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Enantioselective Thiourea-Catalyzed Cationic Polycyclizations

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Advances in cyclase enzymology have provided strong evidence that cation−π interactions play an essential catalytic role in biosynthetic polyene cyclizations.[1,2] Structural, kinetic, and site-directed mutagenesis studies all suggest that the cationic intermediates and transition states accessed in these transformations are stabilized through a series of attractive interactions with aromatic residues that line the cyclase active site.[3] This mechanistic insight suggests the intriguing possibility that analogous stabilizing cation−π interactions might also be engineered into selective small-molecule catalysts.[4]

We became interested in developing an asymmetric polycyclization jointly predicated on this biosynthetic model and our recent work in anion binding thiourea catalysis.[5,6] The ability of arenes to stabilize cations offers a logical complement to the anion binding properties of thioureas.[7] As such, an appropriate bifunctional catalyst would be capable of electrostatically stabilizing both poles of a reactive ion pair in a spatially resolved manner, increasing the probability of strong binding to the enantioselectivity-determining transition state structure (Scheme 1).[8] Herein, we report the development of a new thiourea catalyst for the enantioselective bicyclization of hydroxylactams, together with evidence that stabilizing cation−π interactions play a principal role in asymmetric induction.

Our efforts focused on developing an enantioselective variant of a polycyclization originally reported by Speckamp that proceeds through an *N*-acyliminium ion intermediate (Table 1).[9] In accord with our previous reports on asymmetric transformations utilizing these electrophiles, we envisioned that treatment of a hydroxylactam substrate with hydrochloric acid would result in dehydrative formation of a chlorolactam intermediate.[6c] Hydrogen bond-mediated ionization of this chlorolactam by the thiourea would generate a catalyst-bound iminium•chloride ion pair that would in turn undergo cyclization enantioselectively. In evaluating the bicyclization of hydroxylactam **1**, a preliminary survey of thioureas and solvents produced a lead result with thiourea **3**, with tetracycle **2** generated in 10% yield and 9% ee upon treatment with 25 mol% of HCl in TBME containing 4 Å molecular sieves at −30 °C (Table 1). Catalyst **4**, a conformationally constrained analogue of **3** bearing a 2-phenylpyrrolidine ring, afforded a modest increase in enantioselectivity.[10] Modification of the electronic properties of the aromatic group of **4** by introduction of simple substituents had little effect on catalyst performance. In contrast, 2-arylpyrrolidine catalysts bearing larger aromatic groups proved substantially more reactive and enantioselective. The naphthyl-substituted catalysts **5** and **6** both provided **2** in greater than 60% ee, while 9-phenanthryl-derived catalyst **7** furnished product **2** in 52% yield and 87% ee. Spurred by the apparent correlation between the expanse of the pyrrolidine arene and catalytic performance, we prepared and evaluated 4-pyrenyl-substituted thiourea derivative **8**. This proved to be the optimal catalyst, providing **2** in 78% yield and 95% ee.[11] Under the action of all the catalysts described in Table 1, tetracycle **2** was formed as a single detectable diastereomer, the relative stereochemistry of which was secured by X-ray crystallography (Supporting Information).[12,13] Notably, reactions performed in the absence of a thiourea catalyst provided none of the desired bicyclization product.[14]

Having identified a selective catalyst and suitable reaction conditions, we evaluated the substrate scope of this bicyclization protocol. A variety of aromatic groups were found to be efficient and selective terminating nucleophiles (Table 2). In addition to

Scheme 1. Proposal for Enantioselective Polycyclization

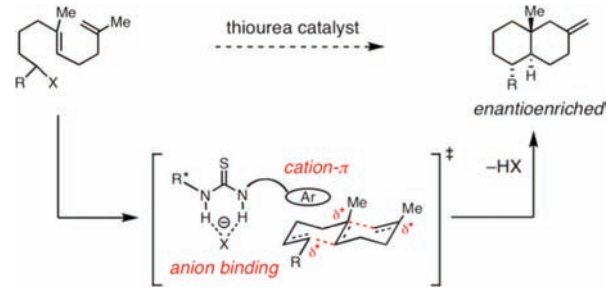
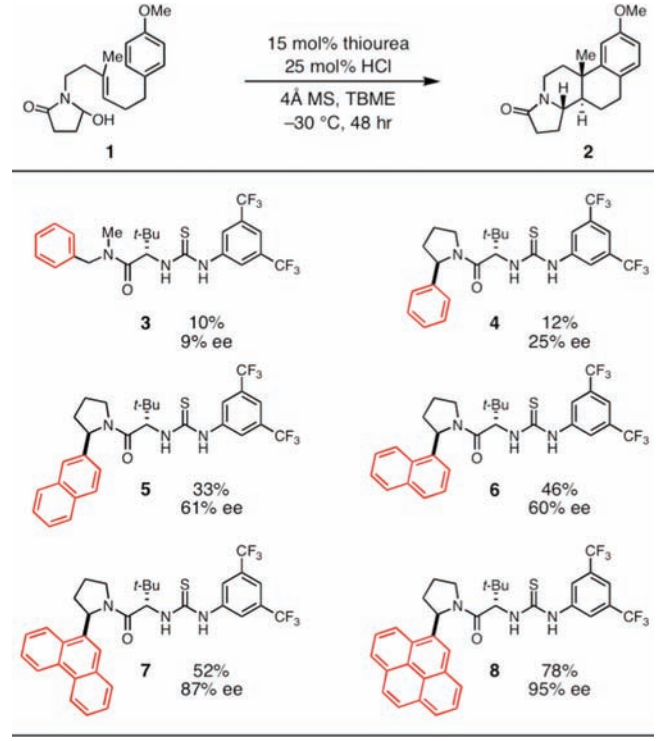


Table 1. Catalyst Optimization[a–c]



[a] Yields determined by GC analysis relative to an internal standard. [b] Enantiomeric excess determined by SFC analysis on commercial chiral columns. [c] Optimization reactions performed on 0.033 mmol scale.

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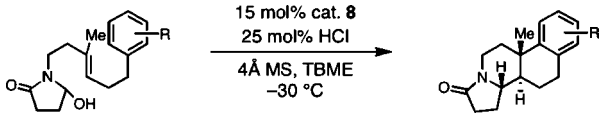
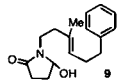
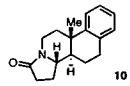
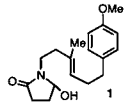
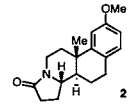
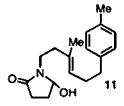
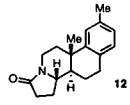
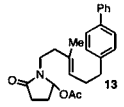
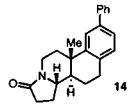
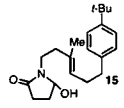
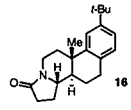
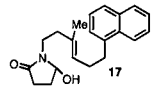
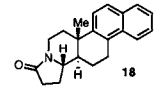
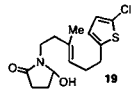
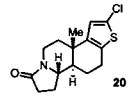
Table 2. Substrate Scope[g]



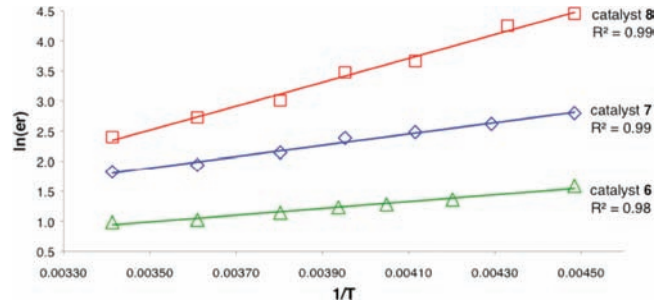
entry	substrate	product	time (h)	yield (%)[a]	ee (%)[b]
1	 9	 10	96	51	89
2	 1	 2	72	72	94
3	 11	 12	96	62	91
4[c]	 13	 14	120	54	91
5	 15	 16	96	71	91
6[d]	 17	 18	72	75	92
7[e,f]	 19	 20	72	77	91

[a] Isolated yields after chromatography on silica gel. [b] Enantiomeric excess determined by SFC analysis on commercial chiral columns. [c] Reaction run with 2.0 equivalents of TMSCl. [d] Reaction run with 50 mol% HCl. [e] Reaction run at −10 °C. [f] The structure and absolute configuration of **20** was established by X-ray crystallography and the stereochemistry of all other products was assigned by analogy. [g] Reactions performed on 0.25 mmol scale.

the model substrate **1**, the unsubstituted phenyl substrate **9** (entry 1), a number of *para*-substituted phenyl derivatives (entries 2−5), an extended naphthyl-containing substrate **17** (entry 6), and a chlorinated thiophene **19** (entry 7) all underwent cyclization with high enantioselectivity under the action of catalyst **8**.[15] Furthermore, in each case the bicyclization products were formed as single diastereomers, as judged by NMR analysis.[16] The use of more electron-rich arene nucleophiles or alteration of the non-aromatic portions of the substrate led to significant losses in either reactivity or enantioselectivity.[17]

The fact that the enantioselectivity observed in these polycyclizations is highly dependent upon the expanse of the catalyst arene, taken together with the cationic nature of the reaction, raises the possibility that stabilizing cation−π interactions may play a key role in asymmetric induction. To evaluate this hypothesis, an Eyring analysis of enantioselectivity was conducted for catalysts **6**, **7**, and **8** in the bicyclization of substrate **1**. All three catalysts displayed linear correlations between ln(er) and reciprocal temperature over a 70 °C range (Table 3). Evaluation of the differential activation parameters derived from these plots revealed that enantioselectivity was enthalpically controlled in all cases and that the magnitude of the differential

Table 3. Eyring Analysis of Enantioselectivity



entry	catalyst	$\Delta\Delta H^{\ddagger}$ (kcal/mol)	$\Delta\Delta S^{\ddagger}$ (cal/mol · K)
1	**6**	-1.12 ± 0.07	-2.0 ± 0.3
2	**7**	-1.87 ± 0.08	-2.8 ± 0.3
3	**8**	-3.95 ± 0.17	-8.9 ± 0.7

enthalpy increased markedly as the catalyst arene increased in size. In fact, this term roughly doubles in magnitude with the addition of each new aromatic ring, reaching nearly four kcal/mol for the optimal catalyst **8**. The effect of this increase was attenuated slightly by a compensating increase in the differential entropy terms across the series.

The energetic benefits of increasing the strength of a noncovalent binding interaction are typically manifested enthalpically.[18] As such, the increasing magnitude of the differential enthalpy in catalysts with more extended arenes is consistent in principle with a progressively more stabilizing cation−π interaction in the dominant transition state structure and with the fact polycyclic aromatic hydrocarbons are known to bind cations more strongly as they increase in size.[19] However, these data do not rule out the possibility that increasing the expanse of the arene energetically destabilizes the minor transition state assembly, presumably through steric interactions.[20] To ascertain whether the extended aromatic system is stabilizing the transition state leading to the major enantiomer or destabilizing the minor pathway, we investigated whether correlations existed between the degree of observed enantioinduction and the physical properties that underlie cation−π interactions. The strength with which a given arene interacts with a positive charge in a transition state is primarily a function of electrostatic and dispersion forces.[21,22] As such, if the strength of a cation−π interaction is a determinant in enantioselectivity, there may be a correlation between the degree of asymmetric induction observed and the quadrupole moment and polarizability of the arene involved. Conversely, if the effect was largely steric and repulsive in origin, no significant correlation with these physical properties would be expected. The enantioselectivity observed with catalysts **4**, **6**, **7**, and **8** under standard conditions was found to correlate strongly with both the polarizability and the quadrupole moment of the arenes found in each catalyst (R^2 = 0.99, 0.97 respectively, see Supporting Information).[23,24] Taken altogether, these data provide compelling evidence for a mechanism incorporating a selectivity-determining cation−π interaction.

In conclusion, the enantioselective cationic polycyclization reactions catalyzed by **8** appear to engage stabilizing cation−π interactions as a principal element of enantioselectivity. In this respect, these findings emulate the particularly striking role cation−π interactions play in the catalysis of biosynthetic polyene cyclizations and provides clear support for the notion that these interactions can dictate stereocontrol in small-molecule catalysis contexts as well. Moreover, this work further advances the view that stabilization of the dominant transition state

structure through noncovalent interactions is a viable means of achieving high levels of enantioselectivity in counterion catalysis.

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Supporting Information Available: Full experimental procedures, syntheses of substrates and catalysts, characterization data for all new compounds, NMR spectra for bicyclization products, SFC traces for scalemic bicyclization products, data sets for Eyring analysis and correlations with arene properties, and crystallographic information for compounds **2**, **18**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) In the absence of the thiourea catalyst, an HCl-catalyzed process forms a monocyclized byproduct.

(15) Higher yields and faster reactions are observed using increasing amounts of HCl, though with diminished enantioselectivities.

(16) In all cases, the only detectable byproduct is a monocyclized and eliminated product formed with low enantioselectivity.

(17) Enantioselectivity is strongly correlated with the electronic properties of the arene nucleophile, with electron-deficient arenes proving optimal. Results for less enantioselective substrates are included in the Supporting Information.

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