Catalytic Photochemical Enantioselective α-Alkylation with Pyridinium Salts

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ABSTRACT: We have developed a chiral amine catalyzed enantioselective α-alkylation of aldehydes with amino acid derived pyridinium salts as alkylating reagents. The reaction proceeds in the presence of visible light (390 nm) and in the absence of a photocatalyst via a light activated charge-transfer complex. We apply this photochemical stereocentric process to the total synthesis of the lignan natural products (−)-enterolactone and (−)-enterodiol. Mechanistic studies support the ground-state complexation of the reactive components followed by divergent charge-transfer processes involving catalyst-controlled radical chain and in-cage radical recombination steps.

Carbonyl compounds with α-stereocenters are key components of many biologically active molecules, including pharmaceutical drugs and secondary metabolites. To access this important class of compounds, chemists have developed numerous transformative concepts in asymmetric catalysis for the enantioselective α-alkylation of enolates. While these reactions are often categorized by the mode of catalysis and the enolate precursor, an underappreciated component of these processes is the identity of the alkylating reagents that are coupled with enolates. Commonly employed alkylating reagents include alkyl halides and sulfonates.

We were interested in developing a general platform for the catalytic enantioselective α-alkylation of aldehydes 1 based on renewable and sustainable sources of alkylating reagents. Although elegant examples of photochemical enantioselective α-functionalizations of carbonyl compounds have been developed with alkyl halides, we identified amino acid derived substrates 4 as ideal reagents for enantioselective alkylations (Scheme 1B), as they possess several inherent advantages over traditionally used alkyl halides with respect to abundance, stability, versatility, and ease of preparation. In light of the poor electrophilicity of amino acid derivatives in enolate alkylations, we were motivated to devise a strategy for the activation of this class of substrates. In this Communication, we report the first catalytic photochemical enantioselective α-alkylation of aldehydes with amino acid derived pyridinium salts as alkylating reagents (Scheme 1C). These compounds are air and moisture stable crystalline solids that can be easily purified and stored for extended periods of time. Moreover, pyridinium salts can be generated on preparative scale from the facile condensation of amino acid derivatives and pyridylum salts.

We hypothesized that pyridinium salts could form ground-state encounter complexes with catalytically generated electron rich chiral enolate equivalents. Our approach was supported by an early report from Katritzky on the α-benzylation of diethylmalonate with pyridinium salts of benzylamine, which he postulated proceeds through the formation of light activated charge-transfer (CT) complexes. More recently, Melehiore has demonstrated the formation of CT complexes between enamines and alkyl halides. In our case, the generation of chiral enamine 7 from the condensation of aldehyde substrate 1 and a chiral amine catalyst could form CT complex 8 with pyridinium salt 6, which would then undergo stereoselective C–C bond formation in the presence of visible light.

Scheme 1. Strategy for Catalytic Enantioselective α-Alkylation with Amino Acid Derivatives

Our proposal to utilize pyridinium salts in enantioselective α-alkylations is motivated by their storied history as radical precursors. More recently, pyridinium salts have been utilized in deaminative transformations through activation by photoredox catalysis or the formation of CT complexes with electron rich molecules. Despite the widespread application of pyridinium salts as radical precursors, the use of...
these substrates in catalytic enantioselective transformations is rare, and enantioselective reactions with prochiral enolate equivalents is unprecedented.

We initiated our studies by coupling hydrocinnamaldehyde 9 with Katritzky salt 10a derived from the ethyl ester of glycine (Table 1). In the presence of MacMillan’s amine catalyst A, 2,6-lutidine, and purple light (390 nm) in CH₂Cl₂, we observed trace amounts of product 11a in 58% ee (entry 1). Interestingly, the deaminated byproduct of Katritzky salt 10a and the corresponding 2,6,4-triphenylpyridinium were formed, suggesting the formation of a light activated CT complex. We reasoned that the radical philicity of intermediates generated by this state complex is unprecedented for an electron withdrawing group. To test this hypothesis, we subjected electron deficient Katritzky salt 10b derived from 2,2,2-trifluoroethyl ester of glycine to the reaction conditions (entry 2). Gratifyingly, we obtained ω-alkylation product 11b in 36% yield and 60% ee, presumably via a more electron deficient α-carboxy radical. In a Lewis basic medium such as DMA, the desired product was formed in 40% yield and 92% ee (entry 3). Although other amine catalysts B−D also furnished product 11b (entries 4−6), catalyst A was still best for enantioselectivity.

**Table 1. Optimization Studies**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pyrimidine Salt</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Additive</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>10a</td>
<td>A</td>
<td>CH₂Cl₂</td>
<td>−</td>
<td>5</td>
<td>58</td>
</tr>
<tr>
<td>2</td>
<td>10b</td>
<td>A</td>
<td>CH₂Cl₂</td>
<td>−</td>
<td>36</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>10b</td>
<td>A</td>
<td>DMA</td>
<td>−</td>
<td>40</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>10b</td>
<td>B</td>
<td>DMA</td>
<td>−</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>10b</td>
<td>C</td>
<td>DMA</td>
<td>−</td>
<td>55</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>10b</td>
<td>D</td>
<td>DMA</td>
<td>−</td>
<td>52</td>
<td>23</td>
</tr>
<tr>
<td>7</td>
<td>10b</td>
<td>A</td>
<td>DMA</td>
<td>NaI</td>
<td>65</td>
<td>92</td>
</tr>
<tr>
<td>8</td>
<td>10b</td>
<td>A</td>
<td>DMA</td>
<td>NaI, H₂O</td>
<td>75</td>
<td>92</td>
</tr>
</tbody>
</table>

**Table 2. Substrate Scope**

| Reaction conditions: 9 (0.30 mmol), 10 (0.1 mmol), catalyst (20 mol%), 2,6-lutidine (0.1 mmol) NaI (0.1 mmol), H₂O (1.0 mmol). 4 °C, 24 h. Isolated yield. Enantiomeric excess determined by chiral HPLC analysis of a lactone derivative (see SI).


With enantioselectivity optimized, we focused on improving the yield of the reaction by employing additives that could enhance the ground-state complexation of the reaction components. Ultimately, the addition of stoichiometric NaI resulted in an increase in yield to 65% (entry 7), presumably through the formation of a multicomponent CT complex. Inclusion of water to help solubilize NaI further improved the yield to 75% while maintaining the enantioselectivity at 92% ee, which represented the optimal conditions for the reaction (entry 8).

We performed a series of control experiments to gain insight into the reaction (entries 9−12). Conducting the reaction at room temperature instead of 4 °C resulted in a loss of enantioselectivity (entry 9). Irradiation with various wavelengths of light resulted in diminished yields (entries 10−11), which confirmed the importance of activating the ground-state encounter complex at the appropriate wavelength. Furthermore, no product was observed in the absence of light (entry 12).

With optimal reaction conditions identified, we examined the substrate scope of the transformation (Table 2A). The Katritzky salt of the trifluoroethyl ester of glycine was coupled with various aldehydes to furnish the desired products in synthetically useful yields and greater than 90% ee (13a−e). We obtained products from linear aldehydes (13a−b), branched aldehydes (13c−d), and a carbamate functionalized aldehyde (13e). Enantioenriched alklylation products were also formed from the coupling of hydrocinnamaldehyde and Katritzky salts derived from various natural amino acids, such as alanine (13f), valine (13g), phenylalanine (13h), methionine (13i), and tyrosine (13j). In addition, we generated the alkylated product derived from an unnatural amino acid (13k). The products were generated with high enantioselectivity but poor diastereoselectivity, presumably because of the formation of open-shell intermediates (vide infra).

To demonstrate the utility of this new mode of activation with other classes of substrates, we reacted hydrocinnamaldehyde with Katritzky salts derived from various amines (Table 2B). Notably, these reactions were performed in CH₂Cl₂ in the absence of NaI and water, and the optimal wavelength of the light source was 427 nm. An electron-withdrawing group adjacent to the amine functionality was necessary for reactivity. For example, several 2-aminoacetoephone pyrimidinium salts were compatible substrates for the enantioselective transformation (15a−f). We also observed the desired product derived from aminoacetonitrile (15g). However, the Katritzky salt derived from 3-phenyl-1-propylamine did not yield alkylation product 15h under the reaction conditions. The requirement for an electron-withdrawing group in the pyrimidinium salt further demonstrates the importance of matching the radical philicities of intermediates generated upon light activated charge transfer.

| Reaction conditions: 15a (0.30 mmol), 15b (0.1 mmol), catalyst (20 mol%), 2,6-lutidine (0.1 mmol) NaI (0.1 mmol), H₂O (1.0 mmol). 4 °C, 24 h. Isolated yield. Enantiomeric excess determined by chiral HPLC analysis of a lactone derivative (see SI).


With enantioselectivity optimized, we focused on improving the yield of the reaction by employing additives that could enhance the ground-state complexation of the reaction components. Ultimately, the addition of stoichiometric NaI resulted in an increase in yield to 65% (entry 7), presumably through the formation of a multicomponent CT complex. Inclusion of water to help solubilize NaI further improved the yield to 75% while maintaining the enantioselectivity at 92% ee, which represented the optimal conditions for the reaction (entry 8).
The synthetic utility of our new catalytic method is highlighted by the enantioselective total synthesis of the lignan natural products (-)-enterolactone 17 and (-)-enterodiol 18 (Scheme 2). Under optimal conditions, 3-(3-hydroxyphenyl)propanal 16 and the pyridinium salt of racemic m-tyrosine (12k) reacted in a stereoenvergent process to form the α-alkylated product, which was subjected to reductive conditions without purification to furnish (-)-enterolactone 17 and its epimer (epi-17) in 46% yield over 2 steps. Although the diastereomeric lactones were obtained in high ee but poor dr, we recognized the opportunity to epimerize the mixture for the synthesis of more complex structures with high diastereoselectivity. Therefore, the diastereomers were subjected to LHMDS and TMSCl to yield (-)-enterolactone 17 in 81% yield, 12:1 dr, and 97% ee. Reduction with LiAlH₄ resulted in the formation of (-)-enterodiol 18 in 70% yield and 97% ee as a single diastereomer. Optical rotations of the synthetic samples of the two natural products also confirmed the absolute stereochernistry of the alkylation products obtained in our enantioselective reaction.

Scheme 2. Synthesis of Lignan Natural Products Via Enantioselective α-Alkylation with Pyridinium Salts

Based on our initial proposal of a light activated CT complex between the pyridinium substrate and a catalytically generated enamine (Scheme 1C), we performed a series of experiments to gain insight into the mechanism of the photochemical process. The subjection of either enantiomer of Katritzky salt 12f to the optimized reaction conditions with aldehyde 9 resulted in the stereovconvergent formation of the same major enantiomer of product 13f (Scheme 3A). This result is consistent with the formation of α-carboxy radical 19 as a common intermediate, which also accounts for the low diastereoselectivity in the transformation.

We were also interested in gaining insight into the role of NaI in the catalytic process. The use of 50 mol% NaI led to 58% isolated yield of the coupled product 11b. In addition, the pyridinium substrate 10b was not converted to the α-iodoester in the presence of NaI and absence of aldehyde. However, NaI caused a bathochromatic shift into the purple region of the absorption spectrum (Scheme 3B). Moreover, the inclusion of NaI had a profound impact on the equilibrium of enamine formation, presumably by affecting the equilibrium of CT complex 21 (Scheme 3B). Therefore, we believe NaI may affect the identity of the CT complex by forming a ternary...
complex with the catalytically generated enamine and pyridinium substrate.\textsuperscript{23}

**Scheme 3. Mechanistic Experiments**

Next, we used the trans and cis isomers of the radical probe 22 as the aldehyde component to determine whether the enantioselective reaction proceeds through a radical chain or in-cage radical recombination process (Scheme 3C and Figure S7).\textsuperscript{42,56} Radical probe trans-22 exclusively formed the alkylation product trans-23 as a mixture of diastereomers at C1, which is consistent with either a radical chain or in-cage radical recombination. With radical probe cis-22, the expectation was that an in-cage radical process would exclusively furnish the thermodynamically stable alkylation product trans-23 via acyclic intermediate 24.\textsuperscript{5} Alternatively, the alkylation product cis-23 would form exclusively if the reaction proceeded through a radical chain.\textsuperscript{56} Surprisingly, starting from radical probe cis-22, we isolated both trans and cis isomers of alkylation product 23 in a 1:2.6 ratio. These observations suggest that the catalytic enantioselective reaction may proceed simultaneously through two highly enantioselective mechanisms. Although we cannot rule out the possibility of a radical chain mechanism with cyclopropane ring opening as an off-cycle process, we believe the measured quantum yield of 4\textsuperscript{2} may be more consistent with the co-existence of two distinct mechanistic pathways.

Based on these experiments, we propose the dual mechanism depicted in Scheme 4. The radical chain mechanism is initiated by the conversion of pyridinium salt 10b to \(\alpha\)-carboxy radical 26, most likely by light-induced single electron transfer from an electron-rich component such as enamine 27 or NaI itself. Electron-deficient radical 26 then reacts with enamine 27 to furnish \(\alpha\)-aminoradical 28. Subsequent single electron transfer to another molecule of pyridinium salt 10b yields enantioenriched iminium ion 29, which hydrolyzes to alkylation product 30. For the in-cage radical recombination pathway, enamine 27 and pyridinium salt 10b can form CT complex 31, which may include a molecule of NaI. In the presence of 390 nm light, CT complex 31 can undergo a single electron transfer to form \(\alpha\)-carboxy radical 26 and \(\alpha\)-iminyl radical 32. Subsequent radical recombination results in the stereoselective formation of iminium ion 29, which hydrolyzes to alkylation product 30.

In conclusion, we have developed a catalytic enantioselective alkylation of aldehydes with pyridinium salts derived from amino acids and other \(\alpha\)-stabilized amines. The reaction is enabled by a visible light activated CT complex between electron-deficient pyridinium salts and electron-rich components of the reaction. The mild conditions are compatible with several functional groups, enabling the enantioselective synthesis of lignan natural products. Future studies will examine the mechanism of this process in more detail. We anticipate this approach may be extended to the photochemical catalytic enantioselective alkylation of several classes of carbonyl compounds with pyridinium salts based on other modes of catalysis.
ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website. Experimental details, characterization data, and spectral data (PDF).

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Author Contributions
The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes
The authors declare no competing financial interest.

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(22) See Supporting Information for details.

(23) We cannot rule out the possibility that DMA and other reaction components, such as 2,6-lutidine, also impact the nature of the CT complex.
derived from amino acids

- visible light activated charge transfer complex
- dual mechanism: radical chain and in-cage radical recombination