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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-pyron functionalities and exhibits an impressive ability to reverse multidrug resistance in vincristine-resistant cells.1 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.2 Inspired by both the structural and biological uniqueness of pleiomaltinine and the relative scarcity of enantioselective catalytic transformations involving quinone methide intermediates,3 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 mechanisms4 led us to consider whether the cooperative action of a chiral thiourea and an achiral Brønsted acid5 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

| 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. a No BzOH was added. |

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.

Table 2. Substrate Scope of Indole−Pyrone Additions

Conditions: [1] = 0.05 M, 3 days. Products were derivatized to the corresponding O-mesylates (3 equiv of RSO₂Cl, 5 equiv of NEt₃, CH₂Cl₂, 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.

Figure 2. Variation of the Brønsted acid cocatalyst. Conditions: [1] = 0.05 M, 3 days. 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.

Figure 3. Variation of the pyrone precursor. Conditions: [1] = 0.05 M, 3 days. 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.

Figure 4. Proposed catalytic cycle.
Communication

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REFERENCES

(6) We have found that indolenines bearing γ-pyrone functionalities preferentially adopt the ring-closed form in settings where the indole nitrogen is alkylated (cf. pleiomaltinine, 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–

ASSOCIATED CONTENT

Supporting Information
Complete experimental procedures, characterization data, additional discussion of catalyst optimization and substrate scope, and crystallographic information (CIF) for compound (R)-3a. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

(11) \( \text{m-Terphenyl} \) groups have been shown to engage productively in cation–π interactions. See: Shukla, R.; Lindeman, S. V.; Rathore, R. Chem. Commun. 2009, 5600–5602.

(12) The low yields obtained for certain addition products (e.g., 3g–j) can be attributed to competitive homodimerization of precursor 1.

(13) The addition step may occur through a conjugate addition mechanism, as proposed in Figure 4, to afford the observed open product directly or via a concerted \([4+2]\) cycloaddition pathway with subsequent ring opening.