Synthetic Studies of 2-Acetoxyfuran and 2(3H)-Furanone as Pronucleophiles in the Asymmetric Synthesis of Butenolides

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SYNTHETIC STUDIES OF 2-ACETOXYFURAN AND 2(3H)-FURANONE AS PRONUCLEOPHILES IN THE ASYMMETRIC SYNTHESIS OF BUTENOLIDES

by

Stephen James Howard

A Dissertation
Submitted in Partial Fulfillment of the Requirements of the Degree of Doctor of Philosophy

Major: Chemistry

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December 2010
Dedication

This work is dedicated to my wife April, my son Andrew and my daughter Allison.

Thank you for providing a constant source of strength, inspiration and love.
Acknowledgements

I express my deepest gratitude to my co-mentors, Dr. Abby Parrill and Dr. Paul Bloom. Without their guidance and support, I could not have undertaken this assignment. Thank you, Dr. Bloom, for encouraging me to undertake doctoral training and for keeping me focused on the important aspects of this research. Thank you, Dr. Parrill, for your years of continuously-encouraging mentorship.

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I am very grateful for the funding provided by Archer Daniels Midland. I am proud to work for a company that appreciates the value of continuing one’s education while being employed.

I am indebted for editorial assistance to my mother, Irmgard K. Howard, Ph.D., my sister, Deborah K. Howard Nikolaeva, Ph.D., and my father, David A. Howard, Ph.D. In addition to the editorial and moral support, I thank my parents for providing me the inspiration for obtaining a doctorate. By dedicating their lives to the academic enrichment of others, they have taught me the value of education.
Abstract


Enantioselective synthesis of γ-substituted butenolides is desirable due to the prevalence of these functionalities in medicinally important natural products. As organic synthons, butenolides contain four carbon atoms, each of which is capable of undergoing regioselective modification. Two complementary approaches for the construction of γ-substituted butenolides have been developed in the present work. The trapped dienolate, 2-acetoxyfuran, couples with aldehydes under mild conditions with diastereocontrol determined by the nature of catalyst, solvent, and temperature employed. An even more efficient synthesis of the butenolide architecture has been developed by the direct coupling of 2(3H)-furanone to aldehydes. Enantioselectivity is afforded by use of Takemoto’s bifunctional thiourea catalysts. The simplicity and versatility of these reactions demonstrate the strong potential that the pronucleophiles 2-acetoxyfuran and 2(3H)-furanone offer for the synthesis of γ-butenolides.
Preface

This dissertation has been formatted to allow for the separate publication of Chapter 3 and Chapter 4. As such, this dissertation and bibliography are written in a style following the American Chemical Society (ACS) style guidelines.
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## SYMBOLS AND ABBREVIATIONS

<table>
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<th>Description</th>
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<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>BF$_3$OEt$_2$</td>
<td>boron trifluoroetherate</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1'-bi-2-naphthol</td>
</tr>
<tr>
<td>BISOX</td>
<td>bisoxazoline</td>
</tr>
<tr>
<td>Br$_2$</td>
<td>bromine</td>
</tr>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>CH$_3$CN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>CDCl$_3$</td>
<td>chloroform</td>
</tr>
<tr>
<td>DCE</td>
<td>dichloroethane</td>
</tr>
<tr>
<td>(DHQD)$_2$AQN</td>
<td>hydroquinidine (anthraquinone-1,4-diyl) diether</td>
</tr>
<tr>
<td>(DHQD)$_2$PYR</td>
<td>hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether</td>
</tr>
<tr>
<td>DIPEA</td>
<td>diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>dppd</td>
<td>1,4-bis(diphenylphosphino)butane</td>
</tr>
<tr>
<td>EWG</td>
<td>electron withdrawing group</td>
</tr>
<tr>
<td>Et$_2$O</td>
<td>diethyl ether</td>
</tr>
</tbody>
</table>
IPA isopropyl alcohol
KO\textsubscript{r}Bu potassium \textit{t}-butoxide
La(OTf\textsubscript{3})\textsubscript{3} lanthanum (III) trifluoromethanesulfonate
LiOAc lithium acetate
LiOPh lithium phenoxide
Ph phenyl
Me methyl
MeOH methanol
MS molecular sieves
MTPA a-methoxy-a-trifluoromethylphenylacetic acid
NaBr sodium bromide
NaOH sodium hydroxide
NaOMe sodium methoxide
NE\textsubscript{t}\textsubscript{3} triethylamine
NHC N-heterocyclic carbene
NMP N-methyl-2-pyrrolidone
pTsOH p-toluenesulfonic acid
PhI(OCOF$_3$)$_2$  
(bis(trifluoroacetoxy)iodo)benzene

(PhSe)$_2$  
diphenyl diselenide

PyBox  
pyridine bixoxazoline

salen  
2,2'-ethylenebis(nitrilomethylidene)diphenol

SbF$_6^-$  
hexafluoroantimonate

SiCl$_4$  
silicon tetrachloride

[Rh(Cod)OH]$_2$  
cycloocta-1,5-diene

TADDOL  
2,2-dimethyl-α,α,α',α'-tetraphenyldioxolane-4,5-dimethanol

TBAF  
tetra-$n$-butylammonium fluoride

TEA  
triethylamine

TfOH  
trifluoromethanesulfonic acid

THF  
tetrahydrofuran

Ti(OiPr)$_4$  
titanium isopropoxide

TMS  
trimethylsilyl

TMEDA  
tetramethylethlenediamine

TMSCl  
trimethylsilyl chloride

2-TMSOF  
2-trimethylsilyloxyfuran

TUC  
thiourea catalyst
Chapter 1. Background: Furanones and Butenolides, Structures and Syntheses

The unsaturated lactones 2(5H)-furanone (1.1) and 2(3H)-furanone (1.2), commonly referred to as butenolides, are frequently encountered functionalities in the field of organic synthesis (Scheme 1.1).

SCHEME 1.1. Positional isomers of 2-furanone, also collectively known as butenolides

For over half a century, scientists have been interested in butenolide chemistry, resulting in the rather frequent publication of reviews.\textsuperscript{1-4} In keeping with current convention in the field, this dissertation uses the term “γ-butenolide” to indicate a “5-substituted 2(5H)-furanone” (Scheme 1.2).

SCHEME 1.2. Identical structures labeled as a 5-substituted 2(5H)-furanone and as a γ-substituted butenolide, respectively
Enantioselective synthesis of γ-substituted butenolides is of interest due to the prevalence of their functionality in natural products as well as their utility as organic synthons. The butenolide and butanolide moieties are represented in several pharmacologically relevant natural products, including ascorbic acid (1.4), bipinnatin J (1.5), and longifolicin (1.6).

**SCHEME 1.3. Selected butenolide-containing natural products**

![Ascorbic Acid](image1.png)

![Bipinnatin J](image2.png)

![Longifolicin](image3.png)

As α,β-unsaturated lactones, 2(5H)-furanones (1.3) can potentially undergo a variety of useful synthetic transformations such as Baylis Hillman addition at the C3 position, Michael addition at the C4 position, and other standard organic transformations shown below in Scheme 1.4.
SCHEME 1.4. γ-Butenolide (1.3) as an organic synthon

Previous syntheses of butenolides

A survey of the literature demonstrates that two general strategies predominate for the synthesis of γ-butenolides. These are (a) reactions which form the lactone ring (Scheme 1.5)\(^5\)\(^{-7}\) and (b) coupling reactions where furanones or activated furanone equivalents behave as nucleophiles and couple with electrophilic systems at the C5 position (Scheme 1.6)\(^8\) The focus of this dissertation is on these coupling reactions and their stereochemical consequences.
SCHEME 1.5. Selected butenolide ring-forming reactions\textsuperscript{5,7}

\[
\begin{align*}
\text{R}^\text{O} & \quad \text{PCy}_3 \\
\text{PCy}_3 & \quad \text{Cl}^{-}
\end{align*}
\]

\[0.1 \text{ eq.} \quad \text{Cl}^- \quad \text{PCy}_3 \quad \text{Ru} \quad \text{Ph} \]

\[3 \text{ eq.} \quad \text{NET}_3 \quad \text{CH}_2\text{Cl}_2, 40^\circ\text{C} \]

\[
\begin{align*}
\text{R} & \quad \text{OH} \\
\text{R}' & \quad \text{OR'}
\end{align*}
\]

\[5 \text{ mol\%} \quad \text{(PhSe)}_2 \quad \text{1.05 eq.} \quad \text{Ph}(\text{OCOCF}_3)_2 \]

\[\text{CH}_3\text{CN, r.t.} \]

\[
\begin{align*}
\text{HO} & \quad \text{R} \\
\text{C} & \quad \text{O} \\
\text{R} & \quad \text{Me}
\end{align*}
\]

\[\text{(2 mol\%)} \quad \text{[Rh(Cod)OH]}_2 \quad \text{(6 mol\% dppb)} \]

Vinyllogous aldol reactions

Coupling reactions at the C5 position between furanones, or activated furanone equivalents, and aldehydes can generate four stereoisomers (Scheme 1.6). The diastereoselectivity of these types of reactions has been investigated for over twenty years. More recently, several enantioselective variations have been reported.\textsuperscript{9}

SCHEME 1.6. Stereoisomers produced by coupling of furanone-based nucleophiles with aldehydes\textsuperscript{6,7}

\[
\begin{align*}
\text{R} & \quad \text{H} \\
\text{Furanone or} & \quad \text{activated furanone}
\end{align*}
\]

\[
\begin{align*}
\text{chiral catalyst} & \quad \text{+} \\
\end{align*}
\]

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

\[
\begin{align*}
\text{1.10} & \quad \text{1.11}
\end{align*}
\]

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

\[
\begin{align*}
\text{1.12} & \quad \text{1.13}
\end{align*}
\]
The most common method for asymmetric synthesis of butenolides is by vinylogous aldol addition of trimethylsilyloxyfuran (TMSOF) (1.14) to aldehydes. Known as the vinylogous Mukaiyama aldol reaction, the first example of enantioselective butenolide synthesis via this pathway was reported by Figadère and coworkers.\textsuperscript{10} A combination of BINOL (1.15) and Ti(OiPr)\textsubscript{4} catalyzed the addition of TMSOF to octanal, tridecanal, and benzaldehyde with moderate to high enantioselectivity and moderate \textit{syn} selectivity. It was noted that Ti(OiPr)\textsubscript{4} without the chiral additive failed to catalyze the coupling reaction. A subsequent report by the same authors provided evidence that the reaction proceeds autocatalytically.\textsuperscript{11} The yield and scope of the reaction was improved by addition of a second chiral alcohol. The sequential addition of BINOL (1.15) followed by TADDOL (1.16) to Ti(OiPr)\textsubscript{4} produced a catalytic system that promoted the coupling of TMSOF to a variety of aldehydes in high yields and with high enantiomeric excess. Surprisingly, the addition of the two chiral alcohols (1.15) and (1.16) together produced \textit{syn} diastereoselectivity with aliphatic aldehydes; however, with aromatic and olefinic aldehydes, the \textit{anti} diastereomers predominated (Table 1.1).
TABLE 1.1. First reported enantioselective coupling of TMSOF (1.14) to aldehydes

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Additives</th>
<th>yield (%)</th>
<th>syn:anti</th>
<th>ee (anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-C7H15</td>
<td>(1.15)</td>
<td>95</td>
<td>70:30</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>C12H25</td>
<td>(1.15)</td>
<td>80</td>
<td>60:40</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>(1.15)</td>
<td>70</td>
<td>70:30</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>(1.15),(1.16)</td>
<td>99</td>
<td>24:76</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>E-non-2-al</td>
<td>(1.15),(1.16)</td>
<td>70</td>
<td>30:70</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>C12H25</td>
<td>(1.15),(1.16)</td>
<td>80</td>
<td>60:40</td>
<td>96</td>
</tr>
</tbody>
</table>

In 2003, Katsuki et al. found that the Cr(III) salen complex (1.17) catalyzed coupling of TMSOF to aldehydes proceeded with high enantioselectivity. They determined that the presence of a secondary alcohol improved the yield and diastereoselectivity of the reaction. They postulated that the alcohol acted to suppress the retro-reaction during the transition state. The reaction gave moderate-to-good syn diastereoselectivity for both the aliphatic and aromatic examples reported (Table 1.2).
TABLE 1.2. Chromium salen-catalyzed enantioselective Mukaiyama aldol addition of TMSOF (1.14) to various aldehydes\textsuperscript{12,13}

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>yield (%)</th>
<th>syn:anti</th>
<th>ee (syn)</th>
<th>ee (anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>86</td>
<td>85:15</td>
<td>75</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>(p-\text{ClC}_6\text{H}_4)</td>
<td>89</td>
<td>89:11</td>
<td>70</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>(C_7\text{H}_15)</td>
<td>98</td>
<td>60:40</td>
<td>99</td>
<td>97</td>
</tr>
</tbody>
</table>

A metal-free catalytic system, developed by Palombi \textit{et al.}, employed SiCl\textsubscript{4} with a Lewis base to achieve high enantioselectivity in the addition of TMSOF (1.14) to a variety of aldehydes.\textsuperscript{14} The most effective Lewis base was found to be Denmark’s bisphosphoramidate (1.18). The reaction was \textit{syn}-diastereoselective and with high enantioselectivity for each aldehyde screened except furfural (Table 1.3).
TABLE 1.3. Lewis base (1.18)-SiCl$_4$ catalyzed enantioselective Mukaiyama aldol addition of TMSOF (1.14) to various aldehydes$^{14}$

![Lewis base catalyst](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>yield (%)</th>
<th>syn:anti</th>
<th>$ee$ (anti)</th>
<th>$ee$ (syn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>67</td>
<td>69:31</td>
<td>98</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>4-MeO-Ph</td>
<td>80</td>
<td>80:20</td>
<td>&gt;99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>4-Br-Ph</td>
<td>64</td>
<td>65:35</td>
<td>&gt;99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>4</td>
<td>2-furyl</td>
<td>60</td>
<td>80:20</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>Ph-CHCH</td>
<td>63</td>
<td>84:16</td>
<td>&gt;95</td>
<td>42</td>
</tr>
</tbody>
</table>

In 1999, Evans et al. developed a copper bisoxazolidine BISOX system (1.19) that resulted in high enantioselectivity and diastereoselectivity for the addition of TMSOF (1.14) to both benzyloxyacetaldehyde and methyl pyruvate$^{15,16}$ (Table 1.4).
TABLE 1.4. Copper bisoxazolidine chromium-catalyzed enantioselective Mukaiyama aldol addition of TMSOF (1.14) to benzyl oxyacetaldehyde and methyl pyruvate\textsuperscript{15,16}

![Copper bisoxazolidine chromium catalyst](image)

\begin{table}
\centering
\begin{tabular}{llcccc}
\hline
Entry & electrophile & R, R’ & yield (%) & syn:anti & ee (anti) \\
\hline
1 & benzyl oxyacetaldehyde & H, CH\textsubscript{2}OBn & 90 & 9:91 & 92\% \\
2 & methyl pyruvate & Me, Ac & 99 & 5:95 & 99\% \\
\hline
\end{tabular}
\end{table}

In 2007 Mukaiyama and coworkers developed a cinchonidine-derived organocatalyst (1.21) that catalyzed the addition of TMSOF (1.14) to several aldehydes in high yield, with moderate enantioselectivity and \textit{syn} diastereoselectivity.\textsuperscript{17} The presence of a methyl group at the C4 position of the TMS activated furanone significantly improved enantioselectivity (Table 1.5).
TABLE 1.5. Cinchonidine-based-catalyst-promoted coupling of TMSOF (1.14) and (1.20) with aldehydes\textsuperscript{17}

![Cinchonidine-based catalyst](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>yield (%)</th>
<th>syn:anti</th>
<th>ee (anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Ph</td>
<td>91</td>
<td>90:10</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>Ph</td>
<td>91</td>
<td>93:7</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>4-Br-Ph</td>
<td>93</td>
<td>83:17</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>4-MeO-Ph</td>
<td>95</td>
<td>86:14</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>PhCH\textsubscript{2}CH\textsubscript{2}</td>
<td>75</td>
<td>78:22</td>
<td>97</td>
</tr>
</tbody>
</table>

Similarly, in 2010 Wang and coworkers used a cinchona-based catalyst with a thiourea functionality (1.22) to promote addition of unsubstituted TMSOF (1.14) to aromatic aldehydes with high enantioselectivity and \textit{anti} diastereoselectivity\textsuperscript{18} (Table 1.6).
TABLE 1.6. Enantioselective addition of TMSOF (1.14) to aldehydes catalyzed by cinchona-derived thiourea (1.22)\textsuperscript{18}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image}
\caption{Reaction scheme for enantioselective addition of TMSOF to aldehydes.}
\end{figure}

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield (%)</th>
<th>anti:syn</th>
<th>ee (anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>78</td>
<td>89:11</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>4-NO\textsubscript{2}-Ph</td>
<td>78</td>
<td>88:12</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>4-Br-Ph</td>
<td>75</td>
<td>88:12</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>4-MeO-Ph</td>
<td>72</td>
<td>60:40</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>4-Me-Ph</td>
<td>83</td>
<td>89:11</td>
<td>88</td>
</tr>
</tbody>
</table>

\textit{Direct coupling of furanones to aldehydes}

A distinct disadvantage of Mukaiyama aldol chemistry is the amount of waste generated by employing silyl functionalized pronucleophiles. Mestres calculated the waste generated by the Mukaiyama aldol reaction to be 543.5 g/mol (Table 1.7).\textsuperscript{19} From an atom economy perspective, the direct coupling of furanones with electrophiles is conceivably the most efficient method for the synthesis of γ-butenolides.
TABLE 1.7. Waste generated by aldol reactions\textsuperscript{19}

<table>
<thead>
<tr>
<th>Method</th>
<th>Molar Waste (g/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Base Catalysis</td>
<td>0</td>
</tr>
<tr>
<td>Stoichiometric Enolate</td>
<td>101</td>
</tr>
<tr>
<td>Wittig Aldol</td>
<td>242</td>
</tr>
<tr>
<td>Boron Enol Ether</td>
<td>251-461</td>
</tr>
<tr>
<td>Silyl Enol Ether (Mukaiyama)</td>
<td>543.5</td>
</tr>
</tbody>
</table>


A difficulty commonly encountered with direct coupling reactions of unsubstituted 2(5H)-furanone (1.1) is that of regiocontrol, as both $\alpha$ and $\gamma$-substitution can occur.\textsuperscript{20} A strategy that has been used to avoid the competition for $\alpha$ substitution is use of a butenolide that already has a substituent at the $\alpha$ position. After the coupling reaction, the $\alpha$-substituent can be removed or replaced as desired. Racemic examples of this strategy include Piancatelli and coworkers’ use of 3-phenylselenylfuran-2(5H)-one, and Curran and coworkers’ use of the dichloro-substituted 2(5H)-butenolide, mucochloric acid, in the addition to aldehydes in the presence of 0.5 equivalents of triethylamine.\textsuperscript{21, 22, 23} In both cases, removal of the blocking group required hydrogenation, which reduced the butenolide to a butanolide.

The Terada group reported a direct asymmetric synthesis of 5-substituted butenolides by vinylogous aldol-type coupling using the blocking group strategy.\textsuperscript{24} Building upon the work of Curran and Piancatelli, Terada demonstrated asymmetric couplings of butenolides with a halogen substituent at the C3 position, as well as examples with phenylthiofuran promoted by chiral guanidine base (1.23) (Table 1.8).
TABLE 1.8. Guanidine-based chiral catalyst (1.23)-promoted enantioselective direct 
addition of substituted 2(5H)-furanone (1.24) to various aldehydes\textsuperscript{24}

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>yield (%)</th>
<th>syn:anti</th>
<th>ee (syn)</th>
<th>ee (anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>77</td>
<td>90:10</td>
<td>98</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>4-OMe-Ph</td>
<td>58</td>
<td>87:13</td>
<td>97</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>4-Me-Ph</td>
<td>95</td>
<td>86:14</td>
<td>99</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>4-Br-Ph</td>
<td>87</td>
<td>87:13</td>
<td>96</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>2-furyl</td>
<td>79</td>
<td>85:15</td>
<td>97</td>
<td>88</td>
</tr>
</tbody>
</table>

The first published report of direct coupling of an unsubstituted furanone to an 
aldehyde was by Yang et al.\textsuperscript{25} The addition of 2(5H)-furanone (1.1) to aldehydes was 
catalyzed by a cinchona-derived bifunctional thiourea catalyst (1.22) which resulted in 
high diastereoselectivity and enantioselectivity. The reaction, catalyzed by 10% molar 
equivalent of a chiral thiourea catalyst, takes 50 hours at 30°C (Table 1.9).
TABLE 1.9. Bifunctional thiourea (1.22)-catalyzed direct coupling of 2(5H)-furanone (1.1) to aldehydes$^{25}$

![Bifunctional Thiourea (1.22)](image)

$$
\text{Furanone (1.1)} + \text{R-CHO} \xrightarrow{(10 \text{ mol} \%) 1.22} \text{Et}_2\text{O, 30°C} \rightarrow \text{Adduct} \text{ with OH group}
$$

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield (%)</th>
<th>syn:anti</th>
<th>ee (anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>87</td>
<td>85:15</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>4-Br-Ph</td>
<td>83</td>
<td>82:18</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>MeO-Ph</td>
<td>93</td>
<td>83:17</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>4-MePh</td>
<td>75</td>
<td>82:18</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>c-hexyl</td>
<td>40</td>
<td>80:20</td>
<td>78</td>
</tr>
</tbody>
</table>

Remarkably, concurrent with the Yang et al. disclosure, our lab reported at the 2010 ACS national meeting in Boston that 2(3H)-furanone (1.2) undergoes highly enantioselective and diastereoselective addition to aldehydes catalyzed by Takemoto’s bifunctional thiourea catalysts (1.25) and (1.26).$^{26}$ The reaction takes as little as half an hour at -20°C with just 5% of catalyst. Chapter 4 of this dissertation provides further detail on the reaction.
Direct coupling of furanones with other electrophiles

In addition to the aldehyde coupling examples, during the past two years, several examples of direct asymmetric coupling of 2(5H)-furanones with other electrophilic systems have been reported. Shibasaki and coworkers reported the first direct asymmetric addition of a 2(5H)-furanone to an electrophile. Using a chiral Lewis acid/amine base/Brønsted acid catalytic system, the Mannich type addition of 2(5H)-furanone to N-diphenylphosphinoyl imines proceeded with high yield, high diastereoselectivity, and moderate enantioselectivity (Table 1.10).
In 2009, Trost and coworkers reported the direct coupling of 2(5H)-furanone to conjugated nitroalkanes. Using a dinuclear zinc-based chiral catalyst (1.29) developed in their lab, the Michael addition reaction proceeded with good-to-excellent diastereoselectivity and moderate enantiomeric excess\textsuperscript{28} (Table 1.11).
TABLE 1.11. Dinuclear zinc-based chiral catalyst (1.29)-promoted conjugate addition reaction$^{28}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>yield (%)</th>
<th>syn:anti</th>
<th>ee (anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C$_6$H$_6$</td>
<td>76</td>
<td>10:1</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>MeO-C$_6$H$_4$</td>
<td>78</td>
<td>20:1</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>Cl-C$_6$H$_4$</td>
<td>70</td>
<td>9:1</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>2-furanyl</td>
<td>77</td>
<td>18:1</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>C$_6$H$_4$CHCH</td>
<td>52</td>
<td>3:1</td>
<td>91</td>
</tr>
</tbody>
</table>

Soon after Trost’s announcement, Zhang and coworkers reported the direct conjugate addition of 2(5H)-furanone (1.1) to chalcones$^{29}$ (1.31). Takemoto’s bifunctional thiourea catalyst (1.26) promoted the Michael type addition reaction with moderate diastereoselectivity and moderate enantiomeric excess (Table 1.12).
TABLE 1.12. Bifunctional thiourea (1.26)-catalyzed conjugate addition of 2(5H)-furanone (1.1) to chalcones (1.31)²⁹

![Bifunctional thiourea](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar₁</th>
<th>R</th>
<th>yield (%)</th>
<th>syn:anti</th>
<th>ee (anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Ph</td>
<td>40</td>
<td>&gt;30:1</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>4-NO₂-C₆H₄</td>
<td>Ph</td>
<td>92</td>
<td>&gt;30:1</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>4-Cl-C₆H₄</td>
<td>Ph</td>
<td>52</td>
<td>&gt;30:1</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>4-NO₂-C₆H₄</td>
<td>83</td>
<td>&gt;30:1</td>
<td>67</td>
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<tr>
<td>5</td>
<td>Ph</td>
<td>Me</td>
<td>&lt;5</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

The first asymmetric coupling reaction of a 2(3H)-furanone functionality with an electrophile was reported by Chen and coworkers.³⁰ The addition of 2(3H)-furanones (1.32) and (1.33) to Morita-Baylis-Hillman carbonates (1.34) was catalyzed by (DHQD)₂AQN. Their findings indicated that the coupling proceeded most smoothly when the electron withdrawing substituent was at the C5 position of the butenolide (Table 1.13).
TABLE 1.13. Direct coupling of 2(3H)-furanones to Baylis-Hillman adducts (1.34)\textsuperscript{30}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>R</th>
<th>yield (%)</th>
<th>ee (anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>CO\textsubscript{2}Me</td>
<td>82</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>4-Cl-Ph</td>
<td>CO\textsubscript{2}Me</td>
<td>66</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>4-MeO-Ph</td>
<td>CO\textsubscript{2}Me</td>
<td>50</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>4-Br-Ph</td>
<td>COMe</td>
<td>67</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>COMe</td>
<td>57</td>
<td>96</td>
</tr>
</tbody>
</table>

Presentation of dissertation research

When our lab began the experimental research described in the following pages, there was no published precedent for many of the techniques which developed as part of this investigation into furanones and butenolide-derivatives. At present, however, papers are rapidly emerging in this field, confirming both the validity and the “cutting-edge” nature of our work. With the above summary of the literature for reference and context, the original research reported in this dissertation focuses on evaluation of 2-acetoxyfuran and 2(3H)-furanone as pronucleophiles in coupling reactions with various aldehydes. Chapter 2 describes two new synthetic processes for 2-acetoxyfuran and elucidates its utility in vinylogous aldol addition reactions. Chapter 3 details the investigation of 2(3H)-furanone in achiral-catalyst coupling reactions with aldehydes. Chapter 4 describes the asymmetric coupling of 2(3H)-furanone to aldehydes promoted by bifunctional thiourea chiral catalysts. Chapter 5 suggests future research and applications.
Chapter 2. Vinylogous Aldol Addition of 2-Acetoxyfuran to Electrophiles

I. Earlier research

Vinylogous aldol reactions

In 1981 Shono and coworkers reported that, under the influence of certain Lewis acids, 2-acetoxyfuran (2.1) couples at the C5 position with various aldehydes and dimethylacetals to make γ-butenolides (2.2) (Scheme 2.1). Concurrently with this work, analogous addition reactions of 2-trimethylsilyloxyfuran, 2-TMSOF (1.4), were also being investigated (Scheme 2.1). In the ensuing years, while the vinylogous aldol reaction with 2-TMSOF has been developed to the point of achieving diastereoselectivity and enantioselectivity, the Shono lab remains the only group to report coupling reactions with 2-acetoxyfuran. The lack of development of 2-acetoxyfuran as a pronucleophile in vinylogous aldol reactions may be due to the success of 2-TMSOF in these reactions, where conditions developed for other silyl activated nucleophiles have translated smoothly to this synthon. Additionally, 2-acetoxyfuran has not been commercially available, and reported methods for its synthesis pose challenges on an industrial scale.

SCHEME 2.1. Vinylogous aldol addition reactions of and 2-trimethylsilyloxyfuran, 2-TMSOF (1.14), and 2-acetoxyfuran (2.1)
Synthesis of 2-acetoxyfuran

As early as 1952, Clauson-Kaas and Elming reported the synthesis of 2-acetoxyfuran in two steps starting from furan. The first step was conversion of furan to 2,5-bisacetoxy-2,5-dihydrofuran which, when subjected to pyrolysis, generated 2-acetoxyfuran (Scheme 2.2). In 1956, Cava and coworkers improved the yield of the pyrolysis step from 40% to over 80% by using an acid catalyst and dibutylphthalate as a solvent. The Cava method was used by the Shono lab in their studies.

SCHEME 2.2. Two-step pathway from furan (2.3) through 2,5-bisacetoxy-2,5-dihydrofuran (2.4) to 2-acetoxyfuran (2.1)

Synthesis of 2,5-bisacetoxy-2,5-dihydrofuran

The original synthesis of 2,5-bisacetoxy-2,5-dihydrofuran by Clauson-Kaas and Elming employed the action of molecular bromine on furan in acetic acid. Unfortunately, this method was prone to spontaneous decomposition of the product during purification, a disadvantage attributed to trace amounts of hydrobromic acid. The authors then developed a more reliable synthesis of 2,5-bisacetoxy-2,5-dihydrofuran using a molar equivalent of lead tetra-acetate in acetic acid. The Shono lab developed a synthesis of 2,5-bisacetoxy-2,5-dihydrofuran by electrochemical oxidation of furan in the presence of sodium acetate in acetic acid.
Considering that these methods did not meet our criteria for scalability and our focus on green chemical processes, we pursued an alternative synthesis of 2-acetoxyfuran as described in the following section.

II. Present work

Objective and proposal

The initial objective of this work was to explore the coupling reactions between 2-acetoxyfuran and aldehydes. For certain Mukaiyama aldol reactions, simple cleavage of a TMS functionality by an active fluoride source promotes coupling with electrophiles. The liberated “naked enolate,” or in the case of 2-TMSOF, a dienolate, is the active nucleophile which couples with an electrophilic partner (Scheme 2.3). Following this methodology, we proposed that cleavage of the acyl functionality of 2-acetoxyfuran would generate the common dienolate intermediate (2.5), setting the stage for a nucleophilic attack on an electrophile. A variety of catalysts known to promote acyl functional group cleavage could then be evaluated for diastereoselectivity. Building upon these results, chiral catalysts could then be investigated for promoting enantioselectivity.
SCHEME 2.3. Proposed pathway for vinylogous aldol coupling to aldehydes of (A) 2-TMSOF (1.14) via fluoride catalyst, and (B) 2-acetoxyfuran (2.1) via acyl cleavage

Results and discussion

To make 2-acetoxyfuran, we chose to follow the model of Clauson-Kaas and Elming in first synthesizing its precursor, 2,5-bisacetoxy-2,5-dihydrofuran, from furan, and then using a pyrolysis reaction similar to that of Cava in order to achieve the final product of 2-acetoxyfuran. However, to avoid the use of highly toxic lead tetraacetate, reduce cost, and provide scalable synthesis, two additional preparations for 2,5-bisacetoxy-2,5-dihydrofuran were developed. Both methods rely upon generation of Br₂ in situ, one from sodium bromide and one from potassium bromate.

Synthesis of 2,5-bisacetoxy-2,5-dihydrofuran from furan, mediated by iodobenzene diacetate oxidation of sodium bromide to Br₂

The first process generated Br₂ by oxidation of sodium bromide by iodobenzene diacetate (2.6). The hypervalent iodine oxidant, iodobenzene diacetate, was selected because of its high solubility in acetic acid, as well as the recoverability of its reduced product iodobenzene (2.7), which can be converted back to the starting material by treatment with peracetic acid (Scheme 2.4). This process resulted in 76% yield of (2.4) as a mixture of diastereomers.
Scheme 2.4. Iodobenzene diacetate (2.6)-mediated synthesis of 2,5-bisacetoxy-2,5-dihydrofuran (2.4)

**Synthesis of 2,5-bisacetoxy-2,5-dihydrofuran by acetic acid in the presence of potassium bromate**

The second process was developed due to the relatively high cost of iodobenzene diacetate. Potassium bromate has low solubility in acetic acid; despite this, as a slurry in acetic acid it is capable of oxidizing furan resulting in 70% isolated yield of 2,5-bisacetoxy-2,5-dihydrofuran. Each mole of potassium bromate oxidizes three moles of furan which generates a favorable mass of product versus mass of reagent ratio. A negative aspect of this reaction is that, in the process, a mole of water is produced which can react with 2,5-bisacetoxy-2,5-dihydrofuran to generate malealdehyde. To minimize the effect of water, 4Å molecular sieves were added to the potassium bromate in an acetic acid slurry. Addition of acetic anhydride was found to be ineffective in scavenging the liberated water and actually retarded the reaction and lowered the overall yield to 56% isolated product (see experimental section).
**Synthesis of 2-acetoxyfuran**

The conversion of 2,5-bisacetoxy-2,5-dihydrofuran to 2-acetoxyfuran was achieved by a slightly modified version of the method of Cava and co-workers. Similar to the Cava method, the reaction was performed at 10 mmHg with an acid catalyst. However, p-toluenesulfonic acid (pTsOH) in NMP (N-methylpyrrolidone) solution was added, as opposed to Cava’s β-napthalenesulfonic acid (Scheme 2.5).

**SCHEME 2.5. Acid-catalyzed conversion of 2,5-bisacetoxy-2,5-dihydrofuran (2.4) to 2-acetoxyfuran (2.1)**

![Scheme 2.5](image)

**Vinyllogous aldol coupling of 2-acetoxyfuran to aldehydes**

Having achieved two scalable pathways for the synthesis of 2-acetoxyfuran, we then evaluated the effectiveness of 2-acetoxyfuran as a pronucleophile in vinyllogous aldol addition to aldehydes. Initially, 2-acetoxyfuran and benzaldehyde were exposed to a catalytic amount of sodium methoxide in methanol at -78°C. The predicted vinyllogous aldol reaction was observed with moderate *anti* diastereoselectivity (Table 2.1). Next, a series of other solvents were screened to investigate the scope of the reaction. Ethanol and isopropanol yielded *anti* diastereoselectivity similar to methanol. However, in aprotic solvents no evidence of the desired product formation was observed; rather, addition of the catalyst resulted in turning the reaction mixture dark red leaving most of the starting
material unaltered. This result suggests that the catalyst was consumed by an undesired reaction with 2-acetoxyfuran.

**TABLE 2.1. Solvent screening**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (hr)</th>
<th>% Yield of (2.9) and (2.10) (anti:syn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Methanol</td>
<td>0.5</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>Ethanol</td>
<td>2.5</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>Isopropanol</td>
<td>12</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Cl₂</td>
<td>12</td>
<td>Not observed</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>12</td>
<td>Not observed</td>
</tr>
</tbody>
</table>

*aConditions: benzaldehyde 1.0 mmol (1 equiv), 2-acetoxyfuran (1.25 equiv), sodium methoxide (5 mol%).

With methanol generating the best results for the sodium methoxide catalyzed reactions, other catalysts known to promote cleavage of the acyl functional group were screened (Table 2.2). The use of the Bronsted acid pTsOH and the Lewis acid neodymium triflate resulted in conversion of 2-acetoxyfuran to 2(5H)-furanone (1.1) with no butenolide product detected. The combination of dimethylaminopyridine (DMAP) and diisopropylethylamine (DIPEA) resulted in the addition of a butenolide product with low diastereoselectivity.
TABLE 2.2. Catalyst screening$^a$

\[
\text{Entry} \quad \text{Catalyst} \quad \text{Time (hr)} \quad \text{Temp \ (°C)} \quad \text{Product}$^b$
\begin{tabular}{lllll}
1 & DMAP&DIPEA & 0.5 & -42 & (2.9), (2.10) \\
2 & pTsOH & 48 & 0 & (1.1) \\
3 & Neodymium triflate & 12 & 0 & (1.1) \\
4 & DMAP & 12 & -42 & (1.2) \\
\end{tabular}
\]

$^a$Conditions: benzaldehyde 1.0 mmol (1 equiv), 2-acetoxyfuran (1.25 equiv), sodium methoxide (5 mol %).  
$^b$Major product(s) as determined by 1H NMR analysis.

Interestingly, in the presence of DMAP, without an added base, 2-acetoxyfuran was converted to 2(3H)-furanone (1.2). If the temperature was maintained at -42°C, 2(3H)-furanone remained unchanged for 12 hours. If DIPEA was added to the mixture of 2(3H)-furanone and benzaldehyde, butenolide product resulted. If no DIPEA was added and the temperature was increased to 20°C, rapid isomerisation of 2(3H)-furanone to 2(5H)-furanone was observed (Scheme 2.6).
**SCHEME 2.6. Summary of observed transformations in the reactions of 2-acetoxyfuran (2.1) with aldehydes under different conditions**

\[
\begin{align*}
&\text{2.1} & \text{1. RCHO} & \text{5%DMAP, 10%DIPEA} & \text{CH₃OH, -42°C} & \rightarrow & \text{2.2} \\
&\text{1.2} & \text{1. RCHO} & \text{5%DMAP} & \text{CH₃OH, -42°C} & \rightarrow & \text{1.1} & + \text{RCHO} \\
\end{align*}
\]

(60:40 anti:syn)

**Conclusions**

Despite the limited utility of 2-acetoxyfuran as a pronucleophile under the conditions that were investigated, the ability of 2(3H)-furanone to behave as a pronucleophile in direct aldol addition reactions was observed. This discovery shifted the focus of our research to direct coupling reactions of 2(3H)-furanones to aldehydes.

The high atom economy of direct coupling reactions and the ability to access 2(3H)-furanone by hydrogen peroxide oxidation of furfural$^{38}$ are advantages over the acyl cleavage-promoted vinylogous aldol coupling of 2-acetoxyfuran. Additionally, the ability to convert 2-acetoxyfuran to 2(3H)-furanone will allow one to use direct coupling chemistry for both molecules. Chapter 3 of this dissertation presents results of the investigation of direct coupling reactions of 2(3H)-furanone to aldehydes promoted by achiral catalysts. Chapter 4 presents results of the investigation of direct coupling reactions of 2(3H)-furanone to aldehydes, promoted by bifunctional thiourea catalysis, producing asymmetric synthesis of γ-butenolides.
Chapter 3. Synthesis of γ-Butenolides by Direct Coupling of 2(3H)-Furanone and Aldehydes: The Effect of Catalyst and Reactant on Diastereoselectivity

A direct synthesis of γ-butenolides has been developed using a variety of catalysts to promote the coupling of 2(3H)-furanone (1.2) to aldehydes. Several bases as well as boron trifluoroetherate effectively mediate the reaction with varying levels of diastereoselectivity. The structure of the reactant aldehyde also influenced diastereoselectivity. This pathway for direct butenolide synthesis provides high atom economy, versatility, and low waste.

Due to their abundance in natural products and utility as organic synthons, γ-substituted butenolides are important synthetic targets. Several methods have been developed for their synthesis, including ring closing metathesis, vinylogous aldol reactions, and direct aldol reactions. While butenolide synthesis by vinylogous aldol coupling of 2-trimethylsilyloxyfuran (TMSOF) (1.14) to aldehydes has been developed to the point of achieving high diastereoselectivity and high enantioselectivity, recent reports by Chen, Buchwald, Shibasaki, and Trost demonstrate a growing interest in the direct coupling of 2(5H)-furanone (1.1) and analogous furanones to electrophilic partners.
SCHEME 3.1. Synthesis of γ-butenolides by vinylogous aldol addition of TMSOF (1.14) or direct vinylogous aldol addition of furanone (1.1) to aldehydes

The advantage of high atom economy is an appealing aspect of direct aldol reactions. Unfortunately, direct vinylogous aldol reactions can be complicated by low regioselectivity, resulting in mixtures of α and γ-addition products.\(^{20}\)

Recently, Yang and coworkers reported the highly regioselective and enantioselective direct coupling of 2(5H)-furanone with aldehydes catalyzed by a bifunctional thiourea catalyst (1.22).\(^{25}\) The authors proposed a mechanism in which a dienolate intermediate adds to the aldehyde by a vinylogous aldol pathway. At the same time, our lab reported the asymmetric direct coupling of 2(3H)-furanone to aldehydes promoted by Takemoto’s bifunctional thiourea catalyst (1.26).\(^{26}\) To the best of our knowledge, this was the first report of direct coupling of unsubstituted 2(3H)-furanone to an aldehyde. The reaction took less time and lower temperatures than the analogous coupling of 2(5H)-furanone reported by Yang et al. (See Scheme 3.2.)
SCHEME 3.2. Thiourea-catalyzed coupling of 2-furanone isomers to aldehydes. The top diagram shows the reaction of 2(5H)-furanone with the catalyst shown, after Yang et al.; the bottom diagram shows the reaction of 2(3H)-furanone with the respective catalyst, our lab.

Synthesis of 2(3H)-furanone was performed according to the process described by Nasman and coworkers. Exposure of furfural to hydrogen peroxide produces a Dakin-type rearrangement which, upon workup, generates 2(3H)-furanone. To screen catalysts, benzaldehyde was selected as a model aldehyde for direct coupling with 2(3H)-furanone. A variety of bases, TBAF, boron trifluoroetherate, and the commercially available N-heterocyclic carbene (3.3) (Figure 3.1) were evaluated. The results of the catalyst screening demonstrated that the base catalyzed reactions tended to favor formation of the anti diastereomers, while the boron trifluoroetherate-mediated reaction was moderately syn selective. (Table 3.1)
TABLE 3.1. Screening of catalysts for direct addition of 2(3H)-furanone to benzaldehyde

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>equiv.</th>
<th>time(hr)</th>
<th>anti:syn&lt;sup&gt;b&lt;/sup&gt;</th>
<th>% yield&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;d&lt;/sup&gt;</td>
<td>BF&lt;sub&gt;3&lt;/sub&gt;.OEt&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1.1</td>
<td>24</td>
<td>40:60</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>NHC (3.3)</td>
<td>0.05</td>
<td>2</td>
<td>80:20</td>
<td>70</td>
</tr>
<tr>
<td>3&lt;sup&gt;e&lt;/sup&gt;</td>
<td>NaOH (powder)</td>
<td>0.63</td>
<td>0.25</td>
<td>80:20</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>lithium phenoxide</td>
<td>1.1</td>
<td>0.5</td>
<td>95:5</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>TBAF</td>
<td>1.1</td>
<td>8</td>
<td>80:20</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>KOtBu</td>
<td>0.05</td>
<td>0.25</td>
<td>90:10</td>
<td>90</td>
</tr>
</tbody>
</table>

<sup>a</sup>Unless otherwise noted, all reactions were performed with 1 mmol of benzaldehyde and 1.25 mmol of 2(3H)-furanone in THF at -78°C. <sup>b</sup>Diastereomeric ratio was determined by <sup>1</sup>H NMR analysis of crude reaction mixture. <sup>c</sup>Isolated yield of mixture of diastereomers. <sup>d</sup>Reaction performed at room temperature in diethyl ether. <sup>e</sup>Reaction performed at -42°C in methylene chloride.
The combination of favorable yield, high diastereoselectivity, and low catalyst loading with potassium \( t \)-butoxide prompted the choice of this catalyst for coupling reactions between 2(3H)-furanone and other aldehydes. The resulting \( \gamma \)-butenolides, reported in Table 3.2, exhibit moderate-to-high \textit{anti} diastereoselectivity for each case, except furfural, which was only slightly \textit{anti} diastereoselective.

TABLE 3.2. Potassium \( t \)-butoxide catalyzed direct butenolide reactions\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>furanone</th>
<th>R</th>
<th>( \gamma )-butenolide product</th>
<th>time (hr)</th>
<th>( \text{dr (anti:} \text{syn)} )</th>
<th>% yield\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2</td>
<td>4-MeOC(_6)H(_4)</td>
<td>( \gamma )-butenolide product</td>
<td>1</td>
<td>96:4</td>
<td>72</td>
</tr>
<tr>
<td>2\textsuperscript{c}</td>
<td>1.2</td>
<td>4-BrC(_6)H(_4)</td>
<td>( \gamma )-butenolide product</td>
<td>0.5</td>
<td>84:16</td>
<td>77</td>
</tr>
<tr>
<td>3\textsuperscript{d}</td>
<td>1.2</td>
<td>4-NO(_2)C(_6)H(_4)</td>
<td>( \gamma )-butenolide product</td>
<td>0.5</td>
<td>99:1</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>1.2</td>
<td>2-Furyl</td>
<td>( \gamma )-butenolide product</td>
<td>1.0</td>
<td>66:44</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>1.2</td>
<td>CH(_3)CH(_2)</td>
<td>( \gamma )-butenolide product</td>
<td>1.5</td>
<td>80:20</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>3.9</td>
<td>C(_6)H(_5)</td>
<td>( \gamma )-butenolide product</td>
<td>1.0</td>
<td>94:6</td>
<td>46</td>
</tr>
</tbody>
</table>

\textsuperscript{a}All reactions were performed with 1 mmol of aldehyde and 1.25 mmol of 2(3H)-furanone in THF at -78°C. \textsuperscript{b}Diastereomeric ratio was determined by \( ^1 \text{H} \) NMR analysis of crude reaction mixture. \textsuperscript{c}Isolated yield of mixture of diastereomers. \textsuperscript{d}Reaction performed at -42°C.
Next, commercially available $\alpha$-angelica lactone (5-methyl-2(3H)-furanone) (3.9) and benzaldehyde were subjected to the potassium $t$-butoxide-catalyzed reaction conditions. The major product of the reaction was the $\gamma$-addition product, albeit in modest yield. This result is in contrast to the product of $\alpha$-angelica lactone and aldehydes in the presence of a Lewis acid, which was reported to be 4-acetyl-5-phenyl-dihydro-furan-2-one (3.11).\textsuperscript{44} (Scheme 3.3)

In conclusion, direct coupling of 2(3H)-furanone with benzaldehyde by several catalysts has been demonstrated with different diastereoselectivities. Using the potassium $t$-butoxide catalyst, a variety of aldehydes was demonstrated to yield $\gamma$-butenolides with different diastereomeric ratios. This methodology offers a useful alternative to the many previously reported routes for butenolide synthesis.
Chapter 4. Bifunctional Thiourea Catalyzed Asymmetric Synthesis of γ-Butenolides

Enantioselective synthesis of γ-butenolides has attracted considerable interest due to the prevalence of the functionality in natural products as well as its potential as a chemical synthon. Vinylogous aldol addition of activated butenolides, such as trimethylsilyloxyfuran (TMSOF) (1.14) to electrophiles, is a commonly utilized pathway for generating butenolides (Scheme 4.1). High enantioselectivity and diastereoselectivity have been achieved catalytically using this strategy.

Direct aldol reactions are desirable from an atom-economic perspective. Reports by Shibasaki, Trost, and Buchwald highlight growing interest in direct asymmetric synthesis of γ-butenolides. Chen and coworkers reported the direct asymmetric coupling of butenolides with Morita Baylis Hillman carbonates, while Zhang and coworkers reported the bifunctional thiourea catalyzed direct Michael addition of 2(5H)-furanone (1.1) to chalcones. Most recently, Yang and co-workers disclosed that unsubstituted 2(5H)-furanone adds to aldehydes with moderate to high enantiomeric
excess, promoted by bifunctional thiourea catalysts (1.22) and (1.26).²⁵ To the best of our knowledge direct coupling of unsubstituted 2(3H)-furanone (1.2) to aldehydes has not yet been reported. Herein we report the direct asymmetric coupling of 2(3H)-furanone with aldehydes catalyzed by bifunctional thiourea catalysts (1.25) and (1.26).

**SCHEME 4.1. Synthesis of γ-butenolides by vinylogous aldol reactions**

The pair of bifunctional thiourea catalysts (1.25) and (1.26), commonly referred to as Takemoto’s thiourea catalysts or “TUC,” have been utilized in several asymmetric reactions including Michael, Aza-Henry, and Morita Baylis Hillman reactions.⁴⁶,⁴⁷,⁴⁸ In the aforementioned work by Yang, et al, the R,R TUC (1.25) catalyzed coupling of 2(5H)-furanone with aldehydes resulted in low yield of the butenolide product which prompted that lab’s shifting focus towards using the cinchona based catalyst (1.22).²⁵
Our synthesis of 2(3H)-furanone was performed following the procedure described by Näsman and co-workers. To determine the effect of solvent and temperature variation on the yield and diastereoselectivity of the reaction, benzaldehyde was used as a model electrophile for coupling with 2(3H)-furanone (Table 4.1). The highest degree of diastereoselectivity was achieved with diethyl ether as the solvent. It was also observed that at elevated temperatures isomerization of 2(3H)-furanone to 2(5H)-furanone occurred.
TABLE 4.1. The enantioselective direct coupling of 2(3H)-furanone and benzaldehyde

\[
\text{O} \quad + \quad \text{O} \quad \xrightarrow{\text{S,S TUC}} \quad \text{O} \quad \text{OH}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>temp</th>
<th>time (hr)</th>
<th>( \text{dr}^{b} ) ( \text{anti:} \text{syn} )</th>
<th>% yield(^{c})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{CH}_2\text{Cl}_2 )</td>
<td>-20</td>
<td>2</td>
<td>85:15</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>MeCN</td>
<td>-20</td>
<td>1</td>
<td>60:40</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>-20</td>
<td>2</td>
<td>80:20</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>( \text{Et}_2\text{O} )</td>
<td>0</td>
<td>0.5</td>
<td>90:10</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>( \text{Et}_2\text{O} )</td>
<td>RT</td>
<td>0.5</td>
<td>80:20</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>( \text{Et}_2\text{O} )</td>
<td>-20</td>
<td>2</td>
<td>88:12</td>
<td>90</td>
</tr>
</tbody>
</table>

\(^{a}\) All reactions were conducted with 1 mmol of benzaldehyde and 1.2 mmol of 2(3H)-furanone at with 5% of SS TUC. \(^{b}\) Determined by \(^1\text{H} \text{NMR} \) analysis of crude reaction mixture. \(^{c}\) Isolated yield of diastereomers.

The relative stereochemistry of the diastereomeric pairs was assigned by comparison with those previously reported in the literature.\(^{18}\) The absolute stereochemistry of (4.1) was assigned by Mosher ester analysis following the guidelines outlined by Hoye et. al.\(^{49}\)

A series of aldehydes was selected to determine the utility of the reaction with substituted aromatic, aliphatic and allylic aldehydes (Table 4.2). It was determined that the conditions developed for the coupling of benzaldehyde to 2(3H)-furanone required slight modification depending upon the nature of the electrophile. For example, THF was used in the reaction with p-nitrobenzaldehyde due to its low solubility in diethyl ether. The coupling reaction with p-methoxybenzaldehyde required slow incremental addition of 2(3H)-furanone over a period of hours due to the slow nature of the reaction.
<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>γ-buteno(lide product)</th>
<th>Time (hr)</th>
<th>% yield$^b$</th>
<th>(anti:syn)$^c$</th>
<th>ee of anti(%)$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₅</td>
<td><img src="image" alt="4.1" /></td>
<td>1</td>
<td>90</td>
<td>96:4</td>
<td>88</td>
</tr>
<tr>
<td>2$^e$</td>
<td>C₆H₅</td>
<td><img src="image" alt="4.2" /></td>
<td>1</td>
<td>86</td>
<td>96:4</td>
<td>86$^f$</td>
</tr>
<tr>
<td>3$^g$</td>
<td>4-MeO-C₆H₅</td>
<td><img src="image" alt="4.3" /></td>
<td>8</td>
<td>60</td>
<td>92:8</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>4-Br-C₆H₅</td>
<td><img src="image" alt="4.4" /></td>
<td>2</td>
<td>80</td>
<td>85:15</td>
<td>82</td>
</tr>
<tr>
<td>5$^h$</td>
<td>4-NO₂-C₆H₅</td>
<td><img src="image" alt="4.5" /></td>
<td>0.5</td>
<td>88</td>
<td>99:1</td>
<td>84</td>
</tr>
<tr>
<td>6$^g,i$</td>
<td>2-Furyl</td>
<td><img src="image" alt="4.6" /></td>
<td>8</td>
<td>54</td>
<td>60:40</td>
<td>-</td>
</tr>
<tr>
<td>7$^i$</td>
<td>Trans-CHCHC₆H₄</td>
<td><img src="image" alt="4.7" /></td>
<td>5</td>
<td>41</td>
<td>70:30</td>
<td>-</td>
</tr>
<tr>
<td>8$^i$</td>
<td>n-Butyl</td>
<td><img src="image" alt="4.8" /></td>
<td>8</td>
<td>38</td>
<td>66:34</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ Unless otherwise noted, all reactions were conducted with 1 mmol of aldehyde and 1.2 mmol of 2(3H)-furanone at -20°C in diethyl ether with 5% of S,S TUC.$^b$ Isolated yield of diastereomers.$^c$ Determined by $^1$H NMR analysis of crude reaction mixture.$^d$ Assigned as R,S isomer, ee determined by HPLC analysis using CHIRALPAK OD-H 80:20 hexane: isopropanol. $^e$ Reaction catalyzed by R,R TUC.$^f$ Assigned S,R isomer.$^g$ Required 10% catalyst and 1.5eq of 2(3H)-furanone.$^h$ Reaction conducted in THF at 0°C.$^i$ Enantiomeric excess not determined due to low diastereoselectivity.
A transition state for the model reaction between 2(3H)-furanone and benzaldehyde is proposed, based upon the absolute configurations of (4.1) and its enantiomer (4.2) (Table 4.2, entry 2). This concerted path is in contrast to the transition state proposed by Yang et al. for direct aldol coupling of the isomeric 2(5H)-furanone with aldehydes, in which tautomerization to the dienol, hydroxyfuran, precedes coupling with the electrophile (Scheme 4.3 A). This differentiation is based upon the temperature and reaction time difference between the two systems. Additionally, competition for α-substitution is not observed.

SCHEME 4.3. Proposed transition states for direct coupling of benzaldehyde with: A. 2(5H)-furanone catalyzed by R,R TUC (1.25) as proposed by Yang, et al.25; B. 2(3H)-furanone catalyzed by R,R TUC (1.25); and C. 2(3H)-furanone catalyzed by S,S TUC (1.26)

In conclusion, reported is a direct asymmetric synthesis of γ-butenolides by direct coupling of 2(3H)-furanone to various aldehydes. The versatility of this reaction was demonstrated with various aromatic aldehydes as well as with the aliphatic aldehyde propanal. A transition state unlike that to the traditional vinylogous aldol reaction has been proposed. Importantly, under optimized conditions, this practical and simple
reaction can achieve high yield and enantioselectivity for the synthesis of $\gamma$-butenolides. Further studies involving other electrophilic systems, as well as substituted 2(3H)-furanone analogs, are ongoing.
Chapter 5. Discussion and Future Considerations

The goal of developing a new method for asymmetric synthesis of γ-butenolides has been achieved. Two synthetic pathways for the synthesis of 2-acetoxyfuran were developed in order to evaluate its potential as coupling partner with aldehydes for the synthesis of butenolides (Chapter 2). However, during this investigation, it was determined that 2(3H)-furanone was an intermediate in the reaction. Thus, 2(3H)-furanone qualified as the superior candidate for the synthesis of γ-butenolides, from the perspectives of atom economy and solvent tolerance (Chapter 2). Screening of selected achiral catalysts revealed that addition of 2(3H)-furanone to benzaldehyde could be accomplished by simple base catalysis and that base catalyzed direct coupling of 2(3H)-furanone to aldehydes was generally anti-diastereoselective (Chapter 3). Asymmetric synthesis of γ-butenolides was achieved by coupling 2(3H)-furanone with several aldehydes. When promoted by either the R, R or S, S isomer of Takemoto’s bifunctional thiourea catalysts, the respective anti enantiomer was achieved in as much as 91% excess (Chapter 4).

Although a rigorous mechanistic investigation of the direct coupling of 2(3H)-furanone to aldehydes was not conducted during the course of this research, it is reasonable to conclude that the reaction does not proceed by way of a dienolate intermediate (2.5, Scheme 5.1). This is in contrast to the mechanisms suggested by authors reporting the direct aldol addition of 2(5H)-furanone (1.1) to electrophiles. Evidence of a non-dienolate pathway is provided by the lack of the γ-substitution product as well as by the more rapid rate of reaction with 2(3H)-furanone (1.2) versus that of 2(5H)-furanone. A possible alternative mechanism (involving conjugation) is
deprotonation of 2(3H)-furanone at the 3-carbon position with concerted coupling to the aldehyde at the 5-position (Scheme 5.1). To determine the most plausible mechanistic path for these reactions, additional work needs to be done.

**SCHEME 5.1. Proposed mechanisms of γ-butenolide synthesis by direct addition of furanone isomers to aldehydes: A. Dienolate intermediate pathway; B. Concerted addition pathway**

A starting point for mechanistic investigation could be comparison of the coupling reaction of 2(3H)-furanone with aldehydes versus the coupling of activated dienolates with aldehydes. A common pronucleophile used in vinylogous Mukaiyama butenolide synthesis is 2-TMSOF (1.14), which is generally prepared by treatment of 2(5H)-furanone with TMSCl in the presence of a non-nucleophilic base (Scheme 5.2). This trapped dienolate is frequently utilized for butenolide synthesis under Lewis acid catalysis (Chapter 1). The actual product of this reaction is the TMS ether (5.1) which produces the final product (2.2) by exposure to acidic conditions.
SCHEME 5.2. Butenolide synthesis by activation of 2(5H)-furanone (1.1) as a TMS dienolate pronucleophile (1.14)

To determine if 2(3H)-furanone adds to aldehydes under basic conditions by way of a dienolate intermediate (vinylogous Mukaiyama aldol pathway), trapping of the TMS dienolate under analogous conditions to 2(5H)-furanone should be observed (Scheme 5.3 A). However, if the butenolide product is formed by a concerted addition of 2(3H)-furanone to the aldehyde, the TMS ether of the butenolide should result (Scheme 5.3 B).

Additionally, if the TMS butenolide product is predominantly syn, then the diastereoselectivity of the reaction may be determined by either the protonation or TMS addition step of the alkoxide intermediate.

SCHEME 5.3. Two possible mechanistic pathways for the coupling of 2(3H)-furanone with aldehydes
It is interesting that, despite a modest yield, the base catalyzed addition of angelica lactone (3.9) to aldehydes has not previously been reported in the literature. This absence is especially puzzling considering the low yield obtained using vinylogous Mukaiyama aldol addition of the TMS activated dienolate of angelica lactone, trimethyl-(5-methyl-furan-2-yloxy)-silane, to aldehydes. One possible explanation of why this reaction remained unreported may be due to the dimerization that occurs when α-angelica lactone [5-methyl, 2(3H)-furanone] is treated with a strong base. A review by Rao in 1964 proposed a mechanism in which α-angelica lactone isomerizes to the beta form [5-methyl, 2(5H)-furanone (5.2)] and adds to itself by Michael addition (Scheme 5.4 A).

An alternative mechanism is suggested by our previous work with 2(3H)-furanone (Scheme 5.4 B). If this mechanism is indeed how the reaction proceeds, then isomerization is actually a competing reaction leading to dimerization and not a requirement for formation of the active nucleophile.

**SCHEME 5.4. Rao mechanism (A) versus concerted addition mechanism (B) for dimerization of α-angelica lactone**

![Scheme 5.4](image-url)
Future directions and related reactions

An asymmetric, syn selective, direct coupling of 2(3H)-furanone to aldehydes is desirable. An added step of performing the Mitsunobu reaction on the anti products may provide access to the pair of syn enantiomers. Chiral Lewis acids may also offer access to syn selectivity, as suggested by the fact that BF$_3$OEt showed moderate syn selectivity in promoting the coupling of 2(3H)-furanone to benzaldehyde (Chapter 3). Likewise, several examples of syn selectivity exist for the Lewis acid catalyzed coupling of 2-TMSOF to aldehydes.$^{14,17,12}$

Along with the development of vinylogous aldol reactions involving trimethylsilyloxyfuran (TMSOF) the related TMS-activated pyrrole (5.3) and thiophene (5.4) nucleophiles have been reported.$^{39}$ Similarly, with 2(5H)-furanone (1.1), direct aldol reactions with the related amide (5.5) and thioester (5.6) have drawn interest.$^{52,53}$ In a like manner, the analogs of 2(3H)-furanone (1.2), pyrrole-2-one (5.7) and thiophene-2-one (5.8), provide additional opportunities for further investigation of direct coupling reactions (Scheme 5.5). Results of this proposed work should then lead in natural progression towards coupling 2(3H)-furanone and related compounds (5.7) and (5.8) with electrophiles other than aldehydes, for example imines in the Mannich reaction.
SCHEME 5.5. A comparison of potential pronucleophilic partners for the synthesis of \(\gamma\)-substituted butenolides, pyrrol-2-ones, and thiophene-2-ones, in the respective reactions of Mukaiyama aldol, direct aldol, and direct coupling.

\[
\begin{array}{ccc}
\text{TMSO} & \text{TMSO} & \text{TMSO} \\
\text{O} & \text{N} & \text{S} \\
\text{1.14} & \text{5.3} & \text{5.4} \\
\hline
\text{Mukaiyama Aldol}
\end{array}
\]

\[
\begin{array}{ccc}
\text{O} & \text{O} & \text{O} \\
\text{1.1} & \text{5.5} & \text{5.6} \\
\hline
\text{Direct Aldol}
\end{array}
\]

\[
\begin{array}{ccc}
\text{O} & \text{N} & \text{S} \\
\text{1.2} & \text{5.7} & \text{5.8} \\
\hline
\text{Direct Coupling}
\end{array}
\]

Conclusion

Ultimately, the work described in this dissertation has revealed 2(3H)-furanone to be a valuable tool in the direct coupling synthesis of \(\gamma\)-butenolides and thus to be a promising addition to the larger field of organic chemistry to which those butenolides lead.
Appendices

General:

All reactions were conducted under a dry nitrogen atmosphere in oven dried glassware. Commercially obtained solvents and reagents were used without further purification. Takemoto's bifunctional chiral thiourea catalysts were purchased from Strem Chemical: 1-[3,5-bis(trifluoromethyl)phenyl]-3-[(1S,2S)-(+)2-(dimethylamino)cyclohexyl]thiourea (S,S-TUC) and 1-[3,5-bis(trifluoromethyl)phenyl]-3-[(1R,2R)-(−)2-(dimethylamino)cyclohexyl]thiourea (R,R-TUC)

Diastereomer ratios were determined by $^1$H NMR analysis. Enantiomeric excess determined by high performance liquid chromatography (HPLC) with CHIRALPAK 0.46cm x 25cm OD-H column. Daicel chemical Ind. LTD., S,S thiourea catalyzed reactions used 80:20 isopropanol:hexane as eluent, R,R thiourea catalyzed reactions used 90:10 isopropanol:hexane as eluent

Amberlyst 26 OH resin was purchased from Rohm and Haas. Silica gel (70-230 mesh) was purchased from Fisher Scientific. Thin layer chromatography (TLC) plates (f_254) were purchased from EMD. All other solvents and reagents were purchased from Sigma-Aldrich.

Reactions were monitored by both TLC analysis and 90 MHz NMR (Anasazi Instruments).

400 MHz $^1$H NMR spectra and 100 MHz $^{13}$C spectra were obtained on a 400 MHz NMR at NMR Analysis and Consulting, 2121 South Imboden Court, Decatur, IL. 62521. NMR Spectra was processed using ACD Labs Academic Edition software, version 12.01.


\(^1\)H and \(^{13}\)C chemical shifts are reported in ppm based upon the standard chemical shift for the respective deuterated solvent. All spectra matched identically with those reported in the literature (references found with structure under structures in experimental section). CIMS (methane) was performed on Shimadzu GCMS-QP2010.
Experimental

Synthesis of 2(3H)-furanone (1.2)

![Furanone](image)

**2(3H)-furanone**, Synthesized by the method described by Näsman et al.,\textsuperscript{38} 17-22% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)): 6.64 (dt, 3.6, 2.5 Hz 1H), 5.44 (dt, 3.6, 2.5 Hz, 1H), 3.0 (dd, 2.4, 2.4 Hz, 2H); \(^1\)C NMR (100 MHz, CDCl\(_3\)): 176.4, 143.4, 105.4, 32.0.

2.1

Synthesis of 2-acetoxyfuran (2.1)

A 2-neck roundbottom flask was fitted with a fractional distillation apparatus on one neck and septum on the other. A solution of 2,5-bisacetoxyfuran-2,5-dihydrofuran (100 g, 793 mmol) in dibutylphthalate (250 mL) was stirred in the flask under vacuum (10 torr). The solution was slowly heated to 80°C at which point a solution of p-toluenesulfonic acid (1 g) in 1-methyl-2-pyrrolidinone (5 mL) was injected into the solution via the septum. Upon addition of the acid, 2-acetoxyfuran began to distill into a collection flask. The recovered 2-acetoxyfuran was further purified by fractional distillation (41g, 60%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) ppm 7.01 - 7.11 (m, 1 H), 6.32 - 6.41 (m, 1 H), 5.83 - 5.93 (m, 1 H), 2.29 (s, 3 H); \(^1\)C NMR (100 MHz, CDCl\(_3\)): 166.81, 151.06, 135.42, 111.12, 92.00, 20.47
Synthesis of 2,5-bisacetoxy-2,5-dihydrofuran (2.4) from furan, mediated by iodobenzene diacetate oxidation of sodium bromide to Br₂

To a solution of iodobenzene diacetate (48 g, 149 mmol) in acetic acid (350 mL) was added furan (16 mL, 220 mmol). The mixture was stirred under a blanket of N₂ as (100 mg) sodium bromide was added. This reaction mixture was stirred until completed, as indicated by NMR analysis (90 MHz Anasazi Inc). Occasionally additional sodium bromate was required to drive the reaction to completion. The reaction mixture was condensed by removal of acetic acid via rotary evaporation. The product was isolated by fractional distillation as a colorless oil (21 g, 76%)

Synthesis of 2,5-bisacetoxy-2,5-dihydrofuran (2.4) by acetic acid in the presence of potassium bromate

A slurry of potassium bromate (50 g, 300 mmol) and 4Å molecular sieves (50 g) in acetic acid (300 mL) was stirred under a nitrogen atmosphere. The temperature of the mixture was maintained between 17-22°C as furan (70 mL, 960 mmol) was added dropwise over a period of 3 hours. After the reaction mixture stirred for 5 hours total, the solid material was filtered and the filtrate as condensed under vacuum via rotary evaporation. Removal of acetic acid yielded a mixture of solid and liquid material. The product mixture was
diluted with ethyl acetate (500 mL) and swirled gently. The remaining solid material was removed by filtration. The product mixture was condensed by removing the ethyl acetate under vacuum. The resulting dark colored oil was fractionally distilled under vacuum to generate 117 g of 2,5-bisacetoxy-2,5-dihydrofuran (70%).

\(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 6.88 (s, 1 H), 6.65 (s, 1 H), 6.17 (s, 1 H), 6.15 (s, 1 H), 2.01 (s, 3 H), 1.99 (s, 3 H); \(^{13}\)C NMR (100 MHz, CDCl\textsubscript{3}): 169.72, 131.26, 130.85, 101.37, 99.90, 21.02, 20.92

**Typical procedure for base catalyzed vinylogous aldol coupling of 2-acetoxyfuran to aldehydes (Table 2.1 and Table 2.2)**

A mixture of 2-acetoxyfuran 2.1 (100 mg, 7.9 mmol) and benzaldehyde (67 mg, .63 mmol) in methanol (1 mL) was stirred under argon at -78°C. To the mixture was added a solution of sodium methoxide (10 mg, 0.18 mmol) in methanol (0.1 mL). The reaction was monitored by TLC analysis (90:10 hexane: ethyl acetate). When all of the starting material 2.1 was consumed, the reaction mixture as treated with 1N HCL (1 mL). To the reaction mixture was added ethyl acetate (5 mL). The organic layer was removed and dried with MgSO\textsubscript{4}. The crude product was purified by silica gel flash chromatography (FC) (80:20 hexane:ethyl acetate) to yield a mixture of 2.9 and 2.10 (96 mg, 80%, 70:30 \textit{anti}:\textit{syn}) of product.
Procedure for boron Trifluoroetherate mediated coupling of 2(3H)-furanone and benzaldehyde (Table 3.1, Entry 1)

A mixture of benzaldehyde (106 mg, 1 mmol) and 2(3H)-furanone (100 mg, 1.19 mmol) in 2.5 mL diethyl ether was cooled to 0°C in an ice water bath. The reaction mixture stirred for 24 hours at 0°C. To the reaction mixture was added 2.5 mL of deionized water. The mixture stirred for 10 minutes and was treated with successive 2 mL washes of methylene chloride. The methylene chloride fractions were combined and the solvent was removed under vacuum. The butenolide product was purified by silica gel flash chromatography (98:2 chloroform:methanol) resulting in 85 mg (45%) mixture of diastereomers, 40:60 anti:syn.

Procedure for the 1,3-bis(2,4,6-trimethylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene (NHC) catalyzed addition of 2(3H)-furanone to benzaldehyde (Table 3.1, entry 2).

To a solution of 1,3-bis(2,4,6-trimethylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene (17.5 mg, 0.05 mmol) in 2.5 mL THF, that had been cooled to -78°C in a dry ice acetone bath, was added a mixture of benzaldehyde (106 mg, 1 mmol) and 2(3H)-furanone (100 mg, 1.19 mmol) in 1 mL THF. The reaction mixture was stirred for 2 hours. A solution of 1N HCl (2 mL) was added to the cold mixture. The mixture was allowed to warm to room temperature. The reaction mixture was washed twice with CH₂Cl₂ to extract the crude product. The crude product was condensed by removing the CH₂Cl₂ under vacuum. The butenolide product was purified by silica gel chromatography (98:2 CHCl₃:methanol) resulting in 133 mg (70%) mixture of diastereomers, 80:20 anti:syn.
Procedure for the sodium hydroxide mediated addition of 2(3H)-furanone to benzaldehyde (Table 3.1, entry 3).

A mixture of benzaldehyde (106 mg, 1 mmol) and 2(3H)-furanone (100 mg, 1.19 mmol) in 2.5 mL methylene chloride was cooled to -42°C in a dry ice acetonitrile bath. To the mixture was added powdered sodium hydroxide (25 mg, 0.625 mmol). The reaction mixture was stirred for 15 minutes. A 2 mL solution of 1N HCl was added to the cold mixture. The mixture was allowed to warm to room temperature. The reaction mixture was washed two times with CH$_2$Cl$_2$ to extract the crude product. The crude product was condensed by removing the CH$_2$Cl$_2$ under vacuum. The butenolide product was purified by silica gel FC (98:2 CHCl$_3$:methanol) resulting in 152 mg (80%) mixture of diastereomers, 80:20 anti:syn.

Procedure for the lithium phenoxide mediated addition of 2(3H)-furanone to benzaldehyde (Table 3.1, entry 4).

A mixture of benzaldehyde (106 mg, 1 mmol) and 2(3H)-furanone (100 mg, 1.19 mmol) in 2.5 mL THF was cooled to -78°C in a dry ice acetone bath. A 1M solution of lithium phenoxide (110 mg, 1.1 mmol) in THF was added drop wise. The reaction mixture was stirred for 30 minutes. A solution of 1N HCl (2 mL) was added to the cold mixture. The mixture was allowed to warm to room temperature. The reaction mixture was washed two times each with 5 mL CH$_2$Cl$_2$ to extract the crude product. The crude product as condensed by removing the CH$_2$Cl$_2$ under vacuum. The butenolide product was purified
Procedure for the tetrabutylammonium fluoride hydrate mediated addition of 2(3H)-furanone to benzaldehyde (Table 3.1, entry 5).

A mixture of benzaldehyde (106 mg, 1 mmol) and 2(3H)-furanone (100 mg, 1.19 mmol) in 1.5 mL THF was cooled to -78°C in a dry ice acetone bath. A solution of tetrabutylammonium fluoride hydrate (285 mg, 1.1 mmol) in 3 mL THF was added dropwise to the mixture. The reaction mixture was stirred for 8 hours. A solution of 2 mL 1N HCl was added to the cold mixture. The mixture was allowed to warm to room temperature. The reaction mixture was washed two times with 5 mL CH₂Cl₂ to extract the crude product. The crude product was condensed by removing the CH₂Cl₂ under vacuum. The butenolide product was purified by silica gel chromatography (98:2 CHCl₃:methanol) resulting in 125 mg (66%) mixture of diastereomers, 80:20 anti:syn.

Procedure 1; for potassium t-butoxide catalyzed addition of 2(3H)-butenolide to aldehydes: benzaldehyde (Table 3.1, entry 6), p-methoxybenzaldehyde (Table 3.2, entry 1), furfural (Table 3.2, entry 4)

A mixture of benzaldehyde (106 mg, 1 mmol) and 2(3H)-furanone (100 mg, 1.19 mmol) in 3.0 mL THF was cooled to -78°C in a dry ice acetone bath. A solution of potassium t-butoxide (5.5 mg, 0.05 mmol) in 0.5 mL THF was added drop wise. The reaction mixture
was stirred for 15 minutes. A solution of 1N HCl was added to the cold mixture. The mixture was allowed to warm to room temperature. The reaction mixture was washed two times with CH$_2$Cl$_2$ to extract the crude product. The crude product was condensed by removing the CH$_2$Cl$_2$ under vacuum. The butenolide product was purified by silica gel chromatography (98:2 CHCl$_3$:methanol) resulting in 172 mg (90%) mixture of diastereomers, 90:10 \textit{anti}:\textit{syn}.

**Procedure 2 for potassium t-butoxide catalyzed addition of 2(3H)-butenolide to aldehydes (for aldehydes with low solubility in THF at -78°C and enolizable aldehydes): bromobenzaldehyde (Table 3.2, entry 2), p-nitro-benzaldehyde (Table 3.2, entry 3), propanal (Table 3.2, entry 5).**

A mixture of 4-methoxybenzaldehyde (136 mg, 1 mmol) and 2(3H)-furanone (100 mg, 1.19 mmol) in 2 mL THF was added drop wise to a solution of potassium t-butoxide (5.5 mg, 0.05 mmol) in 1.5 mL THF that was cooled to -78°C in a dry ice acetone bath. The reaction mixture was stirred for 1hr. A solution of 1N HCl (2 mL) was added to the cold mixture. The mixture was allowed to warm to room temperature. The reaction mixture was washed two times with CH$_2$Cl$_2$ to extract the crude product. The crude product was condensed by removing the CH$_2$Cl$_2$ under vacuum. The butenolide product was purified by silica gel chromatography (98:2 CHCl$_3$:methanol) resulting in 159 mg (72%) mixture of diastereomers, 94:6 \textit{anti}:\textit{syn}. 

56
**General procedure for bifunctional thiourea reactions:** *(Table 4.1 and 4.2).*

To a mixture of 2(3H)-furanone (100 mg, 1.2 mmol) and benzaldehyde (106 mg, 1 mmol) in diethyl ether, stirred under N$_2$ at -20ºC, was added SS TUC (20 mg, 5 mmol) 1-[3,5-bis(trifluoromethyl)phenyl]-3-[(1S,2S)-(+)2-(dimethylamino)cyclohexyl]thiourea (S,S TUC) (*1.26*). The reaction was monitored by TLC analysis. Upon consumption of benzaldehyde, the reaction mixture was treated with 1N HCl. The product was extracted with ethyl acetate and condensed under vacuum. Silica gel chromatography yields 171 mg (90%) mixture of diastereomers (88:12 *anti*:syn), *(ee* 88%) for major product *(R)-5-((S)-hydroxy(phenyl)methyl)furan-2(5H)-one *(4.1).*

![Chemical structure](attachment:image.png)

**((2.9, 2.10)(4.1, 4.2))**

5-((hydroxy(phenyl)methyl)furan-2(5H)-one *(2.9, 2.10, 4.1, 4.2)*, $^1$H NMR (400 MHz, CDCl$_3$) 7.31-7.41 (m, 6H), 7.15 (dd, J=1.5 Hz, 1H ((syn))), 6.15 (d,d, J=6.1, 2.1 Hz *(anti)*), 6.10 (dd, J=5.9, 2.0 Hz, 1H, *(syn)*), 5.17 (m, 1H, *(anti)*), 5.14 (m, 1H, *(syn)*), 5.08 (bs, 1H, *(anti)*), 4.69 (d, J=7.3 Hz, 1H, *(syn)*); $^{13}$C NMR (100 MHz, CDCl$_3$): 173.1, 153.2, 152.9, 138.2, 128.9, 128.7, 128.4, 126.7, 126.0, 123.1, 122.8, 86.9, 86.6, 75.4, 72.9; CIMS *m/s*: 191 (M+1), 174, 173, 172, 146, 145, 135, 131, 126, 124, 121, 118, 117, 116, 115, 113, 109, 108, 107, 106, 105;
5-(hydroxy(4-methoxyphenyl)methyl)furan-2(5H)-one (3.4 and 4.3)

(3.6) Prepared by procedure 1; 4-methoxybenzaldehyde (136 mg, 1 mmol), 2(3H)-furanone (100 mg, 1.19 mmol), potassium t-butoxide (5.5 mg, 0.05 mmol), reaction mixture stirred at -78°C for 1 hour and quenched with 1N HCl. Purification by silica gel flash chromatography (98:2 chloroform: methanol) gave 159 mg (72%) mixture of diastereomers, 94:6 anti:syn.

(4.3) Prepared by general procedure for TUC coupling reactions but with 10% catalyst and 1.5 eq 2(3H)-furanone (126 mg, 1.5 mmol), 4-methoxybenzaldehyde (135 mg, 1 mmol), and S,S TUC (1.26) (20 mg, 5 mmol), reaction mixture stirred in THF at -20°C for 8 hours then quenched with 1 mL of 1N HCl. Purification by silica gel flash CC, gave 132 mg (60%) mixture of diastereomers (anti:syn, 92:8), ee 90% for major enantiomer (R)-5-((S)-hydroxy(4-methoxyphenyl)methyl)furan-2(5H)-one (4.3).

$^1$H NMR (400 MHz, CDCl$_3$): 7.38 (d,d, J= 6, 1.4 Hz, 1H, (anti)), 7.31 (d, J= 8.2 Hz, 2H.), 7.16 (d,d, J=5.3, 1.7 Hz, 1H, (syn)), 6.93 (d, J=8.5 Hz, 2H.), 6.16 (d,d, J=6.0, 2.0 Hz, 1H, (anti)), 6.12 d,d, J=6.0, 2.0 Hz, 1H, (syn)), 5.15 (dt, J= 6.9, 1.8, 2 Hz, 2H, (anti)), 5.00 (dd, J=4.5 Hz, 4.5 Hz, 1H, (anti)), 4.65(dd, J=7.1, 2.7 Hz, 1H, (syn)), 4.38( s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): 172.8, 159.7, 152.9, 130.2, 127.2, 123.1, 114.1, 86.4, 72.9, 55.3; CIMS $m/z$: 203 (M+1)-H$_2$O, 202,138, 137, 136, 135, 109.
5-((4-bromophenyl)(hydroxy)methyl)furan-2(5H)-one (3.5)

Prepared by procedure 2; 4-bromobenzaldehyde (185.02 mg, 1 mmol), 2(3H)-furanone (100 mg, 1.19 mmol), potassium t-butoxide (5.5 mg, 0.05 mmol), reaction mixture stirred at -78 for 0.5 hour and quenched with 1N HCl. Purification by silica gel flash chromatography (98:2 chloroform: methanol) gave 207 mg (77%) mixture of diastereomers, 84:16 anti:syn.

(4.4) Prepared by general procedure 2; 4-bromobenzaldehyde (185 mg, 1 mmol), 2(3H)-furanone (100 mg, 1.19 mmol), S,S TUC (1.26) (20 mg, 5 mmol), reaction mixture stirred at -20°C for 1 hr then quenched with 1N HCl. Purification by silica gel flash CC (70:30 hexane: ethyl acetate) gave 215 mg (80%) mixture of diastereomers (anti:syn, 87:13), ee 82% for major enantiomer (R)-5-((S)-(4-bromophenyl)(hydroxy)methyl)furan-2(5H)-one (4.4).

\[ 1^H \text{NMR (400 MHz, CDCl}_3\text{): 7.47-7.55 ( m, 2H), 7.3 (dd, J=6.2, 1.6 Hz, 1H (anti)), 7.27 (d, J=8 Hz, 1H, (anti)), 7.23 (d, J=6 Hz, 1H, (syn)), 7.20 (dd, J= 5.2 Hz, 1 (syn)), 6.16 (dd, J= 6 Hz, 1.6 Hz, 1H, (anti )), 6.10 (dd, J= 5.8, 2 Hz, 1H, (syn)), 5.10-5.15 (m, 2H), 5.04 (bs, 1H, (anti)), 4.73 (d, J= 7 Hz, 1H, (syn)), 13^C \text{NMR (100 MHz, CDCl}_3\text{): 173.0, 152.9, 152.6, 137.3, 136.7, 131.8, 128.4, 127.7, 123.3, 123.1, 122.4, 86.4, 86.3, 75.5, 72.3.} \]
5-(hydroxy(4-nitrophenyl)methyl)furan-2(5H)-one

(3.6) Prepared by general procedure 2; 4-nitrobenzaldehyde (151.12 mg, 1 mmol), 2(3H)-furanone (100 mg, 1.19 mmol), potassium t-butoxide (5.5 mg, 0.05 mmol), reaction mixture stirred at -78 for 0.5hr and was quenched with 1N HCl. Purification by washing with cold chloroform, 192 mg (82%) mixture of diastereomers 99:1 anti:syn.

(4.5) Prepared by general procedure for TUC coupling reactions but with THF as solvent and at 0°C; 4-nitrobenzaldehyde (151 mg, 1 mmol), 2(3H)-furanone (100 mg, 1.19 mmol), S,S TUC (1.26) (20 mg, 5 mmol), reaction mixture stirred in THF at 0°C for 1 hr then quenched with 1N HCl. White solid is purified by 3 consecutive washes with cold chloroform, 207 mg (88%) mixture of diastereomers (anti:syn 99:1) ee 84% for major enantiomer (R)-5-((S)-hydroxy(4-nitrophenyl)methyl)furan-2(5H)-one (4.5).

\[ ^{1}H\ \text{NMR}\ (400\ \text{MHz},\ \text{DMSO}\ d_{6}): \ 8.27(d, J=8.7\ \text{Hz},\ 2\ H),\ 7.70 (d, J=8\ \text{Hz},\ 2H_{r}),\ 7.68 (dd, J=5.8, 1.6\ \text{Hz},\ 1H),\ 6.33 (d, J=4.6\ \text{Hz},\ 1H),\ 6.28 (dd, J=6.0, 1.8\ \text{Hz},\ 1H),\ 5.40 (m,1H),\ 5.09(dd, J=4.9, 4.9\ \text{Hz},\ 1H); ^{13}C\ \text{NMR}\ (100\ \text{MHz},\ \text{CDCl}_{3}):\ 173.1,\ 155.2,\ 148.2,\ 147.3,\ 128.6,\ 128.2,\ 123.6,\ 86.3,\ 71.7;\ \text{CIMS}\ m/z:\ 219\ (M+1)-H_{2}O,\ 218,\ 217,\ 201,\ 188,\ 187,\ 131,\ 115.\]
5-(furan-2-yl(hydroxy)methyl)furan-2(5H)-one (3.7) Prepared by procedure 1; 2-furfural (96.0 mg, 1 mmol), 2(3H)-furanone (100 mg, 1.19 mmol), potassium t-butoxide (5.5 mg, 0.05 mmol), reaction mixture stirred at -78 for 1 hr and was quenched with 1N HCl. Purification by silica gel flash chromatography (98:2 chloroform: methanol) 118 mg (66%) mixture of diastereomers 66:44 anti:syn.

(4.6) Prepared by general procedure for TUC coupling reactions but with 10% catalyst and 1.5 eq 2(3H)-furanone (126 mg, 1.5 mmol), furfural (96 mg, 1 mmol), and S,S TUC (1.26) (20 mg, 5 mmol), reaction mixture stirred in THF at -20°C for 8 hr then quenched with 1N HCl. Purification by silica gel flash CC (70:30 hexane: ethyl acetate), 97 mg (54%) mixture of diastereomers (anti:syn, 60:40).

$^1$H NMR (400 MHz, CDCl$_3$): 7.57 (dd, J= 5.8, 1.6 Hz, 1H, (anti )), 7.42 (m, 2H), 7.35 (dd, J=5.8, 1.5 Hz, 1H, (syn )), 6.36-6.41 (m, 4H), 6.17 (dd , J=5.8, 2.2 Hz, 1H, (anti)), 6.14 (dd, J=5.8, 2.2 Hz, 1H (syn)), 5.28-5.33 (m, 2H), 5.03( 2, J=4.6 Hz, 1H, (anti)), 4.80 (d, J=6.1 Hz, 1H, (syn )); $^{13}$C NMR (100 MHz, CDCl$_3$): 172.9, 172.6, 153.3, 153.0, 151.3, 151.0, 142.8, 123.1, 122.9, 110.6, 108.6, 108.5, 68.8, 67.6; CIMS m$^+$: 181 (M+1), 164, 163, 163, 136, 135, 125, 119, 113, 111, 107.
3.10

5-(1-hydroxypropyl)furan-2(5H)-one (3.10) Prepared by procedure 2; propanal (59 mg, 1 mmol), 2(3H)-furanone (100 mg, 1.19 mmol), potassium t-butoxide (5.5 mg, 0.05 mmol), reaction mixture stirred at -78 for 1.5 hr and quenched with 1N HCl. Purification by silica gel flash chromatography (98:2 chloroform: methanol) gave 72 mg (51%) mixture of diastereomers, 80:20 anti:syn.

$^1$H NMR (400 MHz, CDCl$_3$): 7.53 (dd, J=5.8, 1.5 Hz, 1H, (anti)), 7.44 (dd, J=5.8, 1.5 Hz, 1H, (syn )), 6.16 (dd, J=5.8, 2.2 Hz, 1H, (anti)), 4.99 (ddd, J=4.6, 2.0, 1.5 Hz, 1H, (syn )), 4.95 (ddd, J=4.5, 2.0, 1.5, 1H, (anti)), 3.77 (m, 1H, (anti)), 3.66 (m, 1H, (syn)), 1.45-1.85 (m , 4H), 9.3-1.06 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): 173.0, 153.8, 153.6, 122.7, 122.6, 85.8, 73.1, 72.8, 70.5, 68.3, 28.3, 26.3, 26.1, 9.9, 9.5; CIMS m/z : 143(M+1), 126, 125, 113.

3.10$^{51}$

5-(hydroxy(phenyl)methyl)-5-methylfuran-2(5H)-one (3.10) Prepared by procedure 2; benzaldehyde (106 mg, 1 mmol), angelica lactone (118 mg, 1.19 mmol), potassium t-butoxide (5.5 mg, 0.05 mmol), reaction mixture stirred at -78 for 1 hr and was quenched with 1N HCl. Purification by silica gel flash chromatography (98:2 chloroform: methanol) 94 mg (41%) mixture of diastereomers 94:6 anti:syn.; $^1$H NMR (400 MHz,
CD$_3$OD): 7.66 (d, J=6.0 Hz, 1H, (anti)), 7.62 (d, J=5.8 Hz, 1H, (syn)), 7.268-7.462 (m, 5H), 6.01 (d, J=5.6 Hz, 1H, (anti)), 5.96 (d, J=5.6 Hz, 1H, (syn)), 1.5 (s, 3H, (syn)), 1.41 (s, 3H, (anti)), $^{13}$C NMR (100 MHz, CDCl$_3$): 172.3, 157.6, 138.0, 128.6, 128.3, 127.10, 121.94, 90.7, 77.6, 20.4; CIMS $m/z$: 187 (M+1)-H$_2$O, 145, 145, 127, 113, 108, 107, 106, 105, 100;

![Chemical structure](image)

4.7\textsuperscript{55}

5-(1-Hydroxy-3-phenyl-allyl)-5H-furan-2-one (4.7)

Prepared by procedure 2; t-cinnamaldehyde (216 mg, 1 mmol), 2(3H)-furanone (100 mg, 1.19 mmol), S,S TUC (1.26) (20 mg, 5 mmol), reaction mixture stirred at -20°C for 5 hr then quenched with 1N HCl. Purification by silica gel flash CC (80:20 hexane: ethyl acetate) gave 89 mg (41%) mixture of diastereomers (anti:syn 70:30).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.47 (dd, $J$=5.83, 1.46 Hz, 1 H), 7.42 (dd, $J$=5.83, 1.46 Hz, 6 H), 6.70 (d, $J$=16.04 Hz, 1 H), 6.19 (d, $J$=5.83 Hz, 1 H), 6.15 (dt, $J$=5.83, 1.64 Hz, 2 H), 5.04 (d, $J$=4.74 Hz, 1 H), 4.52 - 4.66 (m, 1 H), 2.31 (d, $J$=4.74 1 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): 172.7, 153.0, 135.7, 133.4, 128.6, 128.3, 126.7, 126.6, 125.1, 123.2, 85.5, 72.0;
5-(1-Hydroxy-butyl)-5H-furan-2-one (4.8)

Prepared by procedure 2; n-butanal (72 mg, 1 mmol), 2(3H)-furanone (100 mg, 1.19 mmol), S,S TUC (1.26) (20 mg, 5 mmol), reaction mixture stirred at -20°C for 5 hrs then quenched with 1N HCl. Purification by silica gel flash CC, 59 mg (38%) mixture of diastereomers (anti:syn, 66:33; ^1^H NMR (400 MHz CDCl\textsubscript{3}) \(\delta\) ppm 7.50-7.60 (m, 1H), 6.15-6.26 (m, 1H), 4.92-5.03 (m, 1H), 3.82 - 3.94 (m, 1 H), 1.81 - 2.09 (m, 1H), 1.60 (dd, \(J=4.56, 2.37\) Hz, 4H), 0.98 (t, \(J=6.93\) Hz, 3H), ^1^3^C NMR (100 MHz, CDCl\textsubscript{3}): 153.3, 122.9, 85.9, 71.25, 35.0, 18.7, 13.8.

**General procedure for preparation of Mosher esters (S Mosher Ester).** To a solution of (R)-5-((S)-hydroxy(phenyl)methyl)furan-2(5H)-one (4.1) (25 mg, 0.3 mmol) in 1 mL CDCl\textsubscript{3} was added (R)-(−)-\(\alpha\)-methoxy-\(\alpha\)-(trifluoromethyl)phenylacetyl chloride (60 ul, 0.32 mm). The mixture was stirred as pyridine d-6 (50 ul) was added dropwise. The reaction was stirred as a solid precipitated. The solid (pyridinium chloride) was removed via filtration. The crude reaction mixture was analyzed by NMR to determine ee. The product was purified on silica gel by flash chromatography and the ee was reconfirmed by NMR.

The relative stereochemistry of the major products were determined as anti by comparison of NMR spectra to that reported in the literature.\(^{18, 41}\)

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\[\text{HO} \quad \text{OH} \quad \text{O} \quad \text{O} \quad \text{C} \]

4.8\(^{41}\)
The R Mosher ester of (R)-5-((S)-hydroxy(phenyl)methyl)furan-2(5H)-one (4.1) was prepared using the same procedure. The NMR spectra of the Mosher esters were compared to determine the absolute configuration of (4.1) (see table below).

The relative stereochemistry of the major products were determined as anti by comparison of NMR spectra to that reported in the literature.\textsuperscript{18, 41}

\textbf{Δ δ data for the S and R MTPA butenolide Mosher esters 6S and 6R}

<table>
<thead>
<tr>
<th></th>
<th>δ-S-ester (S) (ppm)</th>
<th>δ-R-ester (6R) (ppm)</th>
<th>$\Delta \delta^{SR}$ ($=\delta_S - \delta_R$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4H</td>
<td>6.15</td>
<td>6.10</td>
<td>+0.05 ppm Hz (400 MHz)</td>
</tr>
<tr>
<td>5H</td>
<td>5.26</td>
<td>5.23</td>
<td>+0.03 ppm Hz (400 MHz)</td>
</tr>
<tr>
<td>1’H</td>
<td>6.32</td>
<td>6.30</td>
<td>+0.02 ppm Hz (400 MHz)</td>
</tr>
<tr>
<td>OMe (Mosher ester)</td>
<td>3.51</td>
<td>3.45</td>
<td>+0.06 ppm Hz (400 MHz)</td>
</tr>
</tbody>
</table>

\textbf{R Mosher Ester}

\textbf{S Mosher Ester}
NMR Spectra

2,5-bisacetoxy-2,5-dihydrofuran (2.4)
2,5-bisacetoxy-2,5-dihydrofuran (2.4)
2-acetoxyfuran (2.1)

Chemical Shift (ppm)

Normalized Intensity

M04(s,9)
M02(m,3)
M01(m,5)
M03(m,4)

2.29
2-acetoxyfuran (2.1)
2(3H)-furanone (1.2)

Chemical Shift (ppm)

Normalized Intensity

M01 (m, 5)

M02 (d, 4)

M03 (m, 3)

6.73

5.51

3.09

5

4

3

2

1

0
2(3H)-furanone (1.2)
5-(hydroxy(phenyl)methyl)furan-2(5H)-one (2.9, 2.10, 4.1, 4.2)
5-(hydroxy(phenyl)methyl)furan-2(5H)-one (2.9, 2.10, 4.1, 4.2).
5-(hydroxy(4-methoxyphenyl)methyl)furan-2(5H)-one (3.4 and 4.3)
5-(hydroxy(4-methoxyphenyl)methyl)furan-2(5H)-one (3.4 and 4.3)
5-((4-bromophenyl)(hydroxy)methyl)furan-2(5H)-one (3.5, 4.4)
5-((4-bromophenyl)(hydroxy)methyl)furan-2(5H)-one (3.5, 4.4)
5-(hydroxy(4-nitrophenyl)methyl)furan-2(5H)-one (3.6, 4.5)
5-(hydroxy(4-nitrophenyl)methyl)furan-2(5H)-one (3.6, 4.5)
5-(furan-2-yl(hydroxy)methyl)furan-2(5H)-one (3.7, 4.6)
5-(furan-2-yl(hydroxy)methyl)furan-2(5H)-one (3.7, 4.6)
5-(1-hydroxypropyl)furan-2(5H)-one (3.8)
5-(1-hydroxypropyl)furan-2(5H)-one (3.8)
5-(hydroxy(phenyl)methyl)-5-methylfuran-2(5H)-one (3.10)
5-(hydroxy(phenyl)methyl)-5-methylfuran-2(5H)-one (3.10)
5-(1-Hydroxy-3-phenyl-allyl)-5H-furan-2-one (4.7)
5-(1-Hydroxy-3-phenyl-allyl)-5H-furan-2-one (4.7)
5-(1-Hydroxy-butyl)-5H-furan-2-one (4.8)
5-(1-Hydroxy-butyl)-5H-furan-2-one (4.8)
R Mosher ester of product (R)-5-((S)-hydroxy(phenyl)methyl)furan-2(5H)-one.
S Mosher ester of product (R)-5-((S)-hydroxy(phenyl)methyl)furan-2(5H)-one.
HPLC Chromatograms

5-(hydroxy(phenyl)methyl)furan-2(5H)-one (R,R-TUC catalyzed)

5-(hydroxy(phenyl)methyl)furan-2(5H)-one (S,S-TUC catalyzed)
Reaction mixture for 5-(hydroxy(4-methoxyphenyl)methyl)furan-2(5H)-one (R,R-TUC catalyzed)

Reaction mixture for 5-(hydroxy(4-methoxyphenyl)methyl)furan-2(5H)-one (S,S-TUC catalyzed)
Reaction mixture for 5-((4-bromophenyl)(hydroxy)methyl)furan-2(5H)-one (R,R-TUC catalyzed)

Reaction mixture for 5-((4-bromophenyl)(hydroxy)methyl)furan-2(5H)-one (S,S-TUC catalyzed)
Reaction mixture for 5-(hydroxy(4-nitrophenyl)methyl)furan-2(5H)-one (S,S-TUC catalyzed)

Reaction mixture for 5-(hydroxy(4-nitrophenyl)methyl)furan-2(5H)-one (R,R-TUC catalyzed)
Reaction mixture for 5-(furan-2-yl(hydroxy)methyl)furan-2(5H)-one (S,S-TUC catalyzed)

Reaction mixture for 5-(furan-2-yl(hydroxy)methyl)furan-2(5H)-one (R,R-TUC catalyzed)
Reaction mixture for 5-(1-Hydroxy-3-phenyl-allyl)-5H-furan-2-one (R,R-TUC catalyzed)

Reaction mixture for 5-(1-Hydroxy-3-phenyl-allyl)-5H-furan-2-one (S,S-TUC catalyzed)
Bibliography


