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Dual Catalysis in Enantioselective Oxidopyrylium-Based [5+2] Cycloadditions

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Supporting Information Placeholder

**ABSTRACT:** A new method is reported for effecting catalytic enantioselective intramolecular [5+2] cycloadditions based on oxidopyrylium intermediates. The dual catalyst system consists of a chiral primary amine-thiourea and a second achiral thiourea. Experimental evidence points to a new type of cooperative catalysis with each species being necessary to generate a reactive pyrylium ion pair which undergoes subsequent cycloaddition with high enantioselectivity.

The [5+2] dipolar cycloaddition of oxidopyrylium ylides (1, Scheme 1) and two-carbon dipolarophiles generates complex, chiral 8-oxabicyclo[3.2.1]octane architectures 2. In addition to being a structural motif common to numerous natural products, such cycloadducts have been proven to be highly valuable intermediates in the synthesis of functionalized seven-membered carbocycles and tetrahydrofuran derivatives. Despite the utility of this [5+2] cycloaddition and its widespread use in organic synthesis, asymmetric examples have thus far been limited to diastereoselective variants, and there are currently no catalytic enantioselective methods that engage reactive pyrylium intermediates in cycloaddition chemistry. Herein we report a dual-catalyst system consisting of a chiral primary aminothiourea and an achiral thiourea that promotes an intramolecular variant of the title reaction with high enantioselectivity. Experimental evidence points to a new type of cooperative mechanism of catalysis.

**Scheme 1.** Oxidopyrylium cycloadditions and proposed mode of catalysis

It has been shown recently that small-molecule chiral hydrogen-bond donor catalysts can serve as anion abstractors and binders in the generation and enantioselective transformation of highly reactive cationic intermediates, and we became interested in the potential application of the principle of anion-binding catalysis to oxidopyrylium formation and cycloaddition. These intermediates are generally accessed by thermolysis of the corresponding acetoxypyranones 3 (X = OAc, Scheme 1), or by reaction of 3 with an amine base. Upon elimination of acetic acid, reactive 1 has been shown to undergo [5+2] cycloadditions with both electron-rich and electron-poor dipolarophiles. We hypothesized that a thiourea or thiourea catalyst might induce ionization of an appropriate leaving group from 3 or a tautomeric form thereof, to give pyrylium 4. Our efforts thus focused on identifying an appropriate precursor to this species (i.e., X in 3) as well as the best mode for activation and asymmetric induction in subsequent [5+2] cycloadditions.

**Table 1. Reaction optimization**

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate (R=)</th>
<th>catalyst(s)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
</table>
| 1  
1c | 5a (Ac) | 7 | 37 | 21 |
| 2  
2c | 5a (Ac) | 7 + 8 | 44 | 67 |
| 3 | 5a (Ac) | 7 + 8 | 53 | 67 |
| 4 | 5a (Ac) | 9 + 8 | 41 | 66 |
| 5 | 5a (Ac) | 10 + 8 | 30 | 88 |
| 6 | 5b (Bz) | 10 + 8 | 56 | 91 |
| 7 | 5c (p-MeSBz) | 10 + 8 | 72 | 91 |
| 8 | 5c (p-MeSBz) | 10 + 8 | 76 | 91 |

Reactions performed on a 0.05 mmol scale. * Determined by 1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. * Determined by HPLC using commercial chiral columns. * No added AcOH. * Conditions: 10 mol% 10 + 8, 0.4 M.

Racemic acetoxypyranone 5a was chosen for initial exploratory and ensuing optimization studies. The desired reaction was found to take place in the presence of a variety of chiral thiourea derivatives in combination with stoichiometric triethylamine, but no stereoinduction was observed in the formation of cycloadduct 6. In contrast, bifunctional primary aminothiourea induced formation of 6 with low levels of enantioselectivity in the absence of exogenous base (Table 1, entry 1). An unexpected but ultimately significant observation resulted from a broad screen of additives, with chiral thiourea catalyst 8 dramatically improving the reaction enantioselectivity (entry 2). The addition of acetic acid as a second co-catalyst provided a measurable yield enhancement, with no effect on product ee (entry 3). Other achiral or chiral hydrogen-bond donors (including the urea analogue of 8) proved less beneficial as additives. Whereas the electron-poor bis(trifluoromethyl) anilide group is found to be an optimal chiral catalyst feature in a growing number of enantioselective thiourea-
promoted reactions,\textsuperscript{16} phenylthiourea (entry 4) was found to be comparable to 7. This prompted an exhaustive examination of the effect of aryl substitution on the aminothiourea catalyst,\textsuperscript{15} and led to the identification of 10, which bears a 2,6-diphenylalanilide component, as the most enantioselective aminothiourea catalyst (entry 5). The diminished reactivity displayed by 10 was overcome by utilizing substrate 5b containing a benzoate-leaving group (entry 6). Upon exploring various substituents on the benzoate a further enhancement was observed with para-thiomethylbenzoic acid byproduct (as compared to benzoic or acetic acid), which precipitates during the course of the reaction. Finally, increasing the reaction concentration further improved the rate, allowing for the loadings of 10 and 8 to be reduced with this parent substrate (entry 8).

Table 2. Substrate scope

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{a}\textsuperscript{d}</td>
<td>p-MeSBzO\textsuperscript{5c}</td>
<td>\textbf{6}</td>
<td>15 mol% 10</td>
<td>15 mol% 8</td>
<td>15 mol% AcOH</td>
</tr>
<tr>
<td>2</td>
<td>R = Me</td>
<td>11</td>
<td>72</td>
<td>70</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>R = H</td>
<td>13</td>
<td>72</td>
<td>66</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>R = Me</td>
<td>15</td>
<td>96</td>
<td>51</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>R = H</td>
<td>17</td>
<td>72</td>
<td>48</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>R = CO₂⁺</td>
<td>19</td>
<td>72</td>
<td>66</td>
<td>90</td>
</tr>
<tr>
<td>7\textsuperscript{e}</td>
<td>R = CO₂Me</td>
<td>21</td>
<td>96</td>
<td>37</td>
<td>80</td>
</tr>
<tr>
<td>8\textsuperscript{c}\textsuperscript{d}</td>
<td>p-MeSBzO\textsuperscript{23}</td>
<td>\textbf{24}</td>
<td>72</td>
<td>54</td>
<td>95</td>
</tr>
<tr>
<td>9</td>
<td>p-MeSBzO\textsuperscript{25}</td>
<td>\textbf{26}</td>
<td>72</td>
<td>42</td>
<td>88</td>
</tr>
<tr>
<td>10\textsuperscript{a}</td>
<td>p-MeSBzO\textsuperscript{27}</td>
<td>\textbf{28}</td>
<td>72</td>
<td>77</td>
<td>90</td>
</tr>
</tbody>
</table>

With optimal catalytic conditions in hand, an examination of the substrate scope was undertaken (Table 2). Substitutions at the olefin terminus were tolerated (entries 2–7), despite a diminishment of reactivity occurring upon increased substitution (entries 4 and 7). Allenes are viable cycloaddition substrates (entries 8 and 9), however alkyne-bearing substrates proved unreactive under the current set of conditions. Other viable substrates include those bearing substitution on the tether connecting the dipole and dipolarophile as in diallyl substrate 27 (entry 10), or on the pyrano ring as in 29 (entry 11). Product 30 bears a siloxymethylene unit commonly found in synthetically useful oxidopyrylium cycloadducts.\textsuperscript{18} Substrate variations that were not tolerated include melylation at the internal position of the olefin as well as a homologue of substrate 5c containing an additional methylene in the tether. Initial efforts to extend this system to an asymmetric intermolecular variant have been met with only moderate success.\textsuperscript{15}

Table 3. Catalyst structure-activity relationship study

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>0 mol% 8 yield (%)\textsuperscript{a}</th>
<th>ee (%)\textsuperscript{b}</th>
<th>15 mol% 8 yield (%)\textsuperscript{a}</th>
<th>ee (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>32</td>
<td>72</td>
<td>72</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>7</td>
<td>n.d.</td>
<td>58</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>7</td>
<td>n.d.</td>
<td>58</td>
<td>–85</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>10</td>
<td>n.d.</td>
<td>11</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

Reactions performed on a 0.05 mmol scale. \textsuperscript{a} Determined by \textsuperscript{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. \textsuperscript{b} Determined by HPLC using commercial chiral columns.

In order to probe the possible roles of the different components in this dual thiourea catalyst system, a series of reactions were run with different bifunctional chiral catalysts in the presence and absence of 8 (Table 3). A clear and dramatic cooperative effect is observed between the optimal catalysts as evidenced by the poorer results obtained without achiral catalyst 8 (entry 1). A beneficial effect of 8 has also been reported recently in proline-catalyzed transformations, where its primary role appears to be as a phase-transfer catalyst to solubilize proline in the non-polar media.\textsuperscript{19} Such a role is unlikely in the present system, as all components of this oxidopyrylium-based cycloaddition reaction are initially soluble in toluene (vide supra).

Instead, we propose that the function of 8 in the pyrylium cycloaddition reaction is as a carboxylate-binding agent (Figure 1A),
With the goal of evaluating the viability of aminopyrylium 34 in the cycloaddition chemistry induced by the catalyst combination of 10 and 8, a computational frontier molecular orbital analysis of a variety of dipolarophiles and of oxido-, amido-, and aminopyryliums (4, Y = O, NH, NH$_2$, respectively, Scheme 1) was performed and compared with observed trends in intramolecular cycloadditions. The dominant HOMO-LUMO interactions between each of the three hypothetical pyrylium species and alkenes of varying electronic properties were thereby predicted. With an oxido- or amidopyrylium, either the HOMO or the LUMO of the dipole can be more relevant to cycloaddition depending on the dipolarophile, in line with the experimental observation that oxidopyrylium dipolar intermediates undergo reaction with either electron-rich or electron-deficient alkenes. Alternatively, the LUMO of an aminopyrylium was predicted to be the MO relevant to cycloaddition in all cases, consistent with our observation that intermolecular reactions under thiourea-catalyzed conditions only proceed with electron-rich dipolarophiles containing a high HOMO. The results thus point towards an aminopyrylium – and not an oxido- or amidopyrylium – as the relevant intermediate in the thiourea-catalyzed reactions described herein.

In summary, we have identified a dual thiourea catalyst system for intramolecular oxidopyrylium [5+2] cycloadditions, providing enantioselective access to valuable tricyclic structures. Application of this reaction to the synthesis of biologically active small molecules, further mechanistic studies into the origin of the catalyst cooperativity, and extension of the underlying principles to other multifunctional (thio)urea-catalyzed transformations are the focus of ongoing investigations.

ASSOCIATED CONTENT

Supporting Information. Full experimental procedures, syntheses of substrates and catalysts 10 and 32, characterization data for all new compounds, NMR spectra for cycloaddition products, HPLC traces for scalemic cycloaddition products, geometries and energies of calculated stationary points, and crystallographic information. This material is available free of charge via the internet at http://pubs.acs.org.

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REFERENCES


For examples that include a direct comparison of different aryl thio-
Wittkopp, A.; Schreiner, P. R. 
(7) For an isolated example of Rh-catalyzed benzopyrylium cycloaddi-
(8) A remarkable effect of TNNH in the enantio- and diastereoselectivity of rhodium-catalyzed cyclopropanations of α-cyano diazocacetamide has been noted by Charette and co-workers. The basis for this cooperative effect appears to be entirely different from the one described herein: Marcoux, D.; Azzi, S.; Charette, A. B. J. Am. Chem. Soc. 2009, 131, 6970–6972.
(13) See Supporting Information for details.
(14) For preparation and use, see reference 9g and references therein.
(16) For examples that include a direct comparison of different aryl thio-
Catalyst: 3

Products:
1. 72%, 91% ee
2. 72%, 91% ee
(10 other examples)

Conditions:
15 mol% catalyst(s)
15 mmol, 40 °C, 48 h