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Thiourea-Catalyzed Enantioselective Addition of Indoles to Pyrones: Alkaloid Cores with Quaternary Carbons

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ABSTRACT: We report the development of a catalytic method for the enantioselective addition of indoles to pyrone-derived electrophiles. Arylpyrrolidino-derived thioureas catalyze the addition with high stereoselectivity in the presence of catalytic quantities of an achiral Brønsted acid. The indole–pyrone adducts feature a quaternary stereocenter and represent an unusual class of indolines bearing structural resemblance to the hybrid natural product pleiocarpamine.

Complex indole alkaloids are important compounds that possess a wide range of bioactivities. For instance, pleiomaltinine is a hybrid natural product that features both indoline and γ-pyrones functionalities and exhibits an impressive ability to reverse multidrug resistance in vincristine-resistant cells. Recently, we described a synthetic approach to pleiomaltinine through a Brønsted acid-promoted indole–pyrone annulation (Figure 1) involving a putative quinone methide-like intermediate. Inspired by both the structural and biological uniqueness of pleiomaltinine and the relative scarcity of enantioselective catalytic transformations involving quinone methide intermediates, we sought to explore the development of a general asymmetric annulation of indoles and pyrones. The established ability of neutral hydrogen-bond donors to catalyze enantioselective transformations of cationic intermediates through anion-binding mechanisms led us to consider whether the cooperative action of a chiral thiourea and an achiral Brønsted acid could promote stereoselective additions of nucleophilic indoles to cationic pyrone-derived quinone methide-like intermediates. In such a transformation, the formation of a chiral ion pair could render the formal nucleophilic addition step enantioselective to afford a chiral indoline bearing a quaternary carbon stereocenter at C3.

Table 1. Catalyst Structure Optimization Studies

<table>
<thead>
<tr>
<th>Conditions: [1] = 0.05 M, 3 days. All reactions were conducted on a 0.05 mmol scale. Isolated yields are reported. Enantioselectivities of the O-mesylated derivative of 3a were determined by HPLC analysis on commercial chiral columns. See the Supporting Information for details.</th>
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Figure 1. An indole–pyrone annulation approach to pleiomaltinine and a proposed enantioselective variant.
We describe here the successful development of this strategy. Using the benzoic acid-catalyzed reaction of pyrone precursor 1 and 1,2,3,4-tetrahydrocarbazole (2a) as a model, we evaluated several chiral urea and thiourea derivatives that have been utilized previously with success in Brønsted acid-cocatalyzed reactions. While promising levels of enantioselectivity and reactivity were obtained with different classes of neutral hydrogen-bond-donor catalysts (Table 1), particularly high ee’s were observed with thiourea derivatives bearing a t-leucine arylpyrrolidino amide component (7). Through a systematic investigation of such substituted arylpyrrolidino derivatives, we found that new catalysts bearing the m-terphenyl motif promoted the indole–pyrone addition with >95% ee (7d and 7e). Thiourea 7e was ultimately selected for further evaluation in the addition of various indole nucleophiles to γ-pyrene precursor 1 (Table 2). Both electron-withdrawing (3b–f) and electron-donating (3g–j) substituents on the indole ring were well-tolerated, indicating that the nucleophilicity of the reactive 3-position of the indole is not critical for high enantioselectivity. Variation of both the 2- and 3-substituents on the indole was also possible (3k–m), although substitution at the 3-position was necessary to avoid rearomatization to an

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**Table 2. Substrate Scope of Indole–Pyrone Additions**

<table>
<thead>
<tr>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<tbody>
<tr>
<td>Br</td>
<td>N</td>
<td>Me</td>
<td>91%</td>
<td>92%</td>
</tr>
<tr>
<td>Cl</td>
<td>F</td>
<td>i-Pr</td>
<td>43%</td>
<td>90%</td>
</tr>
<tr>
<td>Br</td>
<td>NC</td>
<td>MeO</td>
<td>69%</td>
<td>84%</td>
</tr>
<tr>
<td>Br</td>
<td>Et</td>
<td>Ph</td>
<td>66%</td>
<td>88%</td>
</tr>
<tr>
<td>Me</td>
<td>Br</td>
<td>Ph</td>
<td>71%</td>
<td>92%</td>
</tr>
<tr>
<td>Me</td>
<td>Br</td>
<td>N</td>
<td>95%</td>
<td>96%</td>
</tr>
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</table>

Conditions: [1] = 0.05 M, 3 days. Products were derivatized to the corresponding O-mesylates (3 equiv of RSO<sub>2</sub>Cl, 5 equiv of NEt<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, overnight) for isolation and ee determination. Products 3b and 3l were derivatized to O-tosylates. Isolated yields of the corresponding sulfonates are reported. All reactions were conducted on a 0.1 mmol scale. Enantioselectivities were determined by HPLC analysis on commercial chiral columns. See the Supporting Information for details.
The N-methylated analogue of the benzoyl derivative terphenyl group as the optimal substituent in this class of chiral method for the addition of 3-substituted indoles to cationic electrophiles. In contrast, variation of the leaving group on the pyrone precursor was found to impact the enantioselectivity, as the chlorinated analogue underwent the reaction to afford adduct 3a with 84% ee using catalyst 7b while the benzoyl derivative proved unreactive (Figure 3). Finally, the N-methylated analogue of 2a reacted with 1 in the presence of chiral thiourea 7e to afford only racemic cycloaddition product, revealing a crucial role of the indole N–H in the catalytic mechanism. Taken together, these findings are most consistent with an enantiodetermining step involving specific interactions between the catalyst and both the pyrone leaving group and the indole N–H moiety. We propose that 1 undergoes desilylation in the presence of the Brønsted acid. A cationic quinone methide-like intermediate is then generated by anion abstraction by the thiourea catalyst, with general base activation of the indole in the stereodetermining addition step (Figure 4). Additional attractive interactions (e.g., π–π or C–H–π) between the cationic electrophile and the catalyst pyrrolidine substituent are suggested by the dependence of the reaction enantioselectivity on the nature of that aromatic group. A mechanistic picture emerges that bears resemblance to that invoked previously in the ring-opening reaction of episulfonium ions with indole nucleophiles, thereby suggesting a possible general principle for enantioselective additions of indoles to cationic electrophiles.

In summary, we have uncovered a highly enantioselective method for the addition of 3-substituted indoles to γ-pyrone-derived electrophiles, providing a route to simplified pleiomaltidine analogues bearing a defined quaternary stereocenter. Investigation of the biological activity of these unusual structures is underway. In addition, identification of the m-terphenyl group as the optimal substituent in this class of chiral thiourea catalysts is new, and we are currently exploring the specific transition-state interactions associated with this aromatic framework in an effort to elucidate the basis for the stereoinduction in this reaction.

**Acknowledgments**

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**References**


6. We have found that indolines bearing γ-pyrone functionalities preferentially adopt the ring-closed form in settings where the indole nitrogen is alkylated (cf. pleiomaltidine, ref 2) and the open form when the indole lacks an N substituent (cf. 3a). The position of this equilibrium is expected to depend strongly on medium effects and specific hydrogen-bonding interactions.

7. For examples of indolines containing quaternary stereocenters, see: (a) Trost, B. M.; Quancard, J. J. Am. Chem. Soc. 2006, 128, 6314–
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