ACTIVATION AND SYNTHETIC TRANSFORMATION OF ALDEHYDES AND ALDEHYDE EQUIVALENTS ENABLED BY ORGANOCATALYSTS

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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ACTIVATION AND SYNTHETIC TRANSFORMATION OF ALDEHYDES AND ALDEHYDE EQUIVALENTS ENABLED BY ORGANOCATALYSTS

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<tr>
<td>$^1$H NMR</td>
<td>proton nuclear magnetic resonance</td>
</tr>
<tr>
<td>$^{13}$C NMR</td>
<td>carbon-13 nuclear magnetic resonance</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1'-binaphthol</td>
</tr>
<tr>
<td>DMF</td>
<td>$N,N$-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>Ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray impact ionisation</td>
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<tr>
<td>HPLC</td>
<td>high Performance Liquid Chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectroscopy</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TFAA</td>
<td>trifluoroacetic acid anhydride</td>
</tr>
<tr>
<td>THF</td>
<td>tetrohydrofuran</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilane</td>
</tr>
<tr>
<td>TS</td>
<td>transition state</td>
</tr>
<tr>
<td>Rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>$p$-TSA</td>
<td>$p$-toluenesulfonic acid</td>
</tr>
<tr>
<td>DNBA</td>
<td>2,4-dinitrobenzenesulfonic acid</td>
</tr>
<tr>
<td>NHC</td>
<td>$N$-heterocyclic carbene</td>
</tr>
<tr>
<td>$^\circ$C</td>
<td>degree centigrade</td>
</tr>
<tr>
<td>microliter(s)</td>
<td></td>
</tr>
<tr>
<td>CDCl$_3$</td>
<td>deuterated chloroform</td>
</tr>
<tr>
<td>h or hrs</td>
<td>hours</td>
</tr>
<tr>
<td>$J$</td>
<td>coupling constant(s)</td>
</tr>
<tr>
<td>$m/z$</td>
<td>mass per charge ratio</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>--------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Min</td>
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<tr>
<td>mol%</td>
<td>mole percent</td>
</tr>
<tr>
<td>Ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>'Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyl dimethylsilane</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butyl diphenylsilane</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicycloundec-7-ene</td>
</tr>
<tr>
<td>DIPEA</td>
<td>N,N-diisopropylethylamine</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>Equiv</td>
<td>equivalent(s)</td>
</tr>
<tr>
<td>Mes</td>
<td>2,4,6-trimethylphenyl</td>
</tr>
<tr>
<td>DHA</td>
<td>1,3-dihydroxyacetone</td>
</tr>
<tr>
<td>PSI</td>
<td>pounds per Square Inch</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butyl carbonate</td>
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<td>Xinqiang Fang, Kun Jiang, <strong>Chong Xing</strong>, Lin Hao and Yonggui Robin Chi*</td>
<td><em>Angew. Chem. Int. Ed.</em> 2011, 50, 1910-1913</td>
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<td>Brønsted Acid Catalyzed α-Alkylation of Aldehydes with Diaryl Methyl Alcohols</td>
<td><strong>Chong Xing</strong>, Hui Sun, Junmin Zhang, Guohui Li, Yonggui Robin Chi*</td>
<td><em>Chem. A. Eur. J.</em> 2011, 17, 12272-12275</td>
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</tr>
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<td>Junmin Zhang, Bhoopendra Tiwari, <strong>Chong Xing</strong>, Xingkuan Chen and Yonggui Robin Chi*</td>
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<td></td>
</tr>
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<td>Highly Enantioselective Addition of Enals to Isatin-Derived Ketimines Catalyzed by N-Heterocyclic Carbenes: Synthesis of Spirocyclic γ-Lactams</td>
<td>Hui Lv, Bhoopendra Tiwari, Junming Mo, <strong>Chong Xing</strong>, and Yonggui Robin Chi*</td>
<td><em>Org. Lett.</em> 2012, 14, 5412-5415</td>
<td></td>
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<td>Junmin Zhang, <strong>Chong Xing</strong>, and Yonggui Robin Chi*</td>
<td><em>J. Am. Chem. Soc.</em> 2013, 135, 8113-8116</td>
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Abstract

Functionalization of carbonyl compounds has been intensively studied for a long time as carbonyl compounds are commonly used building blocks in organic synthesis. Asymmetric organocatalysis is becoming an increasingly useful approach since its first application in 2000. It is complementary and sometimes better approach to metal catalysis. Different activation modes and catalysts were developed to activate the carbonyl compounds. In this thesis, we tried to use various organocatalysts to activate aldehydes to undergo C-C bond formation reactions.

In the second chapter, amine catalysts were used to catalyze the α-alkylation of aldehydes with indole derived diaryl alcohols. *Anti*-selective products with good yields and enantioselectivities were generated, and their selectivities were opposite to that obtained in literature. Brønsted acids were added as co-catalysts to aid the formation of carbocations. Later, similar acids, as sole catalysts, were found to catalyze the S_{N}1-type alkylation of aldehydes with diaryl alcohols as described in the third chapter. Besides the role to generate the carbocations, acids also accelerated the enolization of aldehydes. Allylic alcohols and α,α-disubstituted aldehydes were effective substrates for this strategy. For the above two reactions, DFT calculations were carried out to support the proposed transition states and reaction pathways. The fourth chapter deals with the activation of carbohydrates as formaldehyde equivalent for the Stetter reaction with chalcones using N-heterocyclic carbene (NHC) catalysis. Carbohydrates such as C6-, C5- and
C4-sugars worked well. Among them C5-sugars gave the best results. Paraformaldehyde as formaldehyde precursor was also studied. The Stetter products could be obtained with good yields in both cases.
Chapter 1

Introduction
1.1 Organocatalysis and its development

Organocatalysis has been known for more than a century, as a concept that makes use of small organic molecules as catalysts to facilitate the generation of useful products. In the past decade, this field has seen exponential growth, and has received increasing attention from researchers all over the world. There are several reasons for this rapid development of organocatalysis. First, the organocatalysts are relatively stable in air and water, and easy to synthesize. Some of these catalysts can be obtained from biological materials. Besides, they are non-toxic and less harmful to the environment. Also, it has been shown that organic catalysts are able to facilitate many types of reactions that are found to work with metal catalysts.

Different activation modes have been developed in these years to activate various kinds of nucleophiles and electrophiles. These activation modes can be categorized mainly into 3 different types, namely HOMO activation, LUMO activation and SOMO activation.

1.2 HOMO activation

Highest Occupied Molecular Orbital (HOMO) activation is generally used to activate carbonyl nucleophiles. Enamine catalysis was the first to be realized through HOMO activation, followed by tertiary amine catalysis, phase transfer catalysis and N-heterocyclic carbene catalysis.
1.2.1 Enamine catalysis

In 1971, an enantioselective intramolecular aldol reaction catalyzed by L-proline to synthesize the Wieland-Mischecher ketone was reported by two independent groups (Zoltan Hajos and David Parrish; Rudolf Weichert, Gerhard Sauer and Ulrich Eder) (Scheme 1.1).\(^6\) Although excellent results were reported in these studies, this field did not receive much further attention and virtually remained undeveloped for another three decades. Until 2000, when Barbas and List developed the first intermolecular aldol reaction using L-proline as enamine catalyst.\(^7\) Products with moderate to good yields and high enantioselectivities were obtained (Scheme 1.2). Since then, innumerable studies on enamine catalysis have been reported, thereby expanding substantially the scope of this mode of catalysis.

![Scheme 1.1 L-proline catalyzed intramolecular aldol reaction](image1.png)

**Scheme 1.1** L-proline catalyzed intramolecular aldol reaction

![Scheme 1.2 L-proline catalyzed intermolecular aldol reaction](image2.png)

**Scheme 1.2** L-proline catalyzed intermolecular aldol reaction

The enamine activation involves the use of an amine (primary or secondary
amine) as catalyst. It reacts with a carbonyl compound (ketones and aldehydes) to initially form imine/iminium intermediate, which then tautomerizes to a nucleophilic enamine (Scheme 1.3). This strategy has been successfully applied on many types of transformations, including aldol reactions and Mannich reactions, as well as α-functionalization of aldehydes and ketones.

\[
\text{R} = \text{O} + \text{R}_1^1 \text{NR}_2^2 \overset{\text{R}}{\longrightarrow} \text{R}^1 \text{NR}_2^2 \overset{\text{R}}{\longrightarrow} \text{R}^1 \text{NR}_2^2
\]

Scheme 1.3 Enamine formation

1.2.2 N-heterocyclic carbene catalysis

N-heterocyclic carbene (NHC) catalysis has been extensively investigated in the past decade and has received great interest among researchers due to its ability to reverse the polarity of reactants. In 1958, Breslow achieved a self-benzoin reaction of benzaldehyde in the presence of thiamine (containing a thiazolium moiety) via an acyl anion intermediate (Scheme 1.4).[8] In this paper, he proposed the generation of enol/enaminol, commonly known as the Breslow intermediate, from the condensation of benzaldehyde and reactive thiazolium carbene catalyst. After that, various types of NHC catalysts have been developed and demonstrated to catalyze many benzoin reactions, including asymmetric benzoin condensations and cross-benzoin condensations.
In the early 1970s, Stetter successfully extended the thiazolium-catalyzed nucleophilic acylation to Michael acceptors and used $\alpha,\beta$-unsaturated ketones to trap the acyl anion intermediate. A broad range of thiazolium catalysts could be used to catalyze the Stetter reaction to give products with good yields (Scheme 1.5). Later in 1989 the first asymmetric Stetter reaction was reported by Enders and co-workers. Later, many types of triazolium catalysts were designed to facilitate this reaction, giving the Stetter products with high yields and enantioselectivities.

Build on the path breaking study and mechanistic insights provided by Breslow, the groups of Bode and Glorius independently extended the NHC catalysis to $\alpha,\beta$-unsaturated aldehyde for the generation of a conjugated acyl anion commonly referred as homoenolate. $\gamma$-Butyrolactones were obtained in moderate to good yields, favoring the formation of cis-diastereomers using commercially available bis-arylimidazolium salt as catalyst (Scheme 1.6).
Later in 2006, the Bode group reported the first NHC catalyzed Diels–Alder reaction by trapping the enolate intermediate using α,β-unsaturated imines.\(^{[11]}\) Azadiene Diels–Alder products were obtained with excellent stereoselectivities. More sterically demanding catalysts, such as a mesityl group on the nitrogen atom at the triazolium unit were necessary for this reaction (Scheme 1.7).

Under different reaction conditions, enals in reaction with NHC can produce three different intermediates such as acyl anions, enolates and homoenolates (Scheme 1.8). Therefore, a suitable manipulation of the reaction conditions, such as catalysts, additives and electrophiles, can lead to the formation of different products from the same substrates.

**Scheme 1.6** Homoenoate intermediate of enals

**Scheme 1.7** Enolate intermediate of enals
1.3 LUMO activation

Lowest Unoccupied Molecular Orbital (LUMO) activation, on the other hand, is used to activate electrophiles. In recent years, the LUMO activation strategy has been thoroughly studied employing different class of catalysts like iminium catalysis,\(^{[12]}\) H-bonding catalysis,\(^{[13]}\) Brønsted acid catalysis\(^{[14]}\) and so on.

1.3.1 Iminium catalysis

Around the same time as enamine catalysis, iminium catalysis was first developed by the MacMillan group in 2000.\(^{[15]}\) It was originally designed to activate \(\alpha,\beta\)-unsaturated aldehydes or ketones by the initial formation of an activated iminium species (Scheme 1.9). It has proved to be very useful for certain organocatalytic reactions like cycloadditions, Friedel-Crafts alkylations and so on.
In 2000, MacMillan and co-workers introduced the first enantioselective organocatalytic Diels-Alder reaction between \( \alpha,\beta \)-unsaturated aldehydes and cyclopentadiene using a chiral imidazolidinone as catalyst, which is more commonly known as the MacMillan catalyst.\(^{[15]}\) Products with good yields and enantioselectivities were obtained, giving the \textit{exo} and \textit{endo} diastereomer in the ratio of about 1:1 (Scheme 1.10).

\[
\begin{align*}
\text{H} & \quad \text{C} = \text{O} \quad \text{Ph} \\
& \quad \text{N} \quad \text{H} \\
\text{R} & \quad \text{Cl} \\
\end{align*}
\]

\begin{align*}
\text{H} & \quad \text{C} = \text{O} \quad \text{Ph} \\
& \quad \text{N} \quad \text{H} \\
\text{R} & \quad \text{Cl} \\
\end{align*}

\text{MeOH-H}_2\text{O, rt} \\
\text{75-99\% yield} \\
84-93\% \text{ ee}

\textbf{Scheme 1.10} Cycloaddition via iminium activation

One year later, they disclosed the first enantioselective organocatalytic Friedel-Crafts alkylation using \( N \)-methyl pyrrole and \( \alpha,\beta \)-unsaturated aldehydes as substrates.\(^{[16]}\) The MacMillan catalyst was very effective for this reaction, giving alkylation products with high yields and enantioselectivities (Scheme 1.11).

\[
\begin{align*}
\text{H} & \quad \text{C} = \text{O} \quad \text{Ph} \\
& \quad \text{N} \quad \text{H} \\
\text{R} & \quad \text{N} \\
\end{align*}
\]

\begin{align*}
\text{H} & \quad \text{C} = \text{O} \quad \text{Ph} \\
& \quad \text{N} \quad \text{H} \\
\text{R} & \quad \text{N} \\
\end{align*}

\text{MeOH-H}_2\text{O, rt} \\
\text{72-90\% yield} \\
87-93\% \text{ ee}

\textbf{Scheme 1.11} Alkylation of pyrrole via iminium activation
1.3.2 H-bonding catalysis

In the 1980s, several reports appeared on the asymmetric transformations involving H-bonding interactions in substrates activation.\cite{17} This mode of activation was not well recognized until the late 1990s, when Jacobsen and Corey independently reported the asymmetric Strecker reactions, in which H-bonding catalysts were used to activate the imine electrophiles.\cite{18}

\[ \text{Scheme 1.12 Thiourea catalyzed Strecker reaction} \]

In Jacobsen’s study, a well designed thiourea Schiff base was utilized to catalyze the asymmetric Strecker reaction to give products with good yields and enantioselectivities (Scheme 1.12). While in Corey’s case, a bicyclic guanidine was used instead to generate Strecker products with excellent results (Scheme 1.13).

\[ \text{Scheme 1.13 Guanidine catalyzed Strecker reaction} \]
Later in 2002, the Jacobsen group reported an asymmetric Mannich reaction catalyzed by similar thiourea catalyst to synthesize β-aryl-β-amino acids (Scheme 1.14).\textsuperscript{19} Through this successful example, the H-bonding strategy was proved to be able to catalyze other synthetic reactions. From then on, many H-bonding catalysts and asymmetric reactions have been developed by researchers all over the world.

\begin{center}
\textbf{Scheme 1.14} Thiourea catalyzed Mannich reaction
\end{center}

Besides thiourea catalysts, there are many other useful types of H-bonding catalysts such as taddols and cyclic dipeptide (Figure 1.1). Although they have different framework and $pK_a$ in solvent, they all share the common activation mode to activate the electrophiles through H-bonding interactions.

\begin{center}
\textbf{Figure 1.1} taddol and cyclic dipeptide
\end{center}
1.3.3 Brønsted Acid catalysis

Compared to Lewis acids, Brønsted acids have been much less developed as catalysts for carbon-carbon formation reactions. They are relatively stable toward water and oxygen and are very easy to handle. Very recently, this field has gained momentum and several reports related to Brønsted acids catalyzed reactions have emerged.

Achiral Brønsted acids have been used quite often since the late 1980s. The Denmark group reported the intramolecular addition of allylsilane to acetal.\(^{[20]}\) They investigated a lot of Lewis acids in their research and found that a catalytic amount of trifluoromethanesulfonic acid could also furnish the products efficiently by acting as a Brønsted acid catalyst (Scheme 1.15).

![Scheme 1.15 Brønsted acids catalyzed addition of allylsilane to acetal](image)

Chiral Brønsted acids have been investigated intensively in these past years and it has become a useful strategy for enantioselective carbon-carbon bond formation. They can be also identified as H-bonding catalysts, but due to their strong acidity in reaction conditions, they are typically classified as Brønsted acids and are represented by BINOL derivatives and phosphoric acids.
In 2003, Schaus and co-workers introduced the enantioselective Morita-Baylis-Hillman reaction catalyzed by a BINOL derivative in the presence of a catalytic amount of triethylphosphine, giving products with moderate to good yields and high enantioselectivities.\(^{[21]}\) Both aromatic and aliphatic aldehydes could be used as effective substrates in this transformation (Scheme 1.16).

![Scheme 1.16 BINOL derivative catalyzed Morita-Baylis-Hillman reaction](image)

Then in the year of 2004, Akiyama and Terada group reported the use of chiral phosphoric acids as Brønsted acid catalysts to catalyze the Mannich reactions of \(N\)-aryl\(^{[22]}\) and \(N\)-Boc\(^{[23]}\) imines separately (Scheme 1.17). The catalysts were prepared from chiral BINOL, with different substitution groups on the 3 and 3’ positions. Excellent results were obtained in both cases. In Terada’s case,
Mannich products with high yields and enantioselectivities could be obtained at room temperature with a very low catalyst loading.

1.4 SOMO activation.

Single Occupied Molecular Orbital (SOMO) activation was first developed by the MacMillan group in 2006. It involves the generation of a reactive radical cation intermediate with three π-electrons by removal of one electron from the enamine that can react with different “SOMOphiles”. Enantioselective α-allylation of aldehydes was first realized using the MacMillan catalyst and CAN as the oxidant (Scheme 1.18). Formal aldehyde alkylation products were obtained with good yields and excellent enantioselectivities. Although SOMO catalysis is a relatively new activation mode, it has already been used in many enantioselective transformations.

\[
\begin{align*}
\text{O} & \quad \text{H} \\
\text{R}^1 & \quad \text{R}^1 \\
\text{SiMe}_3 & \quad \text{SiMe}_3
\end{align*}
\]

\[
\begin{align*}
\text{Bn} & \quad \text{Bn} \\
\text{TFA} & \quad \text{TFA}
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{R}^1 & \quad \text{R}^1 \\
\text{R} & \quad \text{R}
\end{align*}
\]

\[
\begin{align*}
\text{70-88\% yield} & \quad \text{70-88\% yield} \\
\text{87-95\% ee} & \quad \text{87-95\% ee}
\end{align*}
\]

**Scheme 1.18** SOMO activation of aldehydes

1.5 Summary and future challenges

Organocatalysis has attracted researchers’ attention in the past few years and
tremendous efforts have been made towards its development. It has many advantages compared to metal catalysis. First, the catalysts used are usually cheap and easy to synthesize from the naturally occurring materials such as amino acids. Also, the reactions do not need inert conditions, and proceed at room temperature most of the time. Besides, they are environmentally benign and do not generate toxic waste.

Although there has been a tremendous success in this area in the past several years, several challenges have still remained. An example would be the catalyst design, since existing organic catalysts are not efficient enough for many reactions and the catalyst loadings are much higher than metal catalysts. This has limited their applications in the complex natural product synthesis. The development of new activation modes is needed to further demonstrate the usage of organocatalysis.

1.6 References


Chapter 2

Proline catalyzed α-alkylation of aldehyde with indole derived alcohols

anti-selective
up to 71% yield, 12:1 d.r., 94% ee
2.1 Introduction

2.1.1 Enamine activation of aldehydes

Asymmetric catalysis has become more and more important in organic synthesis. Primary and secondary amines have been widely used in the functionalization of carbonyl compounds through HOMO,[1] LUMO[2] or SOMO[3] activations. There are generally two types of chiral amine catalysts that are commonly used in enamine catalysis. The first type is hydrogen bonding catalyst represented by the simple L-proline catalyst 2.A and the other type of catalyst mainly brings in enantioselectivities by the steric effects, like the frequently used catalyst 2.B (Figure 2.1).

![Figure 2.1 Commonly used enamine catalysts](image)

L-Proline was first used as amine catalyst in the year of 2000 by List to achieve the direct intermolecular asymmetric aldol reaction between acetone and a variety of aldehydes.[4] Products with moderate to good yields and enantioselectivities were obtained (Scheme 2.1). The reaction could be performed at room temperature in the open air without prior modification of the carbonyl compounds. Also the L-proline catalyst is inexpensive and readily available from nature, and could be easily removed from the reaction mixture by extraction as it is
water soluble.

\[
\begin{align*}
\text{H} & + \text{H} \\
\text{N} & + \text{H} \\
\text{O} & + \text{H} \\
\text{N} & + \text{H} \\
\text{O} & + \text{H} \\
\end{align*}
\]

Scheme 2.1 L-proline catalyzed aldol reaction

In 2005, the Hayashi group developed a new type of diphenylprolinol silyl ether catalyst to catalyze the Michael addition of aldehydes to nitroalkenes (Scheme 2.2).\(^5\) Compared to L-proline, this new catalyst could give products with excellent yields and enantioselectivities due to the steric effect of the bulky trimethylsilyl ether group. This type of catalyst was proved to be very useful in enamine catalysis in subsequent studies.

\[
\begin{align*}
\text{H} & + \text{Ph} \\
\text{Me} & + \text{Ph} \\
\end{align*}
\]

Scheme 2.2 Chiral pyrrolidine catalyzed Michael addition

Also in 2005, the Jørgensen group introduced a modified diphenylprolinol ether catalyst with two trifluoromethyl group on each phenyl ring.\(^6\) It was proved to be very efficient in \(\alpha\)-functionalizations of aldehydes, such as \(\alpha\)-amination, \(\alpha\)-halogenation and \(\alpha\)-sulfenylation, to give products with high yields and enantioselectivities (Scheme 2.3).
Concurrently and independently, the Gellman group reported a Michael addition of aldehydes to simple enones using a diphenylprolinol methyl ether catalyst.\[^7\] This diphenylprolinol methyl ether catalyst efficiently catalyzed the reactions and products were obtained with good yields and high enantioselectivities using a very low catalyst loading (Scheme 2.4).

2.1.2 \(\alpha\)-Alkylation of aldehydes with indole derived alcohols

In 2000, MacMillan and co-workers reported an enantioselective organocatalytic Friedel-Crafts alkylation through iminium catalysis.\[^8\] Indole substrates were utilized to react with \(\alpha,\beta\)-unsaturated aldehydes to give indole alkylation products with good yields and enantioselectivities (Scheme 2.6).
However, only simple α,β-unsaturated aldehydes could be successfully used for this strategy due to the limitations of the iminium activation.

![Scheme 2.5 Indole alkylation of aldehydes](image)

The Gong group introduced an enantioselective alkylation of enamides using indole derived alcohols catalyzed by a chiral Brønsted acid.\[^9\] β-Aryl 3-(3-indolyl) propanones were obtained in high yields and excellent enantioselectivities using BINOL-based chiral phosphoric acid (Scheme 2.6).

![Scheme 2.6 Chiral Brønsted acid catalyzed alkylation of enamides](image)

In 2008, Melchiorre and co-workers used arylsulfonyl as the leaving group to generate in situ reactive carbocation intermediates as the electrophiles with the assistance of KF/alumina as a base.\[^10\] By using L-proline as the amine catalyst, they were able to achieve up to 90% ee for 2-substituted indole-derived substrates (R = H) in good diastereoselectivities (Scheme 2.7). When unsubstituted aryl indole sulfonyl derivatives (R = H) was used as the electrophile, both the
enantioselectivities and diastereoselectivities dropped significantly (3:1 dr, 11% ee).

\[
\begin{align*}
\text{Scheme 2.7} & \quad \text{Indole alkylation using aryl arylsulfonyl type precursor} \\
\end{align*}
\]

2.1.3 Our proposal

As mentioned in the earlier section (Scheme 2.7), Melchiorre and co-workers’ protocol for the alkylation of aldehydes with indole derivatives failed when unsubstituted aryl indole sulfonyl derivatives (R = H) was used. To overcome these limitations, we planned to start our study using indole derived alcohol as the electrophile in the presence of proline or proline-derived catalysts, as the acidity of the catalyst will help in situ the generation of the cation intermediate (Scheme 2.8).

\[
\begin{align*}
\text{Scheme 2.8} & \quad \text{Different conditions to generate indole intermediate} \\
\end{align*}
\]

In the KF/alumina system, basic conditions were necessary to generate the reactive intermediates. However, the basic conditions might diminish the hydrogen
bonding interactions between L-proline and the substrates, leading to decreased enantioselectivities. We hypothesized that the use of indole alcohols as precursors to generate the reactive intermediates under acidic conditions might give better results than those obtained when L-proline were used as the catalyst.

2.2 Results and discussion

The results of our initial studies are summarized in Table 2.1. We initially carried out this reaction using only L-proline as the catalyst, in the absence of an acid co-catalyst (Table 2.1, entry 1). Under this condition, no desired product was observed after 24 hours at room temperature in dichloromethane. We speculated that the carboxylic group in L-proline was not acidic enough to generate the reactive intermediate, so an external acid might be necessary. To our delight, when 10 mol% phenylphosphoric acid was added, the desired product was detected in 42% yield and 5:1 dr in dichloromethane (Table 2.1, entry 2). Further screening of the solvent showed that dichloromethane was the best solvent in terms of product yield and diastereomer selectivity (Table 2.1, entries 3-8). Acetonitrile and toluene barely gave any products, while other solvents like THF, DMF and IPA could generate products with decreased yields and diastereoselectivities.

After obtaining the optimal solvent, we next examined the effect of different acid co-catalysts in this transformation. Various carboxylic acids, boric acid and sulfonic acid were tested in this reaction (Table 2.1, entries 9-17), with all of them
affording the desired products in different yields and diastereoselectivities. Boric acids E and F could give pretty good diastereoselectivities, albeit with poor yields. Different carboxylic acids lead to different yields and diastereoselectivities due to their different acidities. Of all the carboxylic acids that were tested, 3-nitrobenzoic acid could give the best result in 53% yield and 6:1 dr (Table 2.1, entry 15). Two enantiomers of camphorsulfonic acid were found to give the desired product with similar diastereoselectivities and yields (Table 2.1, entries 16-17).

**Table 2.1 Optimization of alkylation of aldehyde 2.1a with indole alcohol 2.2a**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid (mol%)</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>CH₂Cl₂</td>
<td>&lt;1</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>A(10)</td>
<td>CH₂Cl₂</td>
<td>42</td>
<td>5:1</td>
</tr>
<tr>
<td>3</td>
<td>A(10)</td>
<td>THF</td>
<td>33</td>
<td>2:1</td>
</tr>
<tr>
<td>4</td>
<td>A(10)</td>
<td>CH₃CN</td>
<td>&lt;1</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>A(10)</td>
<td>DMF</td>
<td>38</td>
<td>2:1</td>
</tr>
<tr>
<td>6</td>
<td>A(10)</td>
<td>IPA</td>
<td>36</td>
<td>3:1</td>
</tr>
<tr>
<td>7</td>
<td>A(10)</td>
<td>toluene</td>
<td>&lt;1</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>A(10)</td>
<td>DMSO</td>
<td>20</td>
<td>2:1</td>
</tr>
<tr>
<td>9</td>
<td>B(10)</td>
<td>CH₂Cl₂</td>
<td>18</td>
<td>4:1</td>
</tr>
<tr>
<td>10</td>
<td>C(10)</td>
<td>CH₂Cl₂</td>
<td>22</td>
<td>5:1</td>
</tr>
<tr>
<td>11</td>
<td>D(10)</td>
<td>CH₂Cl₂</td>
<td>51</td>
<td>4:1</td>
</tr>
</tbody>
</table>
During our $^1$H NMR analysis of the crude reaction mixture for the estimation of yields and diastereoselectivities, there was always some benzaldehyde detected in the reaction mixture. We believed that it originated from the decomposition of the indole derived alcohols, since the indole substrates were prepared by the direct addition of indole to benzaldehyde under basic conditions. This could explain the moderate yields of this reaction and why different acids could affect the yields so much. When weak acids were used in the reaction, the acidity was not strong enough to generate the reactive intermediates. However, the indole alcohols decomposed quickly when strong acids were utilized, which lead to low yields of desired products.

Table 2.2 Optimization of alkylation of aldehyde 2.1a with indole alcohol 2.2a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid (mol%)</th>
<th>L-Proline (mol%)</th>
<th>Yield (%)&lt;sup&gt;[b]&lt;/sup&gt;</th>
<th>dr&lt;sup&gt;[c]&lt;/sup&gt;</th>
<th>ee&lt;sup&gt;[d]&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>10</td>
<td>&lt;1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>AcOH (10)</td>
<td>10</td>
<td>18</td>
<td>4:1</td>
<td>28</td>
</tr>
</tbody>
</table>

[a] 0.8 mmol 2.1a was reacted with 0.4 mmol 2.2a in 0.4 mL CH$_2$Cl$_2$ for 24 h. [b] NMR yield. [c] Measured via crude $^1$H NMR analysis.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>Ratio</th>
<th>Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>PhCOOH</td>
<td>50</td>
<td>5:1</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>62</td>
<td>6:1</td>
<td>53</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>72</td>
<td>7:1</td>
<td>44</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>80</td>
<td>4:1</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>84</td>
<td>9:1</td>
<td>34</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>94</td>
<td>12:1</td>
<td>32</td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>94</td>
<td>12:1</td>
<td>72</td>
</tr>
</tbody>
</table>

[a] 0.8 mmol 2.1a was reacted with 0.4 mmol 2.2a in 0.4 mL CH$_2$Cl$_2$ for 24 h. [b] NMR yield. [c] Measured via crude $^1$H NMR analysis. [d] Determined via chiral phase HPLC analysis. [e] Reaction at 0 °C. [f] 2.0 mL CH$_2$Cl$_2$ was used. [g] 72h, isolated yield.

Having established the optimal acid and solvent conditions, we continued to tune other parameters to achieve the best enantioselectivity (Table 2.2). Among the carboxylic acids tested previously, 3-nitrobenzoic acid also gave the best enantioselectivity of 62% at room temperature (Table 2.2, entry 4). Further optimization including reducing the L-proline catalyst loading and decreasing the reaction concentration and temperature all contributed to a rise in the enantioselectivity (Table 2.2, entries 5-8). Finally, by using 5 mol% L-proline and 10 mol% 3-nitrobenzoic acid as catalysts, 71% of desired product was isolated after 72 hours at 0 °C (Table 2.2, entry 9).

The effectiveness of the combined L-proline/acid catalytic system was demonstrated to be general for various kinds of aldehydes and indole derived alcohols, as summarized in Table 2.3. Good to excellent diastereo- and enantio-selectivities were observed, and all the reactions gave acceptable isolated yields. First we tried different types of aliphatic aldehydes to react with indole alcohol 2.2a and the results were very good (Table 2.3, entries 1-5) except the one
with \( R^1 \) as bulky isopropyl group (Table 2.3, entry 4) which gave product with low dr and enantioselectivity. We next examined the scope of the indole derived alcohol. Different substitutions could be tolerated on the phenyl ring, such as a methyl and isopropyl group, leading to similar yields and stereoselectivities (Table 2.3, entries 6-10). It is noteworthy that indole substrates with strong electron donating groups (e.g. OMe) on the phenyl ring were not good substrates for this reaction and gave products only in a trace amount. We also subjected bromo substituted indole substrate (\( R^3 = \text{Br} \)) under this standard condition and obtained the product in good yield and selectivity (Table 2.3, entry 11). We used this product 2.3k to determine the absolute configuration by X-ray crystallographic analysis.

![Figure 2.1 X-Ray structures of 2.3a and 2.3k](image-url)
Table 2.3 Scope of alkylation of aldehyde 2.1 with alcohol 2.2

![Diagram of alkylation process]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;, R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Yield (%)&lt;sup&gt;[[b]]&lt;/sup&gt;</th>
<th>dr&lt;sup&gt;[[c]]&lt;/sup&gt;</th>
<th>ee&lt;sup&gt;[[d]]&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.3a</td>
<td>Me</td>
<td>Ph, H</td>
<td>71</td>
<td>12:1</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>2.3b</td>
<td>Et</td>
<td>Ph, H</td>
<td>80</td>
<td>14:1</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>2.3c</td>
<td>Pr</td>
<td>Ph, H</td>
<td>80</td>
<td>11:1</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>2.3d</td>
<td>'Pr</td>
<td>Ph, H</td>
<td>78</td>
<td>8:1</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>2.3e</td>
<td>Bn</td>
<td>Ph, H</td>
<td>70</td>
<td>15:1</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>2.3f</td>
<td>Me</td>
<td>p-Br-Ph, H</td>
<td>76</td>
<td>12:1</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>2.3g</td>
<td>Me</td>
<td>1-Naph, H</td>
<td>71</td>
<td>9:1</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>2.3h</td>
<td>Me</td>
<td>p-1Pr-Ph, H</td>
<td>76</td>
<td>9:1</td>
<td>88</td>
</tr>
<tr>
<td>9</td>
<td>2.3i</td>
<td>Me</td>
<td>p-Me-Ph, H</td>
<td>78</td>
<td>9:1</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td>2.3j</td>
<td>Et</td>
<td>p-Me-Ph, H</td>
<td>79</td>
<td>12:1</td>
<td>88</td>
</tr>
<tr>
<td>11</td>
<td>2.3k</td>
<td>Me</td>
<td>Ph, Br</td>
<td>74</td>
<td>8:1</td>
<td>88</td>
</tr>
</tbody>
</table>

[a] 0.4 mmol 2.1 was reacted with 0.8 mmol 2.2 in 2 mL CH<sub>2</sub>Cl<sub>2</sub>. [b] Yield of isolated product. [c] Measured via crude <sup>1</sup>H NMR analysis. [d] Determined via chiral phase HPLC analysis.

The L-proline and acid combination was also found to be effective when 2-subsituted indole derived alcohols were used as the substrates. In these cases, results similar to those reported by Melchiorre were observed.<sup>[[10]]</sup> The extension of this L-proline and acid approach to other diaryl alcohols like bis(p-dimethyaminophenyl)methanol did not give satisfactory results.
Table 2.4 Syn-selective alkylation of aldehyde 2.1 with alcohol 2.2a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>R</th>
<th>Yield (%)</th>
<th>dr</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>syn-2.3a</td>
<td>Me</td>
<td>92</td>
<td>2.4:1</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>syn-2.3b</td>
<td>Et</td>
<td>88</td>
<td>2.8:1</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>syn-2.3c</td>
<td>Pr</td>
<td>81</td>
<td>3.5:1</td>
<td>96</td>
</tr>
</tbody>
</table>

[a] 0.4 mmol 2.1 was reacted with 0.8 mmol 2.2a in 2 mL CH₂Cl₂. [b] Yield of isolated product. [c] Measured via crude ¹H NMR analysis. [d] Determined via chiral phase HPLC analysis.

We also examined the combined use of chiral pyrrolidine 2.B and 3-nitrobenzoic acid as catalysts for this reaction. In this condition, the reaction favored syn-selective formation of products compared to the anti-selectivity in the presence of L-proline and was completed in two days at room temperature to give good yields and enantioselectivities, as summarized in Table 2.4. The diastereoselectivities were not good in this condition and the products were obtained with 2.4:1 to 3.5:1 dr. Lowering the reaction temperature to 0 °C resulted in a slow reaction without a significant enhancement in diastereo- and enantio-selectivities. It is worthy to note that when 1-propanal was used to generate the product syn-2.3a, the enantioselectivity could only reach 74%, while the use of other long chain aliphatic aldehydes could give up to 96% ee. The reason for low ee with 1-propanal might be that the stereoselectivities were mainly induced by the steric effects of chiral pyrrolidine 2.B. Hence, 1-propanal with a
less sterically bulky methyl group, might not be a good choice for this specific transformation. The group of Loh reported a highly diastereo- and enantio-selective reaction for these types of aldehydes during our condition optimization studies.\textsuperscript{[11]}

Based on the experimental results, we proposed a plausible reaction pathway (Scheme 2.9). The aldehyde is first activated by the enamine catalyst (L-proline or diphenylprolinol silylether) to generate a reactive enamine nucleophile. At the same time, an indole carbocation intermediates is produced from indole alcohols under the acidic conditions. After the reaction of these two reactive intermediates, hydrolysis takes place to give desired products and regenerates the amine catalyst to complete the catalytic circle. Our \textit{anti}-selectivity in product formation using L-proline as the catalyst was different to Melchiorre’s observation\textsuperscript{[10]} of \textit{syn}-selectivity in analogous reactions using 2-substituted indole substrates.
In the L-proline catalyzed reaction, after the formation of two reactive intermediates, the electrophile approached the enamine nucleophile from the same face of the L-proline carboxylate due to the electrostatic interaction between L-proline carboxylate and the carbocation intermediate (Scheme 2.10). As a result, anti-selective products were obtained by using L-proline and acid as the catalysts. However, in the case of chiral diphenylprolinol silyl ether 2.B as the amine catalyst, the stereochemistry was mainly induced by the steric effects. The approach of carbocation intermediates favored the back side of the bulky group in catalyst 2.B and resulted in the syn-selective products (Scheme 2.11). Due to the lack of hydrogen bonding interactions in the transition states in the presence of diphenylprolinol silyl ether catalyst, the diastereoselectivities were not as good as the ones observed in the L-proline catalyzed reactions.
2.3 Calculations

2.3.1 Computational Methods

To confirm our proposed transition states, we also did some computational studies. Our calculations were carried out at both the HF/6-31g(d,p) level and the B3LYP/6-31g(d,p) level. All the stationary points for the isolated reactants, products, possible intermediates and transition states were located by performing full geometry optimization without any symmetric restriction, and their nature (local minima or first-order saddle points) were identified by performing frequency calculations. It should be noted that some transition structures were only obtained at the HF/6-31g(d,p) level and not at the B3LYP/6-31g(d,p) level. However, this would not affect the whole results. All calculations were completed by using Gaussian 03 program package. For all the cited energies, the zero-point energy corrections were taken into account.

2.3.2 Calculation Results and Discussion

The formation and hydrolysis mechanisms of enamine catalysis were widely studied in the theoretical fields. E-enamine A1 (from L-proline) or E-enamine A2 (from catalyst 2.B) was supposed to be formed in the reactions as the reactive intermediates (Figure 2.2). Therefore, their formation and hydrolysis pathways would not be considered in our calculations.
Under the catalysis of the Brønsted acid (3-nitrobenzoic acid), four possible intermediates C1, C2, C3, C4 could be generated from indole alcohol 2.2a (Figure 2.3). Through calculations, we found out that C1 and C3 were generated relatively more easily. Thus we took C1 and C3 into later calculation. We first calculated the energy profiles for the reactions between A1 and C1 or C3 via Re-Si pathway (Figure 2.4). The results showed that C3 was more favourable in the reaction with A1 than C1, so we considered C3 as the major intermediate for later calculations.

We then calculated the four different transition states for the reaction between enamine A1 and C3 through four different pathways (Figure 2.5). The transition states indicated that the Re-Si pathway was the most favourable to give the product anti-2.3a with the absolute configuration as indicated in the above discussion. We then switched the enamine to A2, and the results indicated that the product could be most likely generated through the Si-Re pathway to give syn-2.3a (Figure 2.6).
Figure 2.3 Possible intermediates derived from 2.2a. The values in parentheses are the relative energies (kcal/mol) at the B3LYP/6-31g(d,p) level (black) and at the HF/6-31g(d,p) level (blue).

Figure 2.4 Energy profiles with the optimized geometries for the reaction of enamine A1 with C1 (red) and C3 (black) along the Re-Si pathway. The values in parentheses are the energies (kcal/mol) of stationary points relative to the corresponding isolate reactants at HF/6-31G(d,p) level. Distances are in Å.
Figure 2.5 Transition States for C3 intermediate attacking on the enamine A1 along four pathways. The values in square brackets and parentheses are the energies (kcal/mol) of transition states relative to the corresponding isolate reactants and their precursors at the B3LYP/6-31g(d,p) level (black) and at the HF/6-31g(d,p) level (blue), respectively. Distances are in Å.

Figure 2.6 Transition structures for C3 intermediate attacking on the enamine A2 along four pathways. The values in square brackets and parentheses are the energies (kcal/mol) of transition states relative to the corresponding isolate reactants and their precursors at the HF/6-31g(d,p) level (blue), respectively. Distances are in Å.
2.4 Conclusions

In summary, we have developed a L-proline catalyzed anti-selective alkylation of aldehydes with indole derived diaryl alcohols with the assistance of a Brønsted acid. Various kinds of products could be obtained with good yields and stereoselectivities. By using chiral diphenylprolinol silyl ether catalyst, syn-selective products could be generated with high yields and enantioselectivities, but with moderate diastereoselectivities. The simplicity in substrates preparation and easy access of the L-proline and acid catalysts may make this approach useful and attractive.

2.5 Experimental

2.5.1 Materials and Instrumentation

Commercially available materials purchased from Alfa Aesar or Aldrich were used as received, except aldehydes that were purified via distillation prior use. Proton nuclear magnetic resonance (\(^1\)H NMR) spectra were recorded on a JEOL ECA400 (400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, \(\delta\)) relative to tetramethylsilane (\(\delta 0.00\)). \(^1\)H NMR splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets), m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear
magnetic resonance ($^{13}$C NMR) spectra were recorded on a JEOL ECA400 (400 MHz) spectrometer. High resolution mass spectral analysis (HRMS) was performed on Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). The determination of enantioselectivity was performed via chiral HPLC analysis using Shimadzu LC-20AD HPLC workstation. X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractometer. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a PerkinElmer Model 341 digital polarimeter and are reported as follows: $[\alpha]_D$ (c in g per 100 mL solvent). Analytical thin layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp or potassium permanganate stain.

2.5.2 General Procedures

1) A general procedure for preparation of indole derived diaryl alcohol 2.2a$^{[10]}$:

A 10 mL flask was charged with indole (6 mmol), benzaldehyde (2 mmol), and tetramethylguanidine (TMG, 0.4 mmol). Then 2 mL H$_2$O was added to the flask and the resultant was stirred at room temperature for 24 hours. 10 mL EtOAc and 10 mL H$_2$O were added to the solution. The organic phase was separated and the water phase was extracted three times each by 10 mL EtOAc. Then the organic phase was combined and dried over anhydrous Na$_2$SO$_4$. The product was obtained by flash chromatography (hexane: AcOEt 5:1).
2) **A general procedure of the alkylation of aldehyde:** To a 5 mL vial equipped with a small magnetic stir bar was added 0.4 mmol of indole substrate, 0.04 mmol 3-nitrobenzoic acid (10 mol%), 0.02 mmol amine catalyst (5 mol%) and 0.8 mmol aldehyde (2.0 eq.) in CH$_2$Cl$_2$ (2 mL). The mixture was stirred at 0 °C for 72 hours. The reaction progress was monitored by $^1$H NMR analysis of the crude reaction mixture. For crude $^1$H NMR analysis, 50 μL crude reaction mixture was mixed with 650 μL CDCl$_3$ for $^1$H NMR analysis. After the reaction was completed, the crude reaction mixture was purified via SiO$_2$ column chromatography eluting with EtOAc/hexane to give the desired product (mixture of two diastereomers) with good yield. The diastereoselectivities of the reactions were determined by $^1$H NMR analysis of the crude reaction mixtures before work up.

3) Compound **2.3a** (Table 2.3, entry 1) was recrystallized via evaporation of a solution of the compound in CH$_2$Cl$_2$/hexane to give white crystals as a single (major) diastereomer. The relative configuration was determined via X-ray diffraction to be anti. The anti-selectivity was different from that observed by Melchiorre in their work using 2-substituted indole derived diaryl alcohols. The relative (anti-) stereochemistry was further confirmed by X-Ray structure of compound **2.3k** crystallized at a similar condition as that of **2.3a**. The presence of a Br atom as a heavy atom in **2.3k** also allowed the determination of the absolute configuration of **2.3k**.
4) A general procedure to determine the enantiomeric excess (ee) by reducing the aldehyde product to the corresponding alcohol: To a stirred solution of aldehyde (2.3a-j) in MeOH (10 mL) at 0 °C was added excess NaBH₄ (2.0 mmol, 76 mg). The mixture was stirred for a few minutes, and methanol was then removed by rotation evaporator. Saturated NaHCO₃ aqueous solution (about 10mL) was added and the mixture was extracted with EtOAc (about 3 x 10 mL). Extraction of the product into the organic phase was monitored by TLC analysis. The organic layers were combined, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated to give the crude alcohol product, which was purified via column chromatography eluting with EtOAc/hexane to give the desired alcohol for HPLC analysis.

5) X-Ray data of compound anti-2.3a

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<th>Identification code</th>
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<tr>
<td>Empirical formula</td>
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<td>Formula weight</td>
<td>263.33 g</td>
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<tr>
<td>Temperature</td>
<td>103(2) K</td>
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<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
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Crystal system: Orthorhombic

Space group: P2(1)2(1)2(1)

Unit cell dimensions:
- a = 8.94230(10) Å, a= 90°
- b = 9.5528(2) Å, b= 90°
- c = 16.4907(2) Å, g = 90°

Volume: 1408.70(4) Å³

Z: 4

Density (calculated): 1.242 Mg/m³

Absorption coefficient: 0.077 mm⁻¹

F(000): 560

Crystal size: 0.40 x 0.30 x 0.28 mm³

Theta range for data collection: 2.47 to 36.13°

Index ranges:
- -13≤h≤14, -15≤k≤15,
- -27≤l≤23

Reflections collected: 22851

Independent reflections: 3771 [R(int) = 0.0376]

Completeness to theta = 36.13°: 99.9%

Absorption correction: Semi-empirical from equivalents

Max. and min. transmission: 0.9789 and 0.9700

Refinement method: Full-matrix least-squares on F²

Data / restraints / parameters: 3771 / 0 / 182

Goodness-of-fit on F²: 1.088
Final R indices [I>2\text{sigma}(I)] \quad R1 = 0.0419, \text{ wR2} = 0.1118

R indices (all data) \quad R1 = 0.0545, \text{ wR2} = 0.1245

Largest diff. peak and hole \quad 0.498 and -0.459 e.Å⁻³

6) X-Ray data of compound \textit{anti-2.3k} to determine absolute configuration

- Identification code: cyg20s
- Empirical formula: C₁₈H₁₆BrN₅O
- Formula weight: 342.23
- Temperature: 103(2) K
- Wavelength: 0.71073 Å
- Crystal system: Orthorhombic
- Space group: P2₁2₁2₁
- Unit cell dimensions:
  - a = 18.3331(4) Å \quad \text{a} = 90°.
  - b = 7.4370(2) Å \quad \text{b} = 90°.
  - c = 11.2648(3) Å \quad \text{g} = 90°.
- Volume: 1535.88(7) Å³
- Z: 4
- Density (calculated): 1.480 Mg/m³
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<td>Max. and min. transmission</td>
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2.5.3 Characterization of Products

(1H-Indol-3-yl)(phenyl)methanol (2.2a): 65% yield; ¹H NMR (400 MHz, CDCl₃): δ 2.22 (d, 1H, J = 4.1 Hz), 6.17 (d, 1H, J = 3.6 Hz), 6.95 (d, 1H, J = 2.3 Hz), 7.06-7.51 (m, 8H), 7.60 (d, 1H, 2.2a)
\( J = 7.3 \text{ Hz}), \ 8.06 \text{ (br, 1H).} \ 1^3\text{C NMR (100 MHz, CDCl}_3): \ \delta 70.4, \ 111.3, \ 119.8, \ 119.9, \ 120.0, \ 122.5, \ 122.8, \ 125.9, \ 126.6, \ 127.5, \ 128.4, \ 136.7, \ 143.6. \ HRMS (ESI, \ m/z): \ \text{calcd for C}_{15}\text{H}_{14}\text{NO}^+ [M+H]^+: 224.1075; \ \text{found: 224.1078.}

(4-Bromophenyl)(1H-indol-3-yl)methanol (2.2b): 43% yield;

\[\begin{align*}
\text{1H NMR (400 MHz, CDCl}_3): & \ \delta 2.18 \text{ (d, 1H, } J = 3.7 \text{ Hz)}, \ 6.12 \text{ (d, 1H, } J = 3.6 \text{ Hz)}, \ 6.97 \text{ (d, 1H, } J = 2.3 \text{ Hz)}, \ 7.07-7.48 \text{ (m, 7H)}, \ 7.56 \text{ (d, 1H, } J = 7.8 \text{ Hz)}, \ 8.08 \text{ (br, 1H).} \\
\text{1^3\text{C NMR (100 MHz, CDCl}_3): } & \ \delta 73.7, \ 111.3, \ 116.7, \ 119.9, \ 120.1, \ 121.1, \ 122.5, \ 123.6, \ 126.0, \ 129.1, \ 131.3, \ 136.7, \ 141.5. \ HRMS (ESI, m/z): \ \text{calcd for C}_{15}\text{H}_{13}\text{BrNO}^+ [M+H]^+: 302.0181; \ \text{found: 302.0178.}
\end{align*}\]

(1H-Indol-3-yl)(naphthalen-1-yl)methanol (2.2c): 58% yield;

\[\begin{align*}
\text{1H NMR (400 MHz, CDCl}_3): & \ \delta 2.31 \text{ (d, 1H, } J = 4.6 \text{ Hz)}, \ 6.75 \text{ (d, 1H, } J = 2.3Hz), \ 6.92 \text{ (d, 1H, } J = 4.6Hz), \ 7.15-7.26 \text{ (m, 2H)}, \ 7.36-7.55 \text{ (m, 4H)}, \ 7.80-7.89 \text{ (m, 5H)}, \ 8.01 \text{ (d, 1H, } J = 8.2 \text{ Hz).} \\
\text{1^3\text{C NMR (100 MHz, CDCl}_3): } & \ \delta 57.4, \ 111.4, \ 117.7, \ 119.9, \ 120.2, \ 122.5, \ 123.9, \ 124.5, \ 124.8, \ 125.6, \ 125.7, \ 126.0, \ 126.9, \ 128.4, \ 128.8, \ 131.6, \ 134.1, \ 136.7, \ 136.8. \ HRMS (ESI, m/z): \ \text{calcd for C}_{19}\text{H}_{16}\text{NO}^+ [M+H]^+: 274.1232; \ \text{found: 274.1225.}
\end{align*}\]
(1H-Indol-3-yl)(4-isopropylphenyl)methanol (2.2d): Sticky liquid; 60% yield; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.26 (d, 6H, $J = 6.9$ Hz), 2.29 (br, 1H), 2.88-2.95 (m, 1H), 6.14 (s, 1H), 6.92-7.43 (m, 8H), 7.62 (d, 1H, $J = 8.2$ Hz), 8.10 (br, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 24.1, 33.9, 70.4, 111.3, 119.8, 119.9, 120.0, 122.4, 122.7, 125.9, 126.5, 126.6, 136.7, 141.0, 148.2. HRMS (ESI, $m/z$): calcd for C$_{18}$H$_{20}$NO$^+$ [M+H]$^+$: 266.1545; found: 266.1547.

(1H-Indol-3-yl)(p-tolyl)methanol (2.2e): 62% yield; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.17 (d, 1H, $J = 3.6$ Hz), 2.35 (s, 3H), 6.14 (d, 1H, $J = 2.7$ Hz), 6.97-7.39 (m, 8H), 7.59 (d, 1H, $J = 7.8$ Hz), 8.06 (br, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 21.2, 70.4, 111.3, 119.8, 119.9, 120.1, 122.5, 122.7, 125.9, 126.6, 129.1, 136.7, 137.2, 140.7. HRMS (ESI, $m/z$): calcd for C$_{16}$H$_{16}$NO$^+$ [M+H]$^+$: 238.1232; found: 238.1227.

(5-Bromo-1H-indol-3-yl)(phenyl)methanol (2.2f): 51% yield; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.17 (s, 1H), 6.14 (s, 1H), 6.73 (d, 1H, $J = 2.8$ Hz), 7.06-7.40 (m, 7H), 7.69 (d, 1H, $J = 0.9$ Hz), 8.19 (br, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 70.3, 112.9, 113.2, 119.2, 122.3, 124.2, 125.3, 126.6, 127.7, 127.8, 128.6, 135.3,
HRMS (ESI, m/z): calcd for C_{13}H_{12}BrNO^{+} [M+H]^{+}: 284.0075; found: 284.0076.

\[(2S,3S)-3-(1H-\text{Indol}-3-yl)-2\text{-methyl}-3\text{-phenylpropanal (2.3a):}\]

71% yield; 12:1 dr; 94% ee; \([\alpha]_D = -26.8 (c = 1.27, \text{CHCl}_3)\); \(^1\text{H NMR (400 MHz, CDCl}_3): \delta 1.16 (d, 3H, J = 6.9\text{ Hz}), 3.28-3.32 (m, 1H), 4.55 (d, 1H, J = 8.7\text{ Hz}), 7.02-7.35 (m, 8H), 7.46 (d, 1H, J = 7.8\text{ Hz}), 8.06 (br, 1H), 9.65 (d, 1H, J = 2.8\text{ Hz}). \(^{13}\text{C NMR (100 MHz, CDCl}_3): \delta 13.2, 44.8, 51.0, 111.4, 117.2, 119.5, 119.8, 122.0, 122.5, 126.8, 127.2, 128.5, 128.8, 136.5, 142.3, 205.1. \]

HRMS: \text{m/z} \text{calcd for C}_{18}\text{H}_{18}\text{NO}^{+} [M+H]^{+}: 264.1388; found: 264.1387. HPLC analysis on a Daicel Chiralpak OD-H column: 95/5 hexane/i-PrOH, flow rate 0.75 mL/min, \(t_{\text{major}} = 74.5\text{ min.}; t_{\text{minor}} = 83.4\text{ min.}\).  

\[(S)-2-((S)-(1H-\text{Indol}-3-yl)(phenyl)methyl)butanal (2.3b):\]

80% yield; 14:1 dr; 88% ee; \([\alpha]_D = -22.3 (c = 0.82, \text{CHCl}_3)\); \(^1\text{H NMR (400 MHz, CDCl}_3): \delta 0.90 (t, 3H, J = 7.8\text{ Hz}), 1.69-1.72 (m, 2H), 3.09-3.11 (m, 1H), 4.54 (d, 1H, J = 9.2\text{ Hz}), 7.02-7.35 (m, 9H), 7.50 (d, 1H, J = 7.8\text{ Hz}), 8.06 (br, 1H), 9.55 (d, 1H, J = 4.1\text{ Hz}). \(^{13}\text{C NMR (100 MHz, CDCl}_3): \delta 11.9, 21.6, 43.6, 58.0, 111.3, 117.5, 119.3, 119.7, 121.7, 122.4, 126.7, 127.0, 128.4, 128.7, 136.4, 142.0, 205.1. \]

HRMS: \text{m/z} \text{calcd for C}_{19}\text{H}_{26}\text{NO}^{+} [M+H]^{+}: 278.1545; found: 278.1543. HPLC analysis on a
Daicel Chiralpak OD-H column: 95/5 hexane/i-PrOH, flow rate 0.75 mL/min, \( t_{major} = 53.9 \) min.; \( t_{minor} = 57.8 \) min.

\((S)-2-((S)-(1H-Indol-3-yl)(phenyl)methyl)pentanal (2.3c):\)

80% yield; 11:1 dr; 88% ee; \([\alpha]_{D}^{D} = -16.6 \ (c = 1.03, \text{CHCl}_3); \)

\(^1H\) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 0.84 (t, 3H, \( J = 7.3 \) Hz), 1.23-1.37 (m, 2H), 1.58-1.75 (m, 1H), 3.14-3.21 (m, 1H), 4.53 (d, 1H, \( J = 9.2 \) Hz), 7.14-7.29 (m, 10H), 8.06 (br, 1H), 9.55 (d, 1H, \( J = 4.1 \) Hz). \(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 14.2, 20.7, 30.6, 44.1, 56.3, 111.4, 117.4, 119.3, 119.7, 121.8, 122.4, 126.8, 127.1, 128.5, 128.8, 136.5, 142.1, 205.5. HRMS: \( m/z \) calcd for C\(_{20}\)H\(_{22}\)NO\(^+\) [M+H]\(^+\): 292.1701; found: 292.1701. HPLC analysis on a Daicel Chiralpak AS-H column: 95/5 hexane/i-PrOH, flow rate 0.75 mL/min, \( t_{major} = 44.0 \) min.; \( t_{minor} = 80.3 \) min.

\((S)-2-((S)-(1H-Indol-3-yl)(phenyl)methyl)-3-methylbutanal (2.3d):\)

78% yield; 8:1 dr; 73% ee; \([\alpha]_{D}^{D} = -14.7 \ (c = 0.91, \text{CHCl}_3); \)

\(^1H\) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 0.99 (d, 3H, \( J = 6.9 \) Hz), 1.08 (d, 3H, \( J = 6.9 \) Hz), 2.08-2.10 (m, 1H), 3.09-3.11 (m, 1H), 4.75 (d, 1H, \( J = 10.1 \) Hz), 7.04-7.35 (m, 9H), 7.55 (d, 1H, \( J = 8.2 \) Hz), 8.05 (br, 1H), 9.61 (d, 1H, \( J = 5.0 \) Hz). \(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 18.1, 22.0, 28.5, 41.8, 61.1, 111.5, 117.8, 119.2, 119.7, 121.7, 122.4, 126.8, 126.9, 128.6, 128.8, 136.5, 142.4, 206.7. HRMS: \( m/z \) calcd for C\(_{20}\)H\(_{22}\)NO\(^+\) [M+H]\(^+\):
HPLC analysis on a Daicel Chiralpak OD-H column:
95/5 hexane/i-PrOH, flow rate 0.75 mL/min, $t_{major} = 59.2$ min.; $t_{minor} = 66.3$ min.

(2S,3S)-2-Benzyl-3-(1H-indol-3-yl)-3-phenylpropanal

(2.3e): 70% yield; 15:1 dr; 86% ee; $[\alpha]_D = -18.3$ ($c = 0.75$, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.86-2.91 (dd, 1H, $J = 4.6, 4.6$ Hz), 3.08-3.13 (dd, 1H, $J = 9.2, 8.7$ Hz), 3.55-3.61 (m, 1H), 4.60 (d, 1H, $J = 8.7$ Hz), 7.05-7.36 (m, 14H), 7.47 (d, 1H, $J = 7.8$ Hz), 8.09 (br, 1H), 9.64 (d, 1H, $J = 2.7$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 34.4, 43.8, 57.9, 111.4, 117.1, 119.3, 119.8, 122.1, 122.5, 126.5, 126.8, 126.9, 128.6, 128.7, 128.8, 129.1, 136.5, 139.2, 141.5, 204.9. HRMS: $m/z$ calcd for C$_{24}$H$_{22}$NO$^+$ [M+H]$^+$: 340.1701; found: 340.1702. HPLC analysis on a Daicel Chiralpak AS-H column: 95/5 hexane/i-PrOH, flow rate 0.75 mL/min, $t_{major} = 91.6$ min.; $t_{minor} = 131.8$ min.

(2S,3S)-3-(4-Bromophenyl)-3-(1H-indol-3-yl)-2-methylpropanal (2.3f): 76% yield; 12:1 dr; 89% ee; $[\alpha]_D = -23.6$ ($c = 0.84$, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.16 (d, 3H, $J = 6.9$ Hz), 3.24-3.29 (m, 1H), 4.53 (d, 1H, $J = 8.7$ Hz), 7.07-7.40 (m, 9H), 8.09 (br, 1H), 9.65 (d, 1H, $J = 2.8$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 12.9, 43.9, 50.8, 111.4, 116.4, 119.3, 119.8, 122.0, 122.5, 126.8, 128.8,
129.7, 132.4, 136.4, 140.8, 204. HRMS: \( m/z \) calcld for \( \text{C}_{18}\text{H}_{17}\text{NOBr}^{+} \) [M+H]\(^{+}\) = 342.0494; found: 342.0497. HPLC analysis on a Daicel Chiralpak AS-H column: 95/5 hexane/\( i\)-PrOH, flow rate 0.75 mL/min, \( t_{\text{major}} \) = 88.9 min.; \( t_{\text{minor}} \) = 94.1 min.

\[
(2S,3S)-3-(1H-\text{Indol}-3-\text{yl})-2\text{-methyl}-3-(\text{naphthalen}-1-\text{yl})\text{propanal} \quad (2.3g)
\]

71% yield; 9:1 dr; 90% ee; \([\alpha]_{\text{rt}}^{D} = -21.3 \) (c = 0.95, CHCl\(_3\)); \(^{1}\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 1.22 (d, 3H, \( J = 6.8 \) Hz), 3.41-3.45 (m, 1H), 5.45 (d, 1H, \( J = 9.2 \) Hz), 6.99-7.53 (m, 9H), 7.72 (d, 1H, \( J = 8.2 \) Hz), 7.85 (d, 1H, \( J = 6.9 \) Hz), 8.02 (br, 1H), 8.24 (d, 1H, \( J = 7.8 \) Hz), 9.68 (d, 1H, \( J = 2.8 \) Hz). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 13.1, 38.7, 51.3, 111.3, 117.0, 119.4, 119.8, 122.4, 123.0, 123.2, 125.4, 125.5, 125.7, 126.4, 127.2, 127.5, 129.1, 131.6, 134.2, 136.3, 138.0, 204.8. HRMS: \( m/z \) calcld for \( \text{C}_{22}\text{H}_{22}\text{NO}^{+} \) [M+H]\(^{+}\) = 316.1701; found: 316.1706. HPLC analysis on a Daicel Chiralpak AS-H column: 95/5 hexane/\( i\)-PrOH, flow rate 0.75 mL/min, \( t_{\text{major}} \) = 113.8 min.; \( t_{\text{minor}} \) = 194.2 min.

\[
(2S,3S)-3-(1H-\text{Indol}-3-\text{yl})-3-(4\text{-isopropylphenyl})-2\text{-methylpropanal} \quad (2.3h)
\]

76% yield; 9:1 dr; 88% ee; \([\alpha]_{\text{rt}}^{D} = -18.4 \) (c = 0.87, CHCl\(_3\)); \(^{1}\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 1.16 (d, 3H, \( J = 6.8 \) Hz), 1.19 (d, 6H, \( J = 6.8 \) Hz), 2.80-2.87 (m, 1H), 3.27-3.32 (m, 1H), 4.51 (d, 1H, \( J = 9.2 \) Hz), 7.05-7.35 (m, 8H), 7.52 (d, 1H, \( J = 7.3 \) Hz), 8.06 (br, 1H), 9.65 (d, 1H, \( J = 3.2 \) Hz). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 13.2,
24.0, 33.7, 44.3, 51.0, 111.3, 117.3, 119.4, 119.6, 121.9, 122.3, 126.7, 128.2, 136.4, 138.7, 139.4, 147.0, 205.3. HRMS: m/z calcd for C_{21}H_{24}NO^+ [M+H]^+: 306.1858; found: 306.1866. HPLC analysis on a Daicel Chiralpak AS-H column: 95/5 hexane/i-PrOH, flow rate 0.75 mL/min, t_{major} = 42.8 min.; t_{minor} = 74.2 min.

(2S,3S)-3-(1H-Indol-3-yl)-2-methyl-3-p-tolylpropanal (2.3i): 78% yield; 9:1 dr; 91% ee; [\alpha]_D = -28.3 (c = 0.93, CHCl_3); \textsuperscript{1}H NMR (400 MHz, CDCl_3): \delta 1.16 (d, 3H, J = 6.9 Hz), 2.27 (s, 3H), 3.25-3.30 (m, 1H), 4.50 (d, 1H, J = 9.2 Hz), 7.00-7.33 (m, 8H), 7.47(d, 1H, J = 7.8 Hz), 8.06 (br, 1H), 9.65 (d, 1H, J = 2.8 Hz). \textsuperscript{13}C NMR (100 MHz, CDCl_3): \delta 13.2, 21.1, 44.3, 51.0, 111.3, 117.2, 119.4, 119.6, 121.8, 122.3, 127.0, 128.2, 129.4, 136.2, 136.4, 139.1, 205.2. HRMS: m/z calcd for C_{19}H_{22}NO^+ [M+H]^+: 280.1701; found: 280.1703. HPLC analysis on a Daicel Chiralpak AS-H column: 95/5 hexane/i-PrOH, flow rate 0.75 mL/min, t_{major} = 61.4 min.; t_{minor} = 124.8 min.

(S)-2-((S)-(1H-Indol-3-yl)(p-tolyl)methyl)butanal (2.3j):

79% yield; 12:1 dr; 88% ee; [\alpha]_D = -27.6 (c = 1.21, CHCl_3); \textsuperscript{1}H NMR (400 MHz, CDCl_3): \delta 0.90 (t, 3H, J = 7.3 Hz), 1.66-1.74 (m, 2H), 2.26 (s, 3H), 3.05-3.12 (m, 1H), 4.50 (d, 1H, J = 9.2 Hz), 7.02-7.32 (m, 8H), 7.51 (d, 1H, J = 7.8 Hz), 8.06 (br, 1H), 9.54 (d, 1H, J = 4.1 Hz). \textsuperscript{13}C NMR (100 MHz, CDCl_3): \delta 11.9, 21.1, 21.7, 43.3, 58.0, 111.3,
HRMS: m/z calcd for C$_{20}$H$_{24}$NO$^+$ [M+H]$^+$: 294.1858; found: 294.1860. HPLC analysis on a Daicel Chiralpak AS-H column: 95/5 hexane/i-PrOH, flow rate 0.75 mL/min, $t_{major}$ = 43.9 min.; $t_{minor}$ = 90.3 min.

(2S,3S)-3-(5-bromo-1H-indol-3-yl)-2-methyl-3-phenylpropanal (2.3i): 74% yield; 8:1 dr; 88% ee; $[\alpha]_D^D$ = -64.2 ($c$ = 1.00, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.16 (d, 3H, $J$ = 7.3 Hz), 3.24-3.28 (m, 1H), 4.48 (d, 1H, $J$ = 9.2 Hz), 7.11-7.29 (m, 8H), 7.59 (d, 1H, $J$ = 1.8 Hz), 8.12 (br, 1H), 9.63 (d, 1H, $J$ = 2.7 Hz). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 13.1, 44.5, 50.9, 112.7, 113.0, 116.9, 121.9, 123.1, 125.3, 126.9, 128.2, 128.8, 134.9, 141.5, 141.7, 204.6. HRMS: m/z calcd for C$_{18}$H$_{17}$NOBr$^+$ [M+H]$^+$: 344.0473; found: 344.0483. HPLC analysis on a Daicel Chiralpak OD-H column: 95/5 hexane/i-PrOH, flow rate 0.75 mL/min, $t_{major}$ = 50.7 min.; $t_{minor}$ = 100.1 min.

2.6 References


4212-4215.


Chapter 3

Brønsted acid catalyzed α-alkylation of aldehydes with diaryl methyl alcohols

30 examples

dual catalysis; less stabilized carbocations
3.1 Introduction

3.1.1 $S_N1$ alkylation of aldehydes and ketones with diaryl alcohols through enamine catalysis

The catalytic $\alpha$-alkylation of carbonyl compounds is a frequently used method in organic synthesis. In recent years, many efforts have been made towards activating aldehydes and ketones through enamine catalysis, so that they will react with a broad range of electrophiles.$^{[1]}$ In 2004, List and co-workers introduced the first intramolecular alkylation of aldehydes using alkyl halides catalyzed by L-proline-based amine catalysts.$^{[2]}$ The reaction proceeded through the intramolecular $S_N2$ substitution, and the products were generated with high yields and enantioselectivities (Scheme 3.1).

![Scheme 3.1 Intramolecular $S_N2$ substitution](image.png)

Due to the difficulty in achieving the intermolecular version of enamine catalyzed $S_N2$ type $\alpha$-alkylation of aldehydes$^{[3]}$, an $S_N1$ type $\alpha$-alkylation of aldehydes with carbocation precursors, mainly as diaryl alcohols, was developed instead. During the time when we were doing L-proline catalyzed alkylation of aldehydes with indole derived alcohols (see Chapter 2), several research groups
such as Melchiorre and Cozzi reported the use of diaryl alcohols in an enamine catalyzed $S_N$1 type intermolecular alkylation of aldehydes.

\[
\text{RCHO} + \text{Ar}_1\text{Ar}_2\text{OH} \xrightarrow{20\text{ mol}\%} \text{TFA} \xrightarrow{\text{Et}_2\text{O}} \text{RCHO} \\
\text{Ar}_1\text{Ar}_2 \quad \text{30-95\% yield, 60-92\% ee}
\]

**Scheme 3.2** Enamine catalyzed alkylation of aldehyde with diaryl alcohol

In 2008, Cozzi and co-workers reported the first intermolecular alkylation of aldehydes with diaryl alcohols catalyzed by MacMillan catalyst to give products with good yields and enantioselectivities.$^4$ The substrate scope was very limited and most of the products could be obtained with only moderate enantioselectivities (Scheme 3.2). Later in 2010, they broadened the substrate scope to include preformed stable carbocations.$^5$ The same catalyst was used to give similar alkylation products with good yields, albeit with low to moderate enantioselectivities (Scheme 3.3). Besides simple aldehydes, $\alpha,\beta$-unsaturated aldehydes could also be employed as effective nucleophiles.

\[
\begin{align*}
\text{BF}_4^- & \quad \text{Me}_2\text{N} \\
\text{Me}_2\text{N} & \quad \text{BF}_4^- \\
\end{align*}
\]

**Scheme 3.3** Preformed carbocations used as electrophiles

In 2010, the Melchiorre group developed the cooperative asymmetric $\gamma$-alkylation of $\alpha$-branched enals with diaryl alcohols to generate products with
good yields and enantioselectivities.\textsuperscript{[6]} Chiral Brønsted acids were used to control the enantioselectivities accompanied with chiral amines (Scheme 3.4). Later in 2011, the Christmann group demonstrated α- and γ-alkylation of α, β-unsaturated aldehydes with diaryl alcohols using dienamine activation.\textsuperscript{[7]} Most of the products were obtained with moderate yields and selectivities (Scheme 3.5). In both reports, bis(4-(dimethylamino)phenyl)methanol was the only electrophile that could be successfully applied for the transformation.

**Scheme 3.4** Dienamine activation of α-branched enals

**Scheme 3.5** α- and γ-Alklyation of enals

The Luo and Cheng group later extended the scope of nucleophile from aldehydes to ketones in 2010.\textsuperscript{[8]} Functionalized Chiral Ionic Liquid (FCIL) organocatalysts were applied to catalyze this reaction and the resulting products were obtained with excellent yields and good enantioselectivities (Scheme 3.6).
In 2012, the Xiao group showed that besides Brønsted acids, Lewis acids could also be used to generate carbocations from diaryl alcohols, followed by the addition of aldehydes to give the alkylation products.\textsuperscript{[9]} IrCl\textsubscript{3}, CuCl or InBr\textsubscript{3} were found out to be effective to cooperate with chiral amine to catalyze this transformation (Scheme 3.7).

Besides diaryl alcohols, the Jacobsen group reported the α-alkylation of aldehydes using diaryl halides as precursors using thiourea as the catalyst in 2010.\textsuperscript{[10]} Mechanistic studies were done and it proved that the reactions proceeded through a S\textsubscript{N}1 pathway (Scheme 3.8).
3.1.2 S<sub>N</sub>1 alkylation of aldehydes with other type alcohols

Allylic alcohols are very commonly used in organic synthesis and they are known to generate allylic carbocations in acidic conditions. They can also be used to replace diaryl alcohols in S<sub>N</sub>1 type alkylation of aldehydes via enamine activation.

![Scheme 3.9](image_url)

Scheme 3.9 Allylic alkylation of aldehydes using metal and organocatalyst

Early in 2006, the Córdova group achieved a catalytic intermolecular α-allylic alkylation of aldehydes by using the combination of transition metal and organocatalyst. A palladium catalyst was used to form an electrophilic -allyl complex from allyl acetate (Scheme 3.9). Products were obtained with good yields. However, the asymmetric version of this transformation was unsuccessful due to the low yields obtained when a chiral catalyst was used.

![Scheme 3.10](image_url)

Scheme 3.10 Acid and amine catalyzed alkylation of aldehyde with allylic alcohol

In 2010, Xu and co-workers accomplished the α-alkylation of aldehydes with allylic alcohols catalyzed by amines in the presence of Brønsted acids as co-catalysts. Although various kinds of aldehydes could be employed to give
products with good yields, the enantioselectivities could not be controlled by chiral amines (Scheme 3.10).

In the same year, the Cozzi group developed a catalyst system that made use of indium(III) bromide and a chiral amine catalyst to achieve the asymmetric $\alpha$-allylic alkylation of aldehydes with allylic alcohols.$^{[14]}$ The yields and enantioselectivities of most of the products were acceptable, but the diastereoselectivities were not satisfactory (Scheme 3.11).

```
\begin{center}
\begin{tikzpicture}
  \node at (0,0) {\textbf{Scheme 3.11} Asymmetric alkylation of aldehyde with allylic alcohol};
  \node at (0,0) {O\text{ther than allylic alcohols, propargylic alcohols have also been applied to the \textit{S$_{N}$1} alkylation of aldehydes through enamine activation. In 2010, the Nishibayashi group introduced the enantioselective propargylic alkylation of aldehydes under the catalysis of a thiolate-bridged diruthenium complex and a secondary amine.$^{[15]}$ The corresponding propargylic alkylated products were obtained with excellent yields and enantioselectivities (Scheme 3.12).

```
\begin{center}
\begin{tikzpicture}
  \node at (0,0) {\textbf{Scheme 3.12} Asymmetric alkylation of aldehyde with propargylic alcohol};
  \node at (0,0) {\textbf{Scheme 3.12} Asymmetric alkylation of aldehyde with propargylic alcohol};
\end{center}
One year later, the Cozzi group also reported an enantioselective propargylic alkylation of aldehydes promoted by indium triflate and a chiral amine.\[16\] Propargylic alcohols with an internal alkyne moiety, which were not reactive in previous Nishibayashi’s system, could generate the corresponding products with good yields and enantioselectivities (Scheme 3.13).

Scheme 3.13 Asymmetric alkylation of aldehyde with propargylic alcohol

3.1.3 Brønsted acids catalyzed aldol reactions

In the methodologies developed by Cozzi and others, amine catalysts were used to activate the aldehydes to generate the enamine intermediates, and Brønsted acids were used to mediate the formation of carbocations from the corresponding diaryl alcohols or other precursors. Although this amine/acid co-catalysis system was very successful for the generation of highly stabilized carbocations from diaryl alcohols (e.g. 3.1a), the scope of this transformation was still very limited. Substrates that would generate “less stabilized” carbocations (such as 3.1b-f) were not effective substrates in these S_N1 alkylation reactions (Scheme 3.14).\[4\]
Instead of using enamine/acid catalysts for aldehyde alkylation, we began to wonder if we could use Brønsted acids as the sole catalyst in $S_N 1$ type alkylation of aldehydes. We then looked into the literature and found that Brønsted acids had long been used before in the catalysis of aldol condensations of aldehydes.

\[
2 \text{H}_3\text{C}=\text{CHO} + \text{H}^+ \rightarrow \text{H}_3\text{C}-\text{CH}=\text{CHO} \quad \text{Scheme 3.15 Acid catalyzed condensation}
\]

In 1985, Tidwell reported the acid catalyzed condensation of acetaldehyde through enolization (Scheme 3.15). Later in 1998, Bettolo introduced the aqueous acid catalyzed intramolecular aldol condensation of 3-oxocyclohexaneacetaldehydes with a diastereoselectivity of 85:15 (Scheme 3.16).

\[
\text{O} \quad \text{THF, 2N HCl reflux} \quad \text{OH} \quad \text{HO} \\
\text{85:15}
\]

Then in 2007, Elrod carried out a comprehensive kinetic study on the sulfuric acid catalyzed aldol condensations of aliphatic aldehydes. From the studies, it
was shown that acids accelerated the enolization of aldehydes, which subsequently led to reactions with electrophiles.

\[
\begin{align*}
R^1\text{CHO} + \text{MeOH} &\xrightarrow{\text{(+)Menthyl-TMS LiClO}_4} \text{R}^1\text{CHO} \text{OMe} \\
1 \text{ mol}\% \text{CF}_3\text{COOH} &\quad \text{Scheme 3.17 Cross aldol reaction catalyzed by acid}
\end{align*}
\]

Recently, cross-aldol reactions of \(\alpha\)-branched enolizable aldehydes were achieved by the group of Mahrwald in 2010.\[^{20}\] The reaction was catalyzed by trifluoroacetic acid and could afford the aldol etherification products containing quaternary carbon centers with high stereo- and regioselectivities (Scheme 3.17).

\[
\begin{align*}
R^1\text{CHO} + \text{HCO}_2\text{R} &\xrightarrow{\text{acid catalyst}} \text{R}^1\text{CO}_2\text{R} \\
\text{toluene} &\quad \text{Scheme 3.18 Asymmetric aldol reaction catalyzed by chiral Brønsted acid}
\end{align*}
\]

Later that year, Blanchet and co-workers reported an asymmetric aldol reaction catalyzed by a Brønsted acid.\[^{21}\] Syn-selective products were obtained with good yields and enantioselectivities (Scheme 3.18). It was a complementary approach to enamine catalysis since some of the \(\beta\)-hydroxy ketones synthesized through this method could not be obtained by enamine catalysis.

Inspired by all these previous works, we decided to use Brønsted acids only to catalyze the \(\alpha\)-alkylation of aldehydes with diaryl alcohols. We reasoned that
Brønsted acids could play two roles to make this transformation possible. The first role is that Brønsted acids can accelerate the enolization of aldehydes, which has been demonstrated by the previous literature works. In addition, Brønsted acids can facilitate the generation of the carbocations from the diaryl alcohols or other precursors, as shown in enamine catalysis.

3.2 Results and discussion

3.2.1 Brønsted acid catalyzed -alkylation of aldehydes with diaryl alcohols

We started our studies by using bis(4-methoxyphenyl)methanol 3.1b as the model substrate for the α-alkylation of aldehydes using only Brønsted acid as the catalyst. According to Mayr’s electrophile reactivity scales, this diaryl methanol would lead to the generation of a less stabilized carbocation (compared to 3.1a), which was found to be an ineffective substrate in previous enamine catalyst systems.

Table 3.1 Optimization of Brønsted acid catalyzed alkylation of 3.2a with 3.1b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid (mol%)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>CH₂Cl₂</td>
<td>14</td>
<td>&lt;1</td>
</tr>
<tr>
<td>2</td>
<td>p-TSA (10)</td>
<td>CH₂Cl₂</td>
<td>14</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>p-TSA (10)</td>
<td>(CH₂Cl)₂</td>
<td>14</td>
<td>48</td>
</tr>
<tr>
<td>Entry</td>
<td>Catalyst (mol%)</td>
<td>Solvent</td>
<td>Yield</td>
<td>Remarks</td>
</tr>
<tr>
<td>-------</td>
<td>----------------</td>
<td>----------</td>
<td>-------</td>
<td>---------</td>
</tr>
<tr>
<td>4</td>
<td>p-TSA (10)</td>
<td>CHCl₃</td>
<td>14</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>p-TSA (10)</td>
<td>toluene</td>
<td>14</td>
<td>low</td>
</tr>
<tr>
<td>6</td>
<td>p-TSA (10)</td>
<td>Et₂O</td>
<td>14</td>
<td>&lt;5</td>
</tr>
<tr>
<td>7</td>
<td>p-TSA (10)</td>
<td>THF</td>
<td>14</td>
<td>low</td>
</tr>
<tr>
<td>8</td>
<td>p-TSA (10)</td>
<td>EtOAc</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>9</td>
<td>p-TSA (10)</td>
<td>DMF</td>
<td>14</td>
<td>low</td>
</tr>
<tr>
<td>10</td>
<td>p-TSA (10)</td>
<td>dioxane</td>
<td>14</td>
<td>low</td>
</tr>
<tr>
<td>11</td>
<td>p-TSA (10)</td>
<td>CH₃CN</td>
<td>14</td>
<td>60</td>
</tr>
<tr>
<td>12</td>
<td>p-TSA (10)</td>
<td>CH₂Cl₂</td>
<td>5</td>
<td>55</td>
</tr>
<tr>
<td>13</td>
<td>DNBA (10)</td>
<td>CH₂Cl₂</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>14</td>
<td>AcOH (10)</td>
<td>CH₂Cl₂</td>
<td>5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>15</td>
<td>p-TSA (5)</td>
<td>CH₂Cl₂</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>16</td>
<td>p-TSA (20)</td>
<td>CH₂Cl₂</td>
<td>5</td>
<td>63</td>
</tr>
</tbody>
</table>

[a] 1.2 mmol 3.2a and 0.4 mmol 3.1b were reacted in 2 mL solvent. [b] Determined via crude ¹H NMR analysis.

Initially, we carried out the reaction of aldehyde 3.2a and alcohol 3.1b without any catalyst. Not surprisingly, no new products were detected through TLC and NMR analysis (Table 3.1, entry 1). To our delight, the S₅¹ type alkylation product was detected in 62% yield when 10 mol% of acetic acid was added into the reaction system using dichloromethane as the solvent after 14 hours (Table 3.1, entry 2). Solvents screening showed that dichloromethane gave the best yield (Table 3.1, entries 3-11). Dichloroethane and chloroform gave a slightly lower yield, while acetonitrile gave a similar result as dichloromethane. Other solvents like ether, toluene and DMF could not facilitate this transformation.

After finding out the optimal solvent for this reaction, we turned our attention to other Brønsted acids. Stronger acid such as 2,4-dinitrobenzenesulfonic acid (DNBA) gave a decreased yield (Table 3.1, entry 13), while weaker acids like acetic acid gave no desired product (Table 3.1, entry 14). Decreasing the p-TSA
loading to 5 mol% resulted in very low yield of the product (Table 3.1, entry 15). Eventually, the best yield of 63% was obtained by using 20 mol% of p-TSA (Table 3.1, entry 16).

Further optimization of other parameters, such as acid catalysts and temperatures, could not improve the reaction yield to more than 70%. We then isolated the major side product and characterized it as a product formed after self-redox reaction of the intermediate 3.4a. Under the strong acidic conditions, alcohol 3.1b could form ether 3.4a,\textsuperscript{[23]} which underwent the self-redox pathway\textsuperscript{[23,24]} to give diaryl ketone 3.5a and diaryl methane 3.5b. This side reaction consumed the alcohol substrates and led to a low yield of the desired product 3.3a (Scheme 3.19).

\[ \begin{align*}
3.1b & \xrightarrow{H^+} 3.4a & 3.4a & \xrightarrow{\text{self-redox}} 3.5a, 3.5b \\
\text{Ar} & \text{Ar} & \text{Ar} & \text{Ar}
\end{align*} \]

\[ \text{Ar = 4-OMe-C}_6\text{H}_4 \]

Scheme 3.19 Self-redox reaction of 3.1b

This self-redox reaction is believed to take place after the formation of the ether 3.4a, which can be observed in the experimental reaction. After the formation of the ether 3.4a, it can undergo self-redox reaction directly within the molecule to give 3.5a and 3.5b. Another possible explanation is an intermolecular hydride transfer from 3.1b to the diaryl cation. Under this acidic condition, the intermolecular hydride transfer is not likely to happen compared to the nucleophilic attack of the diaryl alcohol to form ether. So we think that the
intramolecular self-redox reaction is more likely to occur in such condition.

To further improve the yield, we came up with an idea to add some additives into this system with hope of suppressing the undesired self-redox pathway. The first thought was to add another alcohol to compete with 3.1b to form ether 3.4b. The newly formed ether 3.4b should lack the ability to continue the self-redox reaction to generate 3.5a, but be able to regenerate the diaryl carbocation, which can react with aldehyde 3.2a to produce the desired alkylation product 3.3a (Scheme 3.20).

We first tried two equivalents of phenol, tert-butanol and methanol separately as the additive in this reaction system. The reaction yields dropped in the presence of all these additives compared to the reaction without any additive (Table 3.2, entries 1-3). However, we noticed that the ratio of 3.3a to 3.5a after adding tert-butanol was much higher than before (Table 3.2, entry 2). Thus, we decided to slowly increase the amount of tert-butanol from 0.3 equivalents till 4 equivalents (Table 3.2, entries 4-8). Finally, 1.0 equivalent of tert-butanol as an additive was
found to suppress the self-redox pathway effectively, affording the desired product in quantitative yields (Table 3.2, entry 6). It is believed that tert-butanol competes in the ether formation as intended, thereby improving the reaction yield.

Table 3.2 Effects of additives

<table>
<thead>
<tr>
<th>Entry[^a]</th>
<th>Additive</th>
<th>Time (h)</th>
<th>Yield[^b] of 3.3a (%)</th>
<th>Ratio[^b] of 3.3a/(3.5a+3.5b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 eq. Phenol</td>
<td>6</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>2 eq. 'tBuOH</td>
<td>6</td>
<td>31</td>
<td>19:1</td>
</tr>
<tr>
<td>3</td>
<td>2 eq. methanol</td>
<td>6</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>0.3 eq. 'tBuOH</td>
<td>19</td>
<td>89</td>
<td>14:1</td>
</tr>
<tr>
<td>5</td>
<td>0.6 eq. 'tBuOH</td>
<td>19</td>
<td>91</td>
<td>17:1</td>
</tr>
<tr>
<td>6</td>
<td>1 eq. 'tBuOH</td>
<td>19</td>
<td>95</td>
<td>20:1</td>
</tr>
<tr>
<td>7</td>
<td>3 eq. 'tBuOH</td>
<td>19</td>
<td>38</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>4 eq. 'tBuOH</td>
<td>19</td>
<td>32</td>
<td>-</td>
</tr>
</tbody>
</table>

[^a] 1.2 mmol 3.2a and 0.4 mmol 3.1b were reacted in 2 mL CH₂Cl₂.  
[^b] Determined via crude ¹H NMR analysis.

After obtaining the optimized conditions, we next examined the substrate scope of this transformation. We focused on the diaryl alcohols that could not be applied in the previous enamine catalyst systems, paying attention particularly, to those that generated less stabilized carbocations (eg. 3.1b-3.1f). Due to the different reactivities of the diaryl alcohols used, it was difficult to identify a
“universal” acid catalyst and condition that was optimal for all the substrates. Hence, the conditions were slightly modified to achieve the best result for each substrate (Chart 3.1).

**Chart 3.1** Scope of alkylation of aldehydes with diaryl alcohols

<table>
<thead>
<tr>
<th>Me-CHO</th>
<th>Et-CHO</th>
<th>Bn-CHO</th>
<th>Bu-CHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.3a[^a]</td>
<td>3.3b[^a]</td>
<td>3.3c[^a]</td>
<td>3.3d[^a]</td>
</tr>
<tr>
<td>10 mol% p-TSA, 20 h, 95%</td>
<td>10 mol% p-TSA, 40 h, 87%</td>
<td>10 mol% p-TSA, 40 h, 81%</td>
<td>10 mol% p-TSA, 40 h, 91%</td>
</tr>
<tr>
<td>Me-CHO</td>
<td>Et-CHO</td>
<td>Me-CHO</td>
<td>Et-CHO</td>
</tr>
<tr>
<td>3.3e (d.r.:~1:1)</td>
<td>3.3f (d.r.:~1:1)</td>
<td>3.3g[^b,d]</td>
<td>3.3h[^b,d]</td>
</tr>
<tr>
<td>40 mol% p-TSA, 28 h, 93%</td>
<td>40 mol% p-TSA, 62 h, 81%</td>
<td>20 mol% DNBA, 12 h, 93%</td>
<td>20 mol% DNBA, 14 h, 91%</td>
</tr>
<tr>
<td>Et-CHO</td>
<td>Pr-CHO</td>
<td>Et-CHO</td>
<td>Cl-CHO</td>
</tr>
<tr>
<td>3.3[^c,d]</td>
<td>3.3[^c,d]</td>
<td>3.3[^c,d]</td>
<td>3.3[^c,d]</td>
</tr>
<tr>
<td>20 mol% DNBA, 4 h, 49%</td>
<td>20 mol% DNBA, 4 h, 47%</td>
<td>20 mol% TIOH, 3 h, 53%</td>
<td>20 mol% TIOH, 3 h, 51%</td>
</tr>
<tr>
<td>Me-CHO</td>
<td>Me-CHO</td>
<td>Et-CHO</td>
<td>Et-CHO</td>
</tr>
<tr>
<td>3.3[^d]</td>
<td>3.3[^d]</td>
<td>3.3[^d]</td>
<td>3.3[^d]</td>
</tr>
<tr>
<td>20 mol% BNP[^e], 24 h, 86%</td>
<td>20 mol% BNP[^e], 40 h, 76%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[^a] With 1 eq. 'BuOH as additive. [^b] Reaction at 50 °C. [^c] Reaction at 80 °C in MeNO2. [^d] Isolated after reduction to the corresponding alcohols. [^e] BINOL-derived phosphoric acid

In the case of diaryl alcohol 3.1b, all the different aldehydes used afforded the corresponding products in very good yields (Chart 3.1, products 3.3a-d). Mono methoxy-substituted or dimethyl substituted diaryl alcohols required a higher acid
catalyst loading or stronger acids were needed for the full conversion of the diaryl alcohols to give products with satisfactory yield (Chart 3.1, products 3.3e-h). For example, products 3.1i-l from the corresponding diaryl alcohols required the use of a stronger acid such as triflic acid, higher reaction temperature and a very polar solvent such as nitromethane to achieve moderate yields of the desired alkylation products. Diaryl alcohols with strong electron withdrawing groups on the benzene ring such as CF₃ group could not give any desired product, despite the use of various harsh reaction conditions. We also examined substrates that were effective in enamine catalysis, and once again, the reaction yields were very good as expected (Chart 3.1, products 3.3m-n).

**Chart 3.2** Scope of alkylation of α,α-disubstituted aldehydes with diaryl alcohols
We next studied the reaction involving α,α-disubstituted aldehydes as the nucleophiles to react with diaryl alcohols (Chart 3.2). Ether was found as the most suitable solvent for these types of substrates after several optimization studies, instead of dichloromethane used earlier. We examined two types of α,α-disubstituted aldehydes (3.6a, 3.6b) to react with various diaryl alcohols. For substrates that could generate relatively stable carbocations, diethyl ether or n-butyl ether was used as solvent to give the desired products at room temperature or 50 °C with excellent yields (Chart 3.2, 3.7a-f). For diaryl alcohols which were able to generate more reactive carbocations, nitromethane was used to produce alkylation products at room temperature or 50 °C with very good yields (Chart 3.2, 3.7g-j).

[a] Reaction in Bu₂O at 50 °C. [b] Isolated after reduction to the corresponding alcohols. [c] Reaction in MeNO₂. [d] Reaction in MeNO₂ at 50 °C.

---

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} & \quad \text{Ph} & \quad \text{CHO} \\
\text{MeO} & \quad \text{MeO} & \quad \text{Ph} & \quad \text{CHO} \\
\text{MeO} & \quad \text{MeO} & \quad \text{Ph} & \quad \text{CHO}
\end{align*}
\]

---

3.7a 20 mol% p-TSA, 24 h, 95%
3.7b 20 mol% p-TSA, 48 h, 93%
3.7c (d.r.: 1:1) 40 mol% p-TSA, 24 h, 89%
3.7d 40 mol% p-TSA, 24 h, 94%
3.7e 40 mol% DNBA, 24 h, 89%
3.7f 40 mol% DNBA, 24 h, 95%
3.7g 20 mol% DNBA, 24 h, 88%
3.7h 20 mol% DNBA, 24 h, 85%
3.7i 20 mol% DNBA, 24 h, 86%
3.7j 20 mol% DNBA, 24 h, 82%
3.2.2 Brønsted acid catalyzed alkylation of aldehydes with allylic alcohols

After investigating diaryl alcohols as the carbocation precursors, we turned our attentions to allylic alcohols, which could generate allylic cations under acidic conditions.\[11\] We speculated that allylic alcohols might have similar reactivity as diaryl alcohols in reactions with aldehydes under the catalysis of Brønsted acids. Commercially available allylic alcohol 3.8 was used to test our theory to react with simple aldehyde 3.2b (Table 3.3).

![Table 3.3 Optimization of alkylation of 3.2b with 3.8]

<table>
<thead>
<tr>
<th>Entry[a]</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield (%)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>toluene</td>
<td>rt</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>CH₃CN</td>
<td>rt</td>
<td>14</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>rt</td>
<td>14</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>Et₂O</td>
<td>rt</td>
<td>14</td>
<td>&lt;5</td>
</tr>
<tr>
<td>5</td>
<td>CH₃CN</td>
<td>50</td>
<td>6</td>
<td>42</td>
</tr>
<tr>
<td>6</td>
<td>MeNO₂</td>
<td>50</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>7[c]</td>
<td>CH₃CN</td>
<td>50</td>
<td>5</td>
<td>51</td>
</tr>
<tr>
<td>8[c]</td>
<td>CH₂Cl₂</td>
<td>50</td>
<td>5</td>
<td>73</td>
</tr>
<tr>
<td>9[c]</td>
<td>(CH₂Cl)₂</td>
<td>50</td>
<td>5</td>
<td>73</td>
</tr>
<tr>
<td>10[c]</td>
<td>CHCl₃</td>
<td>50</td>
<td>5</td>
<td>78(77)[f]</td>
</tr>
<tr>
<td>11[d]</td>
<td>CHCl₃</td>
<td>50</td>
<td>3</td>
<td>74</td>
</tr>
<tr>
<td>12[e]</td>
<td>CHCl₃</td>
<td>50</td>
<td>3</td>
<td>75</td>
</tr>
</tbody>
</table>

[a] 1.2 mmol 3.2b and 0.4 mmol 3.8 were reacted in 2 mL solvent. [b] Determined via crude ^1H NMR analysis. [c] 1.0 eq. 'BuOH added. [d] 0.5 eq. 'BuOH was added. [e] 2 eq. 'BuOH was added. [f] Isolated yield.
Initial screening of the solvents for this type of substrates showed that acetonitrile was the most effective solvent, affording the desired product at room temperature in 30% yield (Table 3.3, entries 1-4). Raising the reaction temperature to 50 °C slightly improved the conversion (Table 3.3, entries 5-7). Changing of the solvent to dichloromethane in the presence of 1.0 equivalent of tert-butanol as the additive could generate the product with 73% yield (Table 3.3, entry 8). Further optimization with the additive indicated that chloroform was the best solvent, and the desired product was obtained with 77% isolated yield in 5 hours (Table 3.3, entries 9-12). In the case of \( \alpha,\alpha \)-disubstituted aldehydes, toluene turned out to be the optimal solvent to give the desired products with excellent yields.

**Chart 3.3** Scope of alkylation of aldehydes with allylic alcohol

\[
\begin{align*}
\text{HCO} & \quad \text{OH} \\
\text{R} & \quad \text{Ph} \\
\text{R} & \quad \text{Ph} \\
3.2 \text{ or } 3.6 & \quad 20 \text{ mol\% } p\text{-TSA} \\
(1.2 \text{ mmol}) & \quad \text{solvent} \\
\quad & \quad \text{3.8} \\
(0.4 \text{ mmol}) & \quad \text{3.9}
\end{align*}
\]

[a] 1 eq. \(^t\text{BuOH}\) added, dr:~1:1.
Next, we examined the substrate scope of the aldehydes. To our delight, various kinds of aldehydes could react with allylic alcohol 3.8 to give products in good yields (Chart 3.3). Aliphatic aldehydes could produce alkylation products in chloroform in good yields with 1.0 equivalent tert-butanol as additive (Chart 3.3, 3.9a-d). For α,α-disubstituted aldehydes, toluene was the best solvent to give the desired products with excellent yields at room temperature (Chart 3.3, 3.9e-f).

In all these α-alkylation reactions of aldehydes, there are always some self-aldol reactions observed from the crude NMR. The self-aldol reaction is not very easy to take place under acidic conditions. However, there are more and more self-aldol products observed with the raise of temperature, stronger acid used and more polar solvent used. With more reactive carbocation precursors like diphenylmethanol, more aldehydes are needed for the complete consumption of the diaryl alcohols. Since the side products do not interfere the isolation of the products, we used excess aldehydes in most of the alkylation reactions to make sure the diaryl alcohols are fully consumed.

3.2.3 DFT calculations

We also did some DFT calculations of the reaction pathways by studying the reaction between aldehyde 3.2a and diaryl alcohol 3.1e in nitromethane (Scheme 3.21). The activation energy of the aldehyde enolization was found to be 18.4 and 35.4 kcal/mol with and without the acid catalyst respectively, which is relatively very high for this reaction. The formation of IM2 intermediate seemed to
be favoured under acidic conditions, requiring activation energy of only 7.1 kcal/mol. After the generation of intermediates IM1 and IM2, the nucleophilic addition of the enolized aldehyde to the diphenyl carbocation could proceed very effectively, as the energy barrier was only 2.7 kcal/mol. It was not difficult to see that the aldehyde enolization step was the rate determining step in this alkylation transformation. The acid played an important role to accelerate the enolization of aldehyde by reducing the activation energy, as well as to generate the carbocation from the diaryl alcohol precursor.

![Scheme 3.21 DFT calculation of reaction pathways](image)

This reaction had several side reactions, which was investigated in great detail using DFT calculations. One major side reaction was the self aldol reaction of the aldehydes by the addition of intermediate IM1 to aldehyde 3.2a. The activation energy of the enolized aldehyde with aldehyde was determined to be 19.1 kcal/mol, which is very close to the activation energy of aldehyde enolization (18.4 kcal/mol). Due to the similar activation energies, it was inevitable to have self aldol reactions in this reaction system, as evidenced experimentally. The other
major side reaction was the formation of ether 3.10, through the addition of diaryl alcohol 3.1e to intermediate IM2. The activation energy was very small and the ether could be very easily formed. However, this ether formation could be reversible under acidic conditions, and the carbocation could be efficiently regenerated due to the low energy barrier of 4.9 kcal/mol. This was consistent with our experimental results that the ether could be formed very easily and it would not affect the reaction yields.

3.2.4 Enantioselective attempts on the α-alkylation reactions.

After the racemic α-alkylation of aldehydes with the common diaryl alcohols and allylic alcohols, we tried to develop the asymmetric version of this reaction. We first tested bis(4-methoxyphenyl)methanol 3.1b in the known enamine catalytic system to see if we can obtain any product.

After screening a few conditions, we find out that diaryl alcohols 3.1b is not reactive if equal amine and acid are used, which has already been demonstrated in the literature. With excess acid in the enamine catalytic system, desired product can be obtained with high yield but no enantioselectivity. It suggests that this reaction is catalyzed by acid only. So we turned our attention to chiral acid approach without any amine catalyst.

As we have discussed above, strong acid is need to catalyze this reaction. If the acid is too weak, the enolization of aldehyde and the generation of reactive carbocation intermediate will both be affected. The weakest acid we have used for
the alkylation is $p$-toluenesulfonic acid, which has an approximate pKa of 1.6 in DMSO. However, the commonly used chiral Brønsted acids cannot reach the acidity as $p$-toluenesulfonic acid. Therefore, the acid approach may not give satisfactory results either.

![Scheme 3.22 Asymmetric attempts on the α-alkylation of aldehyde](image)

We started with the BINOL-phosphoric acid 3.11 and 3.12 first using diaryl alcohol 3.1b and aldehyde 3.2a as the model substrates (Scheme 3.22). After screening a few reaction conditions, no desired product was observed. The main reason for the failure of this reaction may be the weak acidity of these chiral Brønsted acids. In the near future, maybe we can develop stronger chiral Brønsted acids to solve this problem.
3.3 Conclusions

In summary, we have achieved the Brønsted acids catalyzed $S_N1$ type alkylation of aldehydes with diaryl alcohols. Brønsted acids were used as the sole catalyst and they were found to facilitate the generation of the carbocations from the diaryl alcohols, as well as accelerate the enolization of aldehydes. Diaryl alcohols that would generate less stable carbocations, which were not effective substrates in the previous enamine catalysis systems, could also work well to give alkylation products with high yields. Allylic alcohols and $\alpha,\alpha$-disubstituted aldehydes could also be employed in this transformation. DFT calculations were done to study the reaction pathways and the results obtained were in agreement with the observed experimental outcome. The enantioselective version of this reaction and the expansion of the diaryl alcohols to simpler alcohols that would generate highly unstable carbocations has remained a challenge.

3.4 Experimental

3.4.1 General procedures

1) The diaryl alcohol substrates 3.1a-3.1e were prepared via direct reduction of corresponding ketones. Substrate 1f was prepared via Grignard reaction of the corresponding aldehyde.$^6$

2) General procedures of the catalytic reactions: To a 5 mL vial equipped with a
magnetic stir bar was added 0.4 mmol of diaryl alcohol, 1.2 mmol of aldehyde and acid catalyst in 2 mL solvent as stated in every chart. The mixture was stirred at indicated conditions as stated in every chart. The reaction progress was monitored via $^1$H NMR analysis of the crude reaction mixture. After the completion of the reaction, the reaction mixture was directly subjected to SiO$_2$ column chromatography purification eluting with EtOAc/hexane to give the desired product. In some reactions as indicated in table 3.2-3.4, the aldehyde products were reduced to corresponding alcohols by sodium borohydride before purified via column chromatography to obtain the desired products.

3.4.3 Calculations

Our calculations were carried out at the B3LYP/6-31g(d,p) level by including the dielectric solvent effect of nitromethane, which was taken into account using a simple self-consistent reaction field (SCRF) method, based on the polarizable continuum model (PCM). The dielectric constant of nitromethane was taken as 38.2. All the stationary points for the isolated reactants, products, possible intermediates and transition states were located by performing full geometry optimization without any symmetric restriction, and their nature (local minima or first-order saddle points) were identified by performing frequency calculations. All calculations were completed by using Gaussian 03 program package. For all the cited energies, the zero-point energy corrections were taken into account.

The computational pathways for the acid catalyzed alkylation of aldehyde
3.2a and alcohol 3.1e were summarized in Figure 3.1. The reaction mixture was not anhydrous, thus we conducted the calculation with the assumption that water was present. Initially, aldehyde 3.2a could be transformed into its enol form (IM1) in the presence of H₂O and H₃O⁺ via transition state TS1 with a energy barrier of 18.36 kcal/mol, and the process for the enolization of aldehyde was exothermic by 8.90 kcal/mol with regard to the isolated reactants. In this step, acid played an important role for accelerating the enolization of aldehyde as indicated by the higher barrier (35.4 kcal/mol) and endothermicity (8.24 kcal/mol) for the corresponding process in the absence of acid (shown in Figure 3.2). In the meantime, a proton of H₃O⁺ could be deprived by the hydroxyl oxygen (O) of alcohol 1e to produce the corresponding carbocation intermediate (IM2) and a water molecule. The process from IM2 to IM2 was calculated to be exothermic by 6.28 kcal/mol with a energy barrier of 7.10 kcal/mol. From intermediates IM1 and IM2, acid catalyzed alkylation of aldehyde occurs. The formation of product like intermediate IM4 overcame a barrier of 2.74 kcal/mol and released an energy of 3.06 kcal/mol. From the calculated results shown in Figure 3.1, it was clear that this process for the enolization of aldehyde exhibited the highest barrier, and was the rate determining step of the whole reaction.
Figure 3.1 Computational potential energy surface profile for enolization of aldehyde in the absence of acid.

Besides the desired alkylation of aldehyde, there also existed some side reactions, such as the formation of ether (from two molecules of alcohol) and self aldol reaction of the aldehyde, as shown in Figure 3.2. After the formation of carbocation (IM2), the carbocation could react with another alcohol molecule to generate ether-like intermediate IM23 via transition state TS22. The barrier associated with TS22 was found to be 1.23 kcal/mol, which was lower than that for the alkylation of aldehyde (3.06 kcal/mol). Furthermore, the potential energy surface for the formation of ether lay below the reaction entrance, indicating that the process was extremely favorable thermodynamically. From the aspects of thermodynamics and kinetics, the formation of ether was easier than the aldehyde alkylation, which was consistent with the experimental observations. The aldol reaction of aldehyde occurred via transition state TS12 with a barrier of 19.08 kcal/mol, and was accompanied by an energy release of 2.83 kcal/mol. So it was likely to occur in the conditions that were required for aldehyde enolization.
(energy barrier 18.36 kcal/mol). Correspondingly, the aldol adducts were observed in the experiments.
Figure 3.2 Computational pathways for acid-catalyzed alkylation of aldehyde and the corresponding side reactions.

3.4.4 Characterization of Products

Product 3.7i, 3.9a-3.9f and their characterizations have been reported in the literature.[10,12]

**3,3-Bis(4-methoxyphenyl)-2-methylpropanal (3.3a):**

![3.3a](image)

$^1$H NMR (400 MHz, CDCl$_3$): δ 1.01 (d, 3H, $J = 6.9$ Hz), 3.18-3.21 (m, 1H), 3.74 (s, 3H), 3.76 (s, 3H), 4.00 (d, 1H, $J = 11.0$ Hz), 6.79-6.84 (m, 4H), 7.13-7.25 (m, 4H), 9.55 (d, 1H $J = 3.2$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 13.8, 50.7, 51.9, 55.4, 114.3, 114.4, 129.1, 129.2, 134.8, 134.9, 158.4, 204.7. HRMS (ESI, $m/z$): calcd for C$_{18}$H$_{21}$O$_3^+$ [M+H]$^+$: 285.1491; found: 285.1504.

**2-(Bis(4-methoxyphenyl)methyl)butanal (3.3b):**

![3.3b](image)

$^1$H NMR (400 MHz, CDCl$_3$): δ 0.85 (t, 3H, $J = 15.1$ Hz), 1.48-1.56 (m, 2H), 2.99-3.04 (m, 1H), 3.73 (s, 3H), 3.75 (s, 3H), 4.04 (d, 1H, $J = 11.0$ Hz), 6.77-6.84 (m, 4H), 7.14-7.25 (m, 4H), 9.46 (d, 1H, $J = 4.1$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 11.5, 21.8, 50.6, 55.4, 57.8, 114.3, 114.4, 129.0, 129.1, 134.8, 134.9, 158.4, 204.7. HRMS (ESI, $m/z$): calcd for C$_{19}$H$_{23}$O$_3^+$ [M+H]$^+$: 299.1647; found: 299.1638.
2-Benzyl-3,3-bis(4-methoxyphenyl)propanal (3.3c): $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.75-2.80 (dd, 1H, $J = 3.7, 4.1$ Hz), 2.85-2.92 (dd, 1H, $J = 9.6, 9.6$ Hz), 3.48-3.54 (m, 1H), 3.74 (s, 3H), 3.78 (s, 3H), 4.11 (d, 1H, $J = 11.0$ Hz), 6.78-7.05 (m, 6H), 7.15-7.25 (m, 7H), 9.53 (d, 1H, $J = 3.2$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 35.1, 51.0, 55.4, 57.8, 114.4, 114.5, 126.6, 128.7, 129.1, 134.2, 134.6, 138.8, 158.5, 204.5. HRMS (ESI, $m/z$): calcd for C$_{24}$H$_{25}$O$_3$ $[^{[M+H]+}: 361.1804$; found: 361.1808.

2-(Bis(4-methoxyphenyl)methyl)hexanal (3.3d):

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.80 (t, 3H, $J = 12.4$ Hz), 1.16-1.27 (m, 4H), 1.41-1.44 (m, 1H), 1.51-1.59(m, 1H), 3.73 (s, 3H), 3.76 (s, 3H), 4.02 (d, 1H, $J = 11.0$ Hz), 6.78-6.84 (m, 4 H), 7.14-7.25 (m, 4H), 9.45 (d, 1H, $J = 4.6$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 14.0, 22.8, 28.5, 29.2, 50.9, 55.4, 56.3, 114.3, 114.4, 129.0, 129.1, 134.8, 134.9, 158.4, 204.7. HRMS (ESI, $m/z$): calcd for C$_{21}$H$_{27}$O$_3$ $[^{[M+H]+}: 327.1960$; found: 327.1966.

3-(4-Methoxyphenyl)-2-methyl-3-phenylpropanal (3.3e): $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.01 (d, 3H, $J = 5.5$ Hz), 1.03 (d, 3H, $J = 5.5$ Hz), 3.23-3.27 (m, 2H), 3.74 (s, 3H), 3.75 (s, 3H), 4.01 (d, 1H, $J = 3.6$ Hz), 4.04 (d, 1H, $J = 3.6$ Hz),
6.80-6.84 (m, 4H), 7.15-7.30 (m, 14H), 9.56 (d, 1H, $J = 1.4$ Hz), 9.57 (d, 1H, $J = 0.9$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 13.8, 13.9, 50.5, 52.7, 52.8, 55.4, 114.3, 114.4, 126.8, 126.9, 128.1, 128.2, 128.9, 129.0, 129.2, 129.3, 134.4, 134.5, 142.6, 142.7, 158.5, 204.5. HRMS (ESI, $m/z$): calcd for C$_{17}$H$_{19}$O$_2$ $^{+}$ [M+H]$^+$: 255.1385; found: 255.1390.

2-((4-Methoxyphenyl)(phenyl)methyl)butanal (3.3f):

$^1$H NMR (400 MHz, CDCl$_3$): δ 0.82-0.87 (m, 6H), 1.50-1.55 (m, 4H), 3.05-3.09 (m, 2H), 3.72 (s, 3H), 3.74 (s, 3H), 4.09 (d, 2H, $J = 11.0$ Hz), 6.78-6.84 (m, 4H), 7.14-7.30 (m, 14H), 9.47 (d, 1H, $J = 2.3$ Hz), 9.48 (d, 1H, $J = 1.8$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 11.5, 21.7, 21.8, 51.4, 55.4, 57.6, 114.3, 126.8, 126.9, 128.1, 128.9, 129.1, 134.4, 134.5, 142.6, 142.7, 158.5, 204.5. HRMS (ESI, $m/z$): calcd for C$_{18}$H$_{21}$O$_2$ $^{+}$ [M+H]$^+$: 269.1542; found: 269.1540.

2-Methyl-3,3-dip-tolylpropan-1-ol (3.3g°):

$^1$H NMR (400 MHz, CDCl$_3$): δ 0.94 (d, 3H, $J = 6.9$ Hz), 2.26 (s, 3H), 2.27 (s, 3H), 2.48-2.50 (m, 1H), 3.35-3.40 (dd, 1H, $J = 6.0$, 5.9 Hz), 3.54-3.58 (dd, 1H, $J = 3.7$, 4.1 Hz), 3.62 (d, 1H, $J = 11.0$ Hz), 7.04-7.07 (m, 4H), 7.15-7.19 (m, 4H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 16.3, 21.0, 39.3, 54.7, 66.8, 127.7, 128.0, 129.3, 129.5, 135.6, 135.8, 141.2, 141.3. HRMS (ESI, $m/z$): calcd for C$_{18}$H$_{23}$O $^{+}$ [M+H]$^+$: 255.1749; found: 255.1758.
2-(Dip-tolylmethyl)butan-1-ol (3.3h'): $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.88 (t, 3H, $J = 15.1$ Hz), 1.30-1.42 (m, 2H), 2.26 (s, 3H), 2.27 (s, 3H), 2.23-2.27 (m, 1H), 3.47-3.51 (dd, 1H, $J = 3.7$, 3.7 Hz), 3.62-3.65 (dd, 1H, $J = 3.2$, 3.7 Hz), 3.78 (d, 1H, $J = 11.4$ Hz), 7.04-7.07 (m, 4H), 7.17-7.19 (m, 4H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 11.4, 21.1, 21.7, 45.4, 53.2, 62.3, 127.9, 128.1, 129.4, 129.6, 135.7, 135.9, 141.3, 141.5. HRMS (ESI, m/z): calcd for C$_{19}$H$_{25}$O$^+$ [M+H]$^+$: 269.1905; found: 269.1899.

2-Benzhydrylbutan-1-ol (3.3i'): $^1$H NMR (400 MHz, CDCl$_3$):
$\delta$ 0.89 (t, 3H, $J = 11.0$ Hz), 1.31-1.43 (m, 2H), 2.27-2.33 (m, 2H), 3.47-3.51 (dd, 1H, $J = 4.1$, 3.7 Hz), 3.64-3.67 (dd, 1H, $J = 3.6$, 4.1 Hz), 3.87 (d, 1H, $J = 11.0$ Hz), 7.13-7.33 (m, 10H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 11.3, 21.6, 45.4, 53.9, 62.0, 126.3, 126.4, 128.1, 128.2, 128.7, 128.8, 144.0, 144.1. HRMS (ESI, m/z): calcd for C$_{17}$H$_{21}$O$^+$ [M+H]$^+$: 241.1592; found: 241.1599.

2-Benzhydrylpentan-1-ol (3.3j'): $^1$H NMR (400 MHz, CDCl$_3$):
$\delta$ 0.80 (t, 3H, $J = 12.8$ Hz), 1.25-1.43 (m, 4H), 2.34-2.38 (m, 1H), 3.45-3.49 (dd, 1H, $J = 3.6$, 4.1 Hz), 3.62-3.66 (dd, 1H, $J =$
3.6, 3.6 Hz), 3.88 (d, 1H, J = 11.4 Hz), 7.12-7.33 (m, 10H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 14.4, 20.2, 31.1, 43.7, 54.1, 62.5, 126.3, 126.4, 128.1, 128.3, 128.7, 128.8, 144.0, 144.2. HRMS (ESI, m/z): calcd for C$_{18}$H$_{23}$O$^+$/[M+H]$^+$: 255.1749; found: 255.1752.

2-(Bis(4-chlorophenyl)methyl)butan-1-ol (3.3k'): $^1$H NMR (400 MHz, CDCl$_3$): δ 0.89 (t, 3H, J = 15.1 Hz), 1.31-1.40 (m, 2H), 2.16-2.22 (m, 1H), 3.42-3.46 (dd, 1H, J = 4.1, 4.1 Hz), 3.63-3.67 (dd, 1H, J = 3.2, 3.2 Hz), 3.89 (d, 1H, J = 11.5 Hz), 7.14-7.26 (m, 8H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 11.3, 21.3, 45.1, 52.2, 61.3, 128.9, 129.0, 129.4, 129.5, 132.2, 132.3, 142.0, 142.2. HRMS (ESI, m/z): calcd for C$_{17}$H$_{19}$OCl$_2$+[M+H]$^+$: 309.0813; found: 309.0815.

2-(Bis(4-chlorophenyl)methyl)pentan-1-ol (3l'): $^1$H NMR (400 MHz, CDCl$_3$): δ 0.83 (t, 3H, J = 14.2 Hz), 1.23-1.42 (m, 4H), 2.25-2.28 (m, 1H), 3.42-3.46 (dd, 1H, J = 4.1, 3.7 Hz), 3.62-3.66 (dd, 1H, J = 3.2, 3.2 Hz), 3.90 (d, 1H, J = 11.4 Hz), 7.09-7.30 (m, 8H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 14.4, 20.2, 30.8, 43.4, 52.4, 61.7, 128.9, 129.0, 129.4, 129.5, 132.2, 132.3, 142.0, 142.3. HRMS (ESI, m/z): calcd for C$_{18}$H$_{21}$OCl$_2$+[M+H]$^+$: 325.0940; found: 325.0933.
3,3-Bis(4-methoxyphenyl)-2-methyl-2-phenylpropanal (3.7a): $^1$H NMR (400 MHz, CDCl$_3$): δ 1.54 (s, 3H), 3.70 (s, 3H), 3.75 (s, 3H), 4.93 (s, 1H), 6.65 (d, 2H, $J = 8.7$ Hz), 6.76 (d, 2H, $J = 8.7$ Hz), 6.92 (d, 2H, $J = 8.7$ Hz), 7.08 (d, 2H, $J = 8.7$ Hz), 7.13-7.17 (m, 2H), 7.24-7.30 (m, 3H), 9.75 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 18.6, 55.4, 55.6, 58.3, 113.4, 113.7, 127.4, 128.5, 128.8, 131.3, 131.4, 133.1, 133.5, 139.4, 158.0, 158.3, 202.6. HRMS (ESI, m/z): calcd for C$_{24}$H$_{25}$O$_3$ [M+H]$^+$: 361.1804; found: 361.1791.

3,3-Bis(4-methoxyphenyl)-2,2-dimethylpropanal (3.7b): $^1$H NMR (400 MHz, CDCl$_3$): δ 1.13 (s, 6H), 3.76 (s, 6H), 4.09 (s, 1H), 6.81 (d, 4H, $J = 8.7$ Hz), 7.16 (d, 4H, $J = 8.7$ Hz), 9.67 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 21.6, 49.7, 55.3, 57.1, 113.7, 130.7, 133.2, 158.3, 206.4. HRMS (ESI, m/z): calcd for C$_{19}$H$_{23}$O$_3$ [M+H]$^+$: 299.1647; found: 299.1633.

3-(4-Methoxyphenyl)-2-methyl-2,3-diphenylpropanal (3.7c): $^1$H NMR (400 MHz, CDCl$_3$): δ 1.57 (s, 3H), 3.76 (s, 3H), 4.99 (s, 1H), 6.66 (d, 1H, $J = 9.2$ Hz), 6.78 (d, 1H, $J = 8.7$ Hz) 6.94-7.30 (m, 12H), 9.76 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 18.5, 18.7, 55.2, 55.3, 56.3, 56.4, 58.1, 58.2, 113.3, 113.7, 126.4, 126.7, 127.4, 128.0, 128.3, 128.4, 128.7, 128.8, 130.2, 130.3, 131.3, 131.4, 132.7, 133.0, 139.2, 139.3,
141.0, 141.4, 202.3, 202.4. HRMS (ESI, m/z): calcd for C$_{23}$H$_{23}$O$_2$\(^+\) [M+H]$^+$: 331.1698; found: 331.1699.

**3-(4-Methoxyphenyl)-2,2-dimethyl-3-phenylpropanal**

(3.7d): $^1$H NMR (400 MHz, CDCl$_3$): δ 1.14 (s, 6H), 3.76 (s, 3H), 4.14 (s, 1H), 6.81 (d, 2H, $J = 8.7$), 7.16-7.28 (m, 7H), 9.69 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 21.7, 21.8, 49.6, 55.3, 58.0, 113.8, 126.7, 128.4, 129.7, 130.8, 132.9, 141.1, 158.3, 206.2. HRMS (ESI, m/z): calcd for C$_{18}$H$_{21}$O$_2$\(^+\) [M+H]$^+$: 269.1542; found: 269.1554.

**2-Methyl-2-phenyl-3,3-dip-tolylpropan-1-ol (7e’):** $^1$H NMR (400 MHz, CDCl$_3$): δ 1.47 (s, 3H), 2.20 (s, 3H), 2.27 (s, 3H), 3.53 (d, 1H, $J = 10.6$ Hz), 3.76 (d, 1H, $J = 11.8$ Hz), 6.89-6.93 (m, 4H), 7.00-7.08 (m, 4H), 7.14-7.23 (m, 5H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 20.8, 21.0, 21.1, 47.2, 57.9, 71.1, 126.5, 128.0, 128.3, 128.5, 128.7, 130.3, 130.5, 135.4, 135.9, 138.8, 139.1, 143.6. HRMS (ESI, m/z): calcd for C$_{19}$H$_{25}$O$^+$ [M+H]$^+$: 269.1905; found: 269.1907.

**2,2-Dimethyl-3,3-dip-tolylpropanal (3.7f):** $^1$H NMR (400 MHz, CDCl$_3$): δ 1.14 (s, 6H), 2.28 (s, 6H), 4.11 (s, 1H), 7.06 (d, 4H, $J = 8.2$ Hz), 7.13 (d, 4H, $J = 8.2$ Hz), 9.69 (s,
1H. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 21.0, 21.7, 49.5, 58.2, 129.1, 129.6, 136.3, 138.0, 206.4. HRMS (ESI, $m/z$): calcd for C$_{19}$H$_{23}$O$^+$ [M+H]$^+$: 267.1749; found: 267.1751.

2-Methyl-2,3,3-triphenylpropan-1-ol (3.7g'): $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.49 (s, 3H), 3.53-3.58 (dd, 1H, $J = 7.3, 7.3$ Hz), 3.77-3.81 (dd, 1H, $J = 4.1, 4.1$ Hz), 4.52 (s, 1H), 7.05-7.26 (m, 15H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 20.8, 47.2, 58.6, 71.0, 126.1, 126.6, 127.8, 128.0, 128.1, 128.3, 130.4, 130.7, 141.6, 141.9, 143.3. HRMS (ESI, $m/z$): calcd for C$_{22}$H$_{23}$O: 303.1749$^+$ [M+H]$^+$; found: 303.1745

2,2-Dimethyl-3,3-diphenylpropanal (3.7h): $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.16 (s, 6H), 4.19 (s, 1H), 7.22-7.27 (m, 10H), 9.70 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 21.8, 49.4, 58.9, 126.8, 128.4, 129.8, 140.8, 206.1. HRMS (ESI, $m/z$): calcd for C$_{17}$H$_{19}$O$^+$ [M+H]$^+$: 239.1436; found: 239.1434.

3,3-Bis(4-chlorophenyl)-2,2-dimethylpropanal (3.7j):

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.14 (s, 6H), 4.17 (s, 1H), 7.14-7.17 (m, 4H), 7.24-7.27 (m, 4H), 9.64 (s, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 21.7, 49.3, 57.2, 128.7, 131.0, 133.0, 138.9, 205.3. HRMS (ESI, $m/z$): calcd for C$_{17}$H$_{17}$OCl$_2^+$ [M+H]$^+$: 307.0656; found: 307.0671.
3.5 References


[24] The possible rather complicated radical reactions of the ether-derived diaryl cation intermediates can also lead to unproductive consumption of the alchol substrates, for relavent studies, see: a) C. Y. Choi, L. M. Stock, *J. Org. Chem.*


Chapter 4

*N-heterocyclic carbene catalyzed intermolecular Stetter reaction of formaldehyde with chalcone*

NHC-catalyzed conversion of sugars to one-carbon nucleophile

*carbohydrate activation & C-C bond cleavage*
4.1 Introduction

4.1.1 Stetter reaction

Since the first report of thiazolium-catalyzed nucleophilic acylation to Michael acceptors in the 1970s by Stetter and co-workers, the Stetter reaction has been known as the catalytic 1,4-addition of aldehydes to Michael acceptors. It has been demonstrated as a useful approach to synthesize 1,4-bifunctional compounds like 1,4-diketones, 4-ketoesters, and 4-ketonitriles. Thiazolium salts were first used to catalyze this reaction (Figure 4.1). Benzyl-substituted thiazolium salt 4.A was found to be most effective for aliphatic aldehydes, while 4.B and 4.C were proved to be better for aromatic aldehydes.

![Figure 4.1 Commonly used thiazolium salts](image)

In 1989, the Enders group achieved the first asymmetric Stetter reaction using a chiral thiazolium salt. n-Butanal was used to react with chalcone to generate the desired 1,4-diketone with 39% ee, but with only 4% yield (Scheme 4.1). After that, researchers from all over the world developed many new catalysts to facilitate the Stetter reaction to give useful chiral products.
The first intramolecular Stetter reaction was reported by Ciganek in 1995. 2-Formylphenoxycrotonates and formylphenoxyacrylates were used to give the desired products with moderate to excellent yields (Scheme 4.2). The enantioselective version of this reaction was later developed by the Ender group in 1996. A triazolium salt was applied in this transformation to give various 4-chromanones with moderate yields and enantioselectivities (Scheme 4.3).

Subsequently, various catalysts were developed to achieve better results for this transformation. In 2002, Rovis and co-workers reported a triazolium salt derived from aminoindanol as the catalyst to afford ketoesters with good yields and
Both aromatic and aliphatic aldehydes could be applied in this reaction (Scheme 4.4).

\[
\begin{align*}
\text{Scheme 4.4 Triazolium catalyzed asymmetric Stetter reaction} \\
\end{align*}
\]

Compared to the intramolecular version, the asymmetric intermolecular Stetter reaction was a lot more difficult to achieve. There was no successful report until 2008, when the groups of Enders and Rovis independently reported the asymmetric version of this reaction. The Enders group used a triazolium based catalyst to facilitate the reaction of benzaldehyde and chalcone. Products with moderate to good yields and enantioselectivities could be obtained. The enantioselectivity could reach 99% after recrystallization (Scheme 4.5).

\[
\begin{align*}
\text{Scheme 4.5 Asymmetric intermolecular Stetter reaction} \\
\end{align*}
\]

Similarly, the Rovis group reported the intermolecular Stetter reaction of glyoxamide and alkylidenemalonates catalyzed by a newly developed triazolium salt as the pre-catalyst. Stetter products with excellent yields and enantioselectivities could be generated using this new catalyst (Scheme 4.6).
Later, many reports involving the use of new catalysts and substrates in the asymmetric Stetter reaction emerged.\textsuperscript{[10]} Despite of all these successes, there was still a few challenges in terms of substrate scope. One among them we identified was the development of stereoselective Stetter reactions using simplest aldehydes, formaldehyde, acting as a one carbon nucleophile to generate useful products.

4.1.2 Formaldehyde as a nucleophile

Formaldehyde has been used widely as a one carbon nucleophile in synthetic chemistry.\textsuperscript{[11]} With N-heterocyclic carbenes, formaldehyde has been used as a nucleophile through an acyl anion intermediate. However, it is very difficult to trap this intermediate by using other electrophiles since formaldehyde itself is a very active electrophile. Therefore, it undergoes immediately self-benzoin reactions.\textsuperscript{[12]} The self-benzoin reaction of formaldehyde can produce glycolaldehyde, 1,3-dihydroxyacetone and other long chain carbohydrates (Scheme 4.7).

The benzoin reactions are reversible in some conditions and can regenerate acyl anion intermediates. We speculated that if we could minimize the concentration of free formaldehyde in the reaction mixture and applied more
enforced conditions, the one-carbon acyl anion intermediate might be able to react with other electrophiles. Self-benzoin adducts could be utilized to generate the one-carbon acyl anion intermediate through a retro-benzoin pathway catalyzed by N-heterocyclic carbene.

Scheme 4.7 Self-benzoin reaction of formaldehyde

4.2 Results and discussion

1,3-Dihydroxyacetone 4.1d (DHA), which is a formaldehyde self-benzoin adduct, was first used to test our hypothesis of generating in situ a one-carbon nucleophile. Commercially available chalcone was utilized as an electrophile to trap the reactive intermediate (Scheme 4.8). When NHC pre-catalyst 4.A and K$_2$CO$_3$ were used, no desired product 4.3a was detected at 80°C or 100 °C using a conventional oil bath or microwave heating, and both starting materials could be recovered with very little loss. We then tried using a harsher reaction condition by carrying out the reaction at 130 °C using microwave heating in a sealed tube. To our delight, the Stetter product 4.3a was obtained in 45% isolated yield in a short reaction time of 10 minutes.

Encouraged by this initial success, we then quickly switched to the use of
biomass-based carbohydrates as formaldehyde equivalents. It is particularly noteworthy that biomass chemistry has received great attention as they have the potential to be converted to fuels or chemicals.\footnote{14} We chose glucose, a C6 sugar, and chalcone 4.2a as the model substrates to see if we could obtain any Stetter product using carbohydrates as one-carbon acyl anion intermediate precursors.

![Scheme 4.8 Initial results using DHA](image)

We screened a few parameters for this reaction, as summarized in Table 4.1. Commercially available NHC pre-catalyst 4.B was chosen to get optimized conditions. Solvent screening showed that acetonitrile could give the best result of 23% yield of the desired Stetter product in standard microwave heating conditions. Various organic and inorganic bases were tested (Table 4.1, entries 1-4), and it was found out that stronger bases like DBU and Cs$_2$CO$_3$ gave better yields than weaker bases such as DIPEA and Na$_2$CO$_3$ (Table 4.1, entries 5-9). K$_2$CO$_3$ was chosen for further optimization as it could generate the Stetter product with 40% yield and 37% unreacted chalcone.

After obtaining the optimal solvent and base, we next screened the effect of various NHC pre-catalysts. Benzyl-substituted thiazolium salt 4.C, imidazolium
salt (4.D) and triazolium salt (4.E) were found to be ineffective for this reaction, giving little or no Stetter product (Table 4.1, entries 11-13). Methyl or Ethyl substituted thiazolium salts could give similar results (Table 4.1, entries 14-15). Prolonging the reaction time in the presence of catalysts 4.A and 4.G could further improve the yields to 63% and 80% respectively (Table 4.1, entries 16-17). Changing the glucose loading from 2.0 equivalents to 0.2 equivalent led to slightly lower yields (Table 4.1, entries 18-20). When the reaction was carried out under a similar condition using conventional oil bath heating, a highly diminished yield of 10% was obtained (Table 4.1, entry 21).

**Table 4.1.** Hexose carbohydrate as one-carbon nucleophile: condition optimization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pre-catalyst</th>
<th>Solvent</th>
<th>Base</th>
<th>Yield (%)&lt;sup&gt;[b]&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.B</td>
<td>EtOH</td>
<td>NEt₃</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>4.B</td>
<td>CH₃CN</td>
<td>NEt₃</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>4.B</td>
<td>DMF</td>
<td>NEt₃</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>4.B</td>
<td>toluene</td>
<td>NEt₃</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>4.B</td>
<td>CH₃CN</td>
<td>DBU</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>4.B</td>
<td>CH₃CN</td>
<td>DIEA</td>
<td>19</td>
</tr>
<tr>
<td>7</td>
<td>4.B</td>
<td>CH₃CN</td>
<td>Na₂CO₃</td>
<td>&lt;5</td>
</tr>
<tr>
<td>8</td>
<td>4.B</td>
<td>CH₃CN</td>
<td>Cs₂CO₃</td>
<td>56</td>
</tr>
<tr>
<td>9</td>
<td>4.B</td>
<td>CH₃CN</td>
<td>K₂CO₃</td>
<td>40(37)&lt;sup&gt;[c]&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>4.A</td>
<td>CH₃CN</td>
<td>K₂CO₃</td>
<td>58(12)&lt;sup&gt;[c]&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>4.C</td>
<td>CH$_3$CN</td>
<td>K$_2$CO$_3$</td>
<td>&lt;5</td>
</tr>
<tr>
<td>12</td>
<td>4.D</td>
<td>CH$_3$CN</td>
<td>K$_2$CO$_3$</td>
<td>trace</td>
</tr>
<tr>
<td>13</td>
<td>4.E</td>
<td>CH$_3$CN</td>
<td>K$_2$CO$_3$</td>
<td>&lt;5</td>
</tr>
<tr>
<td>14</td>
<td>4.F</td>
<td>CH$_3$CN</td>
<td>K$_2$CO$_3$</td>
<td>36</td>
</tr>
<tr>
<td>15</td>
<td>4.G</td>
<td>CH$_3$CN</td>
<td>K$_2$CO$_3$</td>
<td>61(23)$^c$</td>
</tr>
<tr>
<td>16$^{[e]}$</td>
<td>4.A</td>
<td>CH$_3$CN</td>
<td>K$_2$CO$_3$</td>
<td>63</td>
</tr>
<tr>
<td>17$^{[e]}$</td>
<td>4.G</td>
<td>CH$_3$CN</td>
<td>K$_2$CO$_3$</td>
<td>80$^{[d]}$</td>
</tr>
<tr>
<td>18$^{[e,f]}$</td>
<td>4.G</td>
<td>CH$_3$CN</td>
<td>K$_2$CO$_3$</td>
<td>45</td>
</tr>
<tr>
<td>19$^{[e,g]}$</td>
<td>4.G</td>
<td>CH$_3$CN</td>
<td>K$_2$CO$_3$</td>
<td>71</td>
</tr>
<tr>
<td>20$^{[e,h]}$</td>
<td>4.G</td>
<td>CH$_3$CN</td>
<td>K$_2$CO$_3$</td>
<td>53</td>
</tr>
<tr>
<td>21$^{[i]}$</td>
<td>4.G</td>
<td>CH$_3$CN</td>
<td>K$_2$CO$_3$</td>
<td>10</td>
</tr>
</tbody>
</table>

[a] 1.0 equiv 4.1e and 0.2 mmol 4.2 were reacted in 2 mL solvent for 10 min. [b] Determined via crude $^1$H NMR analysis. [c] Yield of remaining chalcone. [d] With 79% isolated yield. [e] Reaction for 30 min. [f] 2.0 equiv 4.1e was used. [g] 0.5 equiv 4.1e was used. [h] 0.2 equiv 4.1e was used. [i] Conventional oil bath heating for 30 min.

A plausible pathway to generate one-carbon acyl anion intermediates from carbohydrates represented by glucose was proposed as in Scheme 4.9. The 6-carbon sugar, glucose, could equilibrate between cyclic acetal form 4.1e and acyclic aldehyde form 4.1e'. The free NHC catalyst generated through deprotonation underwent nucleophilic addition to the acyclic aldehyde 4.1e' to give intermediate I. The proton transfer generated intermediate II, followed by retro-benzoin process to give reactive acyl anion intermediate III. The intermediate III subsequently participated in Stetter reaction with chalcone 4.2a to generate the final product 4.3a and released the free NHC catalyst. During the retro-benzoin process, a 5-carbon sugar (4.4a) was produced after the C-C bond cleavage. This degraded sugar could further undergo a similar catalytic process to give an acyl anion intermediate again with a 4-carbon sugar released. This was
partially confirmed experimentally, when 53% Stetter product was obtained with the use of 0.2 equivalent glucose. This indicated that most of the glucose was converted to one-carbon acyl anion intermediates.

We next examined a few commercially available carbohydrates to prove the generality of this methodology (Chart 4.1). 6-Carbon sugars were tested and found to be very effective for this transformation (Chart 4.1, 4.1e-g), giving the Stetter product in 57-81% yields. Prolonging the reaction time to 30 minutes resulted in better yields. Several 5-carbon sugars, like D-(-)-arabinose, were examined and found to be more effective than 6-carbon sugars to give the Stetter products 4.3a in 68-83% yield (Chart 4.1, 4.1h-j). When two disaccharides and one polysaccharide was used in this reaction, Stetter products 4.3a could still be afforded, albeit with
very low yields (7-11%) in 30 minutes (Chart 4.1, 4.1k-m).

**Chart 4.1 Examples of carbohydrates**

<table>
<thead>
<tr>
<th>Carbohydrates</th>
<th>Reaction Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1e-m (0.2 mmol)</td>
<td>PhCHO Ph</td>
<td>4.2a (0.2 mmol)</td>
</tr>
</tbody>
</table>

**6-carbon sugar**
- D(+)-Glucose
- D(-)-Fructose
- D(+)-Galactose

**5-carbon sugar**
- D(-)-Arabinose
- L(+)-Arabinose
- D(-)-Ribose
- D(+)-Xylose

**Di- and poly-saccharides**
- D(+)-Celllobiose
- Sucrose
- Cellulose

[iso] Yields were determined via 1H NMR analysis unless otherwise noted.

We then chose D(-)-arabinose as the one-carbon acyl anion precursor to study the scope of the chalcone substrates, as summarized in Chart 4.2. Most of the reactions were completed within 10 minutes, giving the Stetter products with moderate to good yields. Various functional groups could be tolerated on the benzene ring, including electron withdrawing as well as electron donating groups.
Stetter products could be obtained in 57-86% isolated yields (Chart 4.2, 4.3a-o). β-Alkyl substituted chalcone could also be applied in this reaction, but with lower isolated yield of 43% (Chart 4.2, 4.3p).

**Chart 4.2** Scope of the enones using D-(-)-arabinose

![Chart 4.2](image)

[a] 0.2 mmol 4.1h was reacted with 0.2 mmol 4.2 in 2 mL CH3CN in indicated conditions. [b] Isolated yield.

β-Formyl ketones are very commonly used synthones in synthetic chemistry, but not very easy to prepare by known literature methods.15 By using this strategy, Stetter products (β-formyl ketones) was obtained in a single step that could be further transformed to furans and pyrroles.16 After removing the solvents from the first step, the crude product, without further purification, was used directly for the
next step to give furan or pyrroles in 48-63% yields (Scheme 4.10).

Scheme 4.10 Formation of furans and pyrroles

After successfully developing reaction condition for using carbohydrates as one-carbon acyl anion precursors, we wondered whether we could use formaldehyde itself in the Stetter reactions with enones. We first tried paraformaldehyde 4.1n with chalcone 4.2a using the commercially available catalyst 4.B under microwave conditions. Different solvents were tested, and acetonitrile was found to be the best solvent, giving the Stetter product 4.3a in 38% yield (Table 4.2, entry 2). Other solvents paled in comparison, with ethanol generating the desired product with a slightly lower yield of 28% (Table 4.2, entries 1-7). Examination of several bases showed that K$_2$CO$_3$ was the best, furnishing product with 65% yield (Table 4.2, entries 8-12).

After obtaining the optimized solvent and base, we next evaluated the NHC catalysts. Commonly used triazolium salts and thiazolium salts were all applied in this reaction. We found that besides the simplest thiazolium salts, other types of NHC catalysts could not afford any Stetter products. Methyl or ethyl substituted
thiazolium salts (4.A and 4.B) could generate the desired products in good yields (Table 4.2, entries 13-22), while changing the reaction temperature led to no improvement in the yields (Table 4.2, entries 23-24). Varying of the reaction time, catalyst loading and substrate ratio could not give a better yield of Stetter product 4.3a (Table 4.2, entries 25-28). It was worthy to note that conventional oil bath heating could afford 34% of the desired product under otherwise identical condition (Table 4.2, entry 29).

Table 4.2 Paraformaldehyde as one-carbon nucleophile: condition optimization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pre-catalyst</th>
<th>Solvent</th>
<th>Base</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.B</td>
<td>EtOH</td>
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[a] 4.0 equiv 4.1n and 0.2 mmol 4.2a were reacted in 2 mL solvent in indicated conditions. [b] Yields were determined via ¹H NMR analysis. [c] Isolated yield. [d] 140 °C. [e] 120 °C. [f] 30 min. [g] 30 mol% NHC catalyst was used. [h] 10.0 equiv 4.1n was used. [i] 2.0 equiv 4.1n was used. [j] Conventional oil bath heating.

With the optimized conditions in hand, we examined the scope of the enone (Chart 4.3). The results were similar with those obtained using carbohydrates as one-carbon acyl anion precursors. Different enones with various substitution groups could all give the desired Stetter products with good yields. Generally, the yields using paraformaldehyde were slightly lower than those obtained using carbohydrates.

**Chart 4.3** Scope of the enones using paraformaldehyde
(HCHO)_n + R'\text{CHO} \rightarrow R'\text{CO} (\text{CH}_3\text{CN, } \nu\text{W, 130°C, 10 min})

4.1n 4.2 4.3a-q

4.1n was reacted with 0.2 mmol 4.2 in 2 mL CH_3CN in indicated conditions. [b] Isolated yield.

4.3 Conclusions

In summary, we have achieved the first NHC catalyzed activation of carbohydrates and paraformaldehyde as formaldehyde equivalents to generate one-carbon acyl anion intermediates for the Stetter reactions with enones. The one-carbon acyl anion intermediates were generated through a retro-benzoin-type process, accompanied by the C-C bond cleavage of carbohydrates. Carbohydrates such as 5-carbon sugars could produce multiple acyl anion intermediates from one molecule that could undergo the Stetter reaction to afford the β-formyl ketones in good yields. These β-formyl ketones could be easily converted to furans and
pyrroles after simple transformation.

4.4 Experimental

4.4.1 General Procedure

1) General procedure for the NHC-catalyzed reactions of carbohydrates or paraformaldehyde with enones:

A 10 mL microwave reaction tube was charged with carbohydrates 4.1 (0.2 mmol) or formaldehyde 4.1n (0.8 mmol), enones 4.2 (0.2 mmol), NHC catalyst (0.04 mmol), K₂CO₃ (0.04 mmol) and acetonitrile (2 mL). The reaction tube was sealed with a Teflon-lined snap cap, and heated in a microwave reactor at 130 °C (inner pressure: 40–60 PSI) for 10 or 30 minutes. After cooled by compressed air flow, the reaction mixture was transferred to a round bottom flask and the vessel was rinsed with CH₂Cl₂. The solvent was then evaporated under vacuum. The residue was purified via flash column chromatography over silica gel eluting with EtOAc/hexane to give the desired pure product 4.3. The ¹H NMR yields were determined by adding 0.1 mmol of 1,3,5-trimethoxy benzene as an internal standard to the crude reaction mixture after the reaction was complete.

2) Purification of 4.3a via only a simple work-up for further transformations:

The crude reaction mixture, obtained using the general procedure above, was concentrated under reduced pressure. The residue was dissolved in Et₂O (4 mL)
and washed with H$_2$O for three times (3 x 4 mL). The organic layers were dried over anhydrous MgSO$_4$, and filtered. The solvent was removed in vacuum to give the “crude” product $3a$ with high purity (by TLC and NMR analysis) that could be directly subjected to further transformations.

3) General procedure for one-pot synthesis of furans and pyrroles (4.5-4.7):

The crude β-formyl ketone product (Stetter product) $4.3a$ could be easily converted to furan and pyrroles (4.5-4.7) by adopting known procedures.$^{[16a]}$

One-Pot Synthesis of furan 4.5: The crude reaction mixture containing $4.3a$, obtained in the reaction of Arabinose $4.1h$ (0.2 mmol) and chalcone $4.2a$ (0.2 mmol), was concentrated under reduced pressure. The same reaction tube containing crude $4.3a$ was subsequently charged with ethanol (2 mL) and 1M HCl (aqueous solution, 0.2 mL) and sealed with a Teflon-lined snap cap. After heating in a microwave reactor at 150 °C for 15 minutes, the crude reaction mixture was diluted with EtOAc, and washed successively with aqueous saturated NaHCO$_3$ and brine solutions. The organic layer was collected, dried over Na$_2$SO$_4$, and filtered. The solvent was removed in vacuum. The resulting residue was purified via flash column chromatography over silica gel eluting with EtOAc/hexane to give $4.5$ in 63% yield.

One-Pot Synthesis of pyrrole 4.6: The crude reaction mixture containing $4.3a$,
obtained in the reaction of Arabinose 4.1h (0.2 mmol) and chalcone 4.2a (0.2 mmol), was concentrated under reduced pressure. The same reaction tube containing crude 4.3a was subsequently charged with THF (1 mL), AcOH (1 mL) and PhNH₂ (0.4 mmol). The reaction tube was sealed with a Teflon-lined snap cap, and heated in a microwave reactor at 170 °C for 15 minutes. The crude reaction mixture was diluted with EtOAc, and washed successively with aqueous saturated NaHCO₃ and brine solutions. The organic layer was collected, dried over Na₂SO₄, and filtered. The solvent was removed in vacuum. The resulting residue was purified via flash column chromatography over silica gel eluting with EtOAc/hexane to give 4.6 in 55% yield.

One-Pot Synthesis of pyrrole 4.7: The crude reaction mixture containing 4.3a, obtained in the reaction of Arabinose 4.1h (0.2 mmol) and chalcone 4.2a (0.2 mmol), was concentrated under reduced pressure. The same reaction tube containing crude 4.3a was subsequently charged with THF (1 mL), AcOH (1 mL) and AcONH₄ (0.8 mmol). The reaction tube was sealed with a Teflon-lined snap cap, and heated in a microwave reactor at 170 °C for 15 minutes. The crude reaction mixture was diluted with EtOAc, and washed successively with aqueous saturated NaHCO₃ and brine solutions. The organic layer was collected, dried over Na₂SO₄, and filtered. The solvent was removed in vacuum. The resulting residue was purified via flash column chromatography over silica gel eluting with EtOAc/hexane to give 4.7 in 48% yield.
4.4.2 Characterization of Stetter Products 4.3

**4-Oxo-2,4-diphenylbutanal (4.3a):** $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.81 (s, 1H), 7.98-7.95 (m, 2H), 7.58-7.54 (m, 1H), 7.47-7.43 (m, 2H), 7.40-7.36 (m, 2H), 7.33-7.25 (m, 3H), 4.46 (dd, $J$ = 8.4, 4.9 Hz, 1H), 3.96 (dd, $J$ = 18.0, 8.4 Hz, 1H), 3.23 (dd, $J$ = 18.0, 4.9 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 199.2, 197.5, 136.7, 135.7, 133.6, 129.5, 129.3, 128.9, 128.4, 128.2, 53.9, 39.7; HRMS (ESI, $m/z$): calcd for C$_{16}$H$_{15}$O$_2$ $^{[M+H]^+}$: 239.1072; found: 239.1075.

**4-(4-Chlorophenyl)-4-oxo-2-phenylbutanal (4.3b):**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.78 (s, 1H), 7.90 (d, $J$ = 8.5 Hz, 2H), 7.45-7.36 (m, 4H), 7.34-7.29 (m, 1H), 7.26-7.24 (m, 2H), 4.44 (dd, $J$ = 8.5, 4.8 Hz, 1H), 3.91 (dd, $J$ = 18.0, 8.5 Hz, 1H), 3.16 (dd, $J$ = 17.9, 4.8 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 198.9, 196.2, 139.9, 135.3, 134.9, 129.7, 129.4, 129.2, 129.0, 128.1, 53.8, 39.5; HRMS (ESI, $m/z$): calcd for C$_{16}$H$_{14}$O$_2$Cl $^{[M+H]^+}$: 273.0682; found: 273.0682.

**4-(4-Bromophenyl)-4-oxo-2-phenylbutanal (4.3c):**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.78 (s, 1H), 7.91-7.74 (m, 2H), 7.66-7.54 (m, 2H), 7.40-7.29 (m, 3H),
7.26-7.24 (m, 2H), 4.44 (dd, J = 8.5, 4.8 Hz, 1H), 3.90 (dd, J = 17.9, 8.5 Hz, 1H), 3.15 (dd, J = 17.9, 4.7 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 198.9, 196.4, 135.3, 132.0, 129.7, 129.4, 129.1, 128.6, 128.1, 53.8, 39.4; HRMS (ESI, m/z): calcd for C$_{16}$H$_{14}$O$_2$Br$^+$ [M+H]$^+$: 317.0177; found: 317.0176.

4-(4-Methoxyphenyl)-4-oxo-2-phenylbutanal (4.3d): $^1$H NMR (400 MHz, CDCl$_3$): δ 9.81 (s, 1H), 7.95 (d, J = 9.0 Hz, 2H), 7.39-7.35 (m, 2H), 7.32-7.29 (m, 1H), 7.28-7.24 (m, 2H), 6.92 (d, J = 9.0 Hz, 2H), 4.44 (dd, J = 8.4, 4.9 Hz, 1H), 3.90 (dd, J = 18.1, 8.4 Hz, 1H), 3.86 (s, 3H), 3.19 (dd, J = 18.1, 5.2 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 199.3, 195.9, 163.8, 135.7, 130.5, 129.6, 129.3, 129.2, 127.9, 113.8, 55.6, 53.8, 39.2; HRMS (ESI, m/z): calcd for C$_{17}$H$_{17}$O$_3$+ [M+H]$^+$: 269.1178; found: 269.1174.

2-(4-Chlorophenyl)-4-oxo-4-phenylbutanal (4.3e): $^1$H NMR (400 MHz, CDCl$_3$): δ 9.78 (s, 1H), 7.99-7.92 (m, 2H), 7.59-7.55 (m, 1H), 7.48-7.44 (m, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 4.42 (dd, J = 8.0, 5.3 Hz, 1H), 3.92 (dd, J = 18.0, 8.1 Hz, 1H), 3.22 (dd, J = 18.0, 5.1 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 198.6, 197.1, 136.4, 134.1, 133.6, 130.5, 129.5, 128.8, 128.2, 53.0, 39.5; HRMS (ESI, m/z): calcd for C$_{16}$H$_{14}$O$_2$Cl$^+$ [M+H]$^+$: 273.0682; found: 273.0680.

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**4-Oxo-4-phenyl-2-p-tolylbutanal (4.3f):** ¹H NMR (400 MHz, CDCl₃): δ 9.77 (s, 1H), 8.00-7.93 (m, 2H), 7.58-7.54 (m, 1H), 7.47-7.43 (m, 2H), 7.20-7.14 (m, 4H), 4.41 (dd, J = 8.4, 4.9 Hz, 1H), 3.92 (dd, J = 17.9, 8.4 Hz, 1H), 3.20 (dd, J = 17.9, 4.9 Hz, 1H), 2.34 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 199.3, 197.6, 137.9, 136.7, 133.5, 132.5, 130.2, 129.2, 128.8, 128.3, 53.5, 39.7, 21.3; HRMS (ESI, m/z): calcd for C₁₇H₁₇O₂⁺ [M+H]⁺: 253.1229; found: 253.1227.

**2-(4-Methoxyphenyl)-4-oxo-4-phenylbutanal (4.3g):** ¹H NMR (400 MHz, CDCl₃): δ 9.77 (s, 1H), 7.97 (dd, J = 8.4, 1.3 Hz, 2H), 7.56 (dd, J = 10.5, 4.3 Hz, 1H), 7.50–7.41 (m, 2H), 7.18 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 4.40 (dd, J = 8.3, 5.0 Hz, 1H), 3.91 (dd, J = 18.0, 8.3 Hz, 1H), 3.80 (s, 3H), 3.20 (dd, J = 17.9, 5.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 199.3, 197.7, 159.5, 136.7, 133.5, 130.4, 128.8, 128.3, 127.4, 114.9, 55.5, 53.1, 39.7; HRMS (ESI, m/z): calcd for C₁₇H₁₇O₃⁺ [M+H]⁺: 269.1178; found: 269.1178.

**2,4-Bis(4-chlorophenyl)-4-oxobutanal (4.3h):** ¹H NMR (400 MHz, CDCl₃): δ 9.76 (s, 1H), 7.89 (d, J = 7.9 Hz, 2H), 7.44-7.41 (m, 2H), 7.37-7.34 (m, 2H), 7.19 (d, J = 8.2 Hz, 2H), 4.41 (dd, J = 8.0, 5.1 Hz, 7H), 3.88 (dd, J = 18.0, 8.2 Hz, 7H), 3.16 (dd, J = 17.9, 5.2 Hz, 7H); ¹³C NMR (100 MHz, CDCl₃): δ 198.4,
195.9, 140.0, 134.7, 134.2, 133.8, 130.5, 129.6, 129.1, 53.0, 39.4; HRMS (ESI, m/z): calcd for C_{16}H_{13}O_{2}Cl^2 [M+H]^+: 307.0293; found: 307.0291.

4-Oxo-2,4-dip-tolybutanal (4.3i): ¹H NMR (400 MHz, CDCl₃): δ 9.77 (s, 1H), 7.86 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.3 Hz, 1H), 7.16 (q, J = 8.2 Hz, 2H), 4.40 (dd, J = 8.3, 5.0 Hz, 1H), 3.89 (dd, J = 17.9, 8.4 Hz, 1H), 3.18 (dd, J = 17.9, 5.0 Hz, 1H), 2.40 (s, 3H), 2.34 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 199.4, 197.2, 144.3, 137.9, 134.2, 132.6, 130.2, 129.5, 129.2, 128.4, 53.5, 39.6, 21.9, 21.3; HRMS (ESI, m/z): calcd for C_{18}H_{19}O₂ [M+H]^+: 267.1385; found: 267.1386.

2,4-Bis(4-methoxyphenyl)-4-oxobutanal (4.3j): ¹H NMR (400 MHz, CDCl₃): δ 9.77 (s, 1H), 7.94 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.6 Hz, 3H), 6.96-6.88 (m, 4H), 4.38 (dd, J = 8.2, 5.1 Hz, 2H), 3.86 (s, 3H), 3.85 (dd, J = 17.7, 8.2 Hz, 1H), 3.80 (s, 3H), 3.16 (dd, J = 17.7, 5.1 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 199.2, 195.9, 163.7, 159.3, 130.5, 130.2, 129.7, 127.4, 114.8, 113.8, 55.6, 55.4, 53.0, 39.3; HRMS (ESI, m/z): calcd for C_{18}H_{19}O₄ [M+H]^+: 299.1283; found: 299.1283.
**2-(3,4-Dimethoxyphenyl)-4-oxo-4-phenylbutanal (4.3k):**

$^1$H NMR (400 MHz, CDCl$_3$): δ 9.71 (s, 1H), 7.94-7.86 (m, 2H), 7.49 (d, $J = 7.4$ Hz, 1H), 7.48-7.42 (m, 2H), 6.86 (d, $J = 8.2$ Hz, 1H), 6.79 (dd, $J = 8.2$, 2.0 Hz, 1H), 6.74 (d, $J = 1.9$ Hz, 1H), 4.32 (dd, $J = 8.4$, 4.9 Hz, 1H), 3.87 (dd, $J = 17.9$, 8.3 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.14 (dd, $J = 17.9$, 4.9 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 198.9, 197.5, 149.5, 148.8, 136.5, 133.4, 128.8, 128.1, 127.7, 121.3, 112.0, 111.6, 56.1, 53.1, 39.4; HRMS (ESI, $m/z$): calcd for C$_{18}$H$_{19}$O$_4^+$ [M+H]$^+$: 299.1283; found: 299.1284.

**2-(3-Bromophenyl)-4-oxo-4-phenylbutanal (4.3l):**

$^1$H NMR (400 MHz, CDCl$_3$): δ 9.79 (s, 1H), 7.98-7.95 (m, 2H), 7.63-7.52 (m, 1H), 7.50-7.39 (m, 4H), 7.27-7.20 (m, 2H), 4.42 (dd, $J = 8.2$, 5.0 Hz, 1H), 3.93 (dd, $J = 18.0$, 8.2 Hz, 1H), 3.23 (dd, $J = 18.0$, 5.0 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 198.5, 197.1, 138.0, 136.4, 133.7, 132.3, 131.3, 131.0, 128.9, 128.3, 128.0, 123.5, 53.4, 39.6; HRMS (ESI, $m/z$): calcd for C$_{16}$H$_{14}$O$_2$$_{79}$Br$^+$ [M+H]$^+$: 317.0177; found: 317.0174.

**4-(Naphthalen-2-yl)-4-oxo-2-phenylbutanal (4.3m):**

$^1$H NMR (400 MHz, CDCl$_3$): δ 9.84 (s, 1H), 8.50 (s, 1H), 8.02 (dd, $J = 8.6$, 1.5 Hz, 1H), 7.94 (d, $J = 7.9$ Hz, 1H), 7.90-7.82 (m, 2H), 7.63-7.49 (m, 2H), 7.40 (t, $J = 7.3$ Hz, 2H), 7.32 (dd, $J$
= 10.7, 6.6 Hz, 3H), 4.51 (dd, \( J = 8.3, 4.9 \text{ Hz}, 1\text{H} \)), 4.09 (dd, \( J = 18.2, 8.4 \text{ Hz}, 1\text{H} \)), 3.37 (dd, \( J = 17.9, 5.0 \text{ Hz}, 1\text{H} \)); \( ^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 199.2, 197.3, 135.8, 135.6, 133.9, 132.6, 130.0, 129.7, 129.4, 129.2, 128.7, 128.6, 128.0, 127.9, 126.9, 123.9, 53.9, 39.6; HRMS (ESI, \( m/z \)): calcd for C\(_{20}\)H\(_{17}\)O\(_2\)^+[M+H]^+: 289.1229; found: 289.1227.

4-(Furan-2-yl)-4-oxo-2-phenylbutanal (4.3n): \(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 9.75 (s, 1H), 7.56 (d, \( J = 1.9 \text{ Hz}, 1\text{H} \)), 7.37 (dd, \( J = 7.9, 6.6 \text{ Hz}, 2\text{H} \)), 7.33-7.27 (m, 1H), 7.24 (d, \( J = 7.2 \text{ Hz}, 2\text{H} \)), 7.20 (d, \( J = 3.6 \text{ Hz}, 1\text{H} \)), 6.52 (dd, \( J = 3.5, 1.5 \text{ Hz}, 1\text{H} \)), 4.41 (dd, \( J = 8.3, 5.3 \text{ Hz}, 1\text{H} \)), 3.78 (dd, \( J = 17.7, 8.5 \text{ Hz}, 1\text{H} \)), 3.10 (dd, \( J = 17.7, 5.3 \text{ Hz}, 1\text{H} \)); \( ^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 198.8, 186.5, 152.4, 146.6, 135.3, 129.4, 129.2, 128.0, 117.4, 112.4, 112.5, 53.4, 38.9; HRMS (ESI, \( m/z \)): calcd for C\(_{14}\)H\(_{13}\)O\(_3\)^+[M+H]^+: 229.0865; found: 229.0865.

4-(4-Bromophenyl)-4-oxo-2-p-tolylbutanal (4.3o): \(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 9.75 (s, 1H), 7.82 (d, \( J = 8.6 \text{ Hz}, 2\text{H} \)), 7.59 (d, \( J = 8.5 \text{ Hz}, 2\text{H} \)), 7.16 (dd, \( J = 23.9, 8.0 \text{ Hz}, 4\text{H} \)), 4.39 (dd, \( J = 8.4, 4.9 \text{ Hz}, 1\text{H} \)), 3.87 (dd, \( J = 17.9, 8.4 \text{ Hz}, 1\text{H} \)), 3.13 (dd, \( J = 18.0, 4.9 \text{ Hz}, 1\text{H} \)), 2.34 (s, 3H); \( ^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 199.0, 196.5, 137.9, 135.3, 132.1, 132.0, 130.1, 129.7, 129.0, 128.6, 53.4, 39.4, 21.2; HRMS (ESI, \( m/z \)): calcd for C\(_{17}\)H\(_{16}\)O\(_2\)^{79}\text{Br}^+[M+H]^+: 331.0334; found: 331.0336.
2-Methyl-4-oxo-4-phenylbutanal (4.3p): $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.80 (s, 1H), 7.99-7.97 (m, 2H), 7.60-7.56 (m, 1H), 7.50-7.46 (m, 2H), 3.50 (dd, $J = 17.7$, 6.6 Hz, 1H), 3.17-3.08 (m, 1H), 3.01 (dd, $J = 17.7$, 5.9 Hz, 1H), 1.25 (d, $J = 7.4$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 203.4, 197.7, 136.5, 133.3, 128.6, 128.1, 41.6, 39.4, 13.7; HRMS (ESI, $m/z$): calcd for C$_{11}$H$_{13}$O$_2$$^+$$[M+H]^+$: 177.0916; found: 177.0918.

### 4.5 References


Chapter 5

Summary and Outlook
5.1 Asymmetric -alkylation of aldehydes with diaryl alcohols

Built on the developments made in enamine catalysis, the asymmetric -alkylation of aldehydes was successfully achieved using diaryl alcohols as the substrates (Chapter 2 and Chapter 3). Although different co-catalysts such as chiral Brønsted acids and Lewis acids have been utilized, the substrate scope was very limited. Only several diaryl alcohols could be successfully employed in previously reported enamine systems to give alkylation products with good yields and enantioselectivities (Figure 5.1). In chapter 2, we successfully developed the -alkylation of aldehydes with indole derived alcohols using L-proline as the enamine catalyst to give good results. In chapter 3, the scope of diaryl alcohols was expanded to those that could generate more reactive carbocations by using only Brønsted acids as the catalysts. Racemic products were obtained with good yields.

![Effective substrates](3.1a)

![Ineffective substrates](3.1b, 3.1c, 3.1d, 3.1e, 3.1f)

**Figure 5.1** Substrates used in enamine catalysis

Future efforts can be directed on the asymmetric α-alkylation of aldehydes with reactive carbocation precursors. Diaryl alcohols or diaryl halide can be
effective substrates in these transformations. Lewis acids with chiral ligands may induce enantioselectivities in the enamine or acid catalyzed reactions. Also, other type of cations such as oxocarbenium ions can also be generated *in situ* to undergo alkylation reactions.\(^1\)

### 5.2 Stetter reaction of formaldehyde equivalents with enones

Aldehydes have been frequently used in the organocatalysis as nucleophiles. List and co-workers reported the first use of acetaldehyde in the Mannich reaction with N-Boc imine in the year of 2008.\(^2\) Formaldehyde has never been used in organocatalysis as a nucleophile before with other electrophiles as formaldehyde itself is also a very reactive electrophile. We have successfully used paraformaldehyde and carbohydrates as formaldehyde equivalents to generate one-carbon acyl anion intermediates to react with enones. Stetter products could be obtained with very good yield. However, there are still a few limitations.

First, the reaction was carried out at 130 °C in microwave heating conditions. The high temperature used would make the enantioselective version of this reaction very difficult. It is necessary to identify a milder condition to trap the reactive one-carbon acyl anion intermediates in order for the enantioselective synthesis to be successful. Another challenge would be to expand the variety of electrophile used. At this moment, only chalcones could be efficiently used to trap the reactive intermediates. Attempts to use other types of Michael acceptors such
as nitrostyrene and other enones gave negligible amounts of the Stetter products under the optimized conditions. There is thus potential for the development of new catalysts and methodologies that make use of formaldehyde as the substrates.

5.3 References
