tetrafluoroborate [omim]BF$_4$

Solvent: CDCl$_3$

<table>
<thead>
<tr>
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<td>3</td>
<td>1.89</td>
<td>t</td>
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<td>4-8</td>
<td>1.40-1.20</td>
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<tr>
<td>9</td>
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<tr>
<td>12</td>
<td>8.78</td>
<td>s</td>
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<tr>
<td>13</td>
<td>7.42</td>
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<tr>
<td>14</td>
<td>7.35</td>
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Plate 12: $^1$H NMR spectrum of 1-Butyl-3-methylimidazolium hexafluorophosphate [bmim]PF$_6$

Solvent: CDCl$_3$

<table>
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<tr>
<th>Proton</th>
<th>PPM</th>
<th>Multiplicity</th>
<th>Coupling Constant (J)</th>
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<tbody>
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<td>1</td>
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<tr>
<td>2</td>
<td>4.12</td>
<td>t</td>
<td>7.0</td>
</tr>
<tr>
<td>3</td>
<td>1.86-4.77</td>
<td>m</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>1.35-1.25</td>
<td>m</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>0.88</td>
<td>t</td>
<td>7.0</td>
</tr>
<tr>
<td>6</td>
<td>0.37</td>
<td>br s</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>7.34</td>
<td>br s</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>7.30</td>
<td>br s</td>
<td>-</td>
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Diagram showing NMR peaks at various ppm values, including assignments for H9, H10, H8, H5, and H4.
Plate 14: $^1$H NMR spectrum of 1-Octyl-3-methylimidazolium hexafluorophosphate [omim]PF$_6$

Solvent: CDCl$_3$

<table>
<thead>
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<th>PPM</th>
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<th>Coupling Constant, (J)</th>
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<tr>
<td>3</td>
<td>1.90-1.83</td>
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<td>-</td>
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<tr>
<td>4-8</td>
<td>1.35-1.23</td>
<td>m</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>0.87</td>
<td>t</td>
<td>7.0</td>
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<tr>
<td>10</td>
<td>9.45</td>
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<tr>
<td>11</td>
<td>7.33</td>
<td>br s</td>
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<tr>
<td>12</td>
<td>7.30</td>
<td>br s</td>
<td>-</td>
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</table>
Plate 15. $^1$H NMR spectrum of 1-Butyl-3-methylimidazolium trifluoromethane sulfonimide [bmim]BTA

Solvent: CDCl$_3$

<table>
<thead>
<tr>
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<th>PPM</th>
<th>Multiplicity</th>
<th>Coupling Constant, (J)</th>
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<tbody>
<tr>
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<td>3.89</td>
<td>s</td>
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<td>4.12</td>
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<td>3</td>
<td>1.85</td>
<td>m</td>
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</tr>
<tr>
<td>4</td>
<td>1.36</td>
<td>m</td>
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<td>5</td>
<td>0.81</td>
<td>t</td>
<td>7.5</td>
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<tr>
<td>8</td>
<td>8.88</td>
<td>s</td>
<td>-</td>
</tr>
<tr>
<td>9-10</td>
<td>7.28</td>
<td>m</td>
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</table>
Plate 16: $^1H$ NMR spectrum of 1-Octyl-3-methylimidazolium trifluoromethane sulfonimide [omim]BTA

Solvent: CDCl$_3$

<table>
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<td>3</td>
<td>1.40-1.30</td>
<td>m</td>
<td>-</td>
</tr>
<tr>
<td>4-8</td>
<td>1.15-0.90</td>
<td>m</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>0.75-0.70</td>
<td>m</td>
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<tr>
<td>12</td>
<td>7.82</td>
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<tr>
<td>13-14</td>
<td>6.60</td>
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<td>1.3, 37.9</td>
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Plate 17: $^1$H NMR spectrum of anisole after treatment with DF/BF$_3$/CO
Plate 18: $^{13}$C NMR spectrum of anisole after treatment with DF/BF$_3$/CO
Plate 20: NOESY of anisole after treatment with DF/TF$_2$/CO

'H-6 in 15

OCH$_3$
Plate 21: $^1$H NMR spectrum of toluene after treatment with DF/BF$_3$/CO
Plate 22: $^{13}$C NMR spectrum of toluene after treatment with DF/BE$_3$/CO

$R=H$ or $D$
Plate 23: $^1$H NMR spectrum of toluene-$d_5$ after treatment with HF/BF$_3$/CO
Plate 24: $^1$H NMR spectrum of toluene-d$_8$ after treatment with $HF$/$BF_3$/ICO
Plate 25: Extension of $^{13}$C NMR spectrum of toluene-$d_8$ after treatment with HFBF$_3$ICO.
Plate 26: Example of a GC chromatogram on the formylation of anisole.
Plate 27: Mass spectrum of Methoxyacetophenone

M.W. = 150
Plate 28: Mass spectrum of Methoxybenzaldehyde
Plate 29: Mass spectrum of Di-(methoxyphenyl)methane
Plate 30: Mass spectrum of Dimethoxybenzophenone