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Enantioselective Pictet−Spengler-Type Cyclizations of Hydroxylactams: H-Bond Donor Catalysis by Anion Binding

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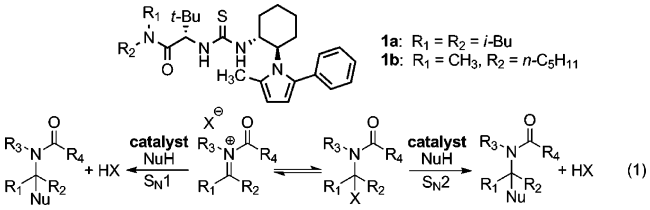
N-Acyliminium ions are highly reactive electrophilic species[1] that have been demonstrated only recently to engage successfully in asymmetric catalytic reactions.[2−4] Our own studies in this area led to the discovery that the chiral thiourea derivative **1a** promotes highly enantioselective Pictet−Spengler- and Mannich-type reactions through initial acylation of imines and isoquinolines, respectively.[3] The process by which the resulting *N*-acyliminium ions are induced to undergo enantioselective additions with a simple hydrogen-bond donor catalyst such as **1a** is intriguing. Two limiting mechanisms consisting of S_N1 and S_N2 pathways may be considered (eq 1), but in neither case is the mode of catalyst interaction with



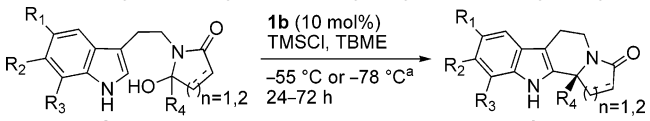
(1)

the enantioselectivity-determining transition state apparent. In efforts to glean insight into this reaction mechanism while broadening the scope of the reaction class in synthetically interesting new directions, we have investigated the acid-catalyzed cyclization of β-indolyl ethyl hydroxylactams (Table 1).[5] We report herein the successful application of thiourea catalysis to the Pictet−Spengler-type cyclization of such compounds, affording highly enantioenriched indolizidinones and quinolizidinones. Key experimental observations, supported by DFT computational analyses, point to an S_N1-type pathway in these cyclizations, with catalysis via a heretofore unprecedented anion-binding mechanism.

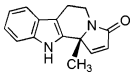
A model reaction (**2a** → **3a**) was examined under a broad set of conditions, with catalyst structure, solvent, additive, temperature, and concentration identified as crucial parameters.[6] As in the case of the acylative *N*-acyl-Pictet−Spengler and *N*-acyl-Mannich reactions,[3] pyrrole-thiourea derivatives of general structure **1** proved optimal, with compounds bearing the 2-methyl-5-phenylpyrrole substituent affording highest ee's. The *N*-methylpentyl amide derivative **1b** was established as the most enantioselective catalyst. A thorough screen of acidic additives revealed that either chlorotrimethylsilane or the combination of HCl and 3 Å molecular sieves afforded high levels of conversion and enantioselectivity, but that water had a deleterious effect on catalyst activity. Finally, a quite significant inverse correlation between conversion and reaction concentration was observed, with reactions run at lower concentrations affording substantially improved yields.

Under the optimal reaction conditions, good-to-excellent yields and enantioselectivities were obtained in the cyclization of hydroxylactams derived from a variety of succinimide and glutarimide precursors (Table 1). Hydroxylactams generated either by imide reduction using $NaBH_4$ or by imide alkylation with organolithium reagents were suitable substrates, with the latter undergoing cyclization under milder conditions (−78 °C, 12 to 48 h), and

Table 1. Asymmetric Cyclization of Hydroxylactams Catalyzed by **1b**

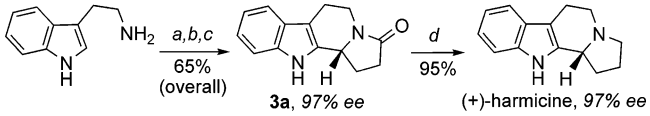


2a–o **3a–o**

entry	product	substituents	yield[b] (%)	ee[c] (%)
		$n = 1$		
1	**3a**	$R_1 = R_2 = R_3 = R_4 = H$	90	97
2	**3b**	$R_1 = OCH_3$, $R_2 = R_3 = R_4 = H$	86	95
3	**3c**	$R_1 = H$, $R_2 = OCH_3$, $R_3 = R_4 = H$	51	90
4	**3d**	$R_1 = Br$, $R_2 = R_3 = R_4 = H$	88	96
5	**3e**	$R_1 = F$, $R_2 = R_3 = R_4 = H$	89	99
6	**3f**	$R_1 = H$, $R_2 = F$, $R_3 = R_4 = H$	94	97
7	**3g**	$R_1 = R_2 = H$, $R_3 = CH_3$, $R_4 = H$	91	93
8	**3h**	$R_1 = R_2 = R_3 = H$, $R_4 = CH_3$	92	96
9	**3i**	$R_1 = R_2 = R_3 = H$, $R_4 = n$-Bu	74	98
10	**3j**	$R_1 = R_2 = R_3 = H$, $R_4 = C_6H_5$	68	85
11	**3k**	$R_1 = OCH_3$, $R_2 = R_3 = H$, $R_4 = CH_3$	84	91
		$n = 2$		
12	**3l**	$R_1 = R_2 = R_3 = R_4 = H$	52	81
13	**3m**	$R_1 = R_2 = R_3 = H$, $R_4 = CH_3$	63	92
14	**3n**	$R_1 = R_2 = R_3 = H$, $R_4 = n$-Bu	65	96
15[d]	**3o**		59	88

[a] Unless noted otherwise, reactions of hydroxylactams generated by $NaBH_4$ reduction were carried out at −55 °C, while those generated by alkylation were run at −78 °C. [b] Isolated yield determined after flash chromatography on SiO_2. [c] Determined by chiral SFC analysis on commercial columns. The absolute configuration of **3d** was established by X-ray crystallographic analysis (see Supporting Information). [d] Reaction run for 72 h at −55 °C with 15 mol % of **1b**.

Scheme 1. Total Synthesis of (+)-Harmicine[a]



3a, *97% ee* (+)-harmicine, *97% ee*

[a] Conditions: (a) succinic anhydride, toluene/AcOH (1:3), 120 °C, 24 h; (b) $NaBH_4$, MeOH, 0 °C; (c) **1b** (10 mol %), TMSCl, TBME, −55 °C, 48 h; (d) $LiAlH_4$, THF, rt, 16 h.

providing products bearing fully substituted stereogenic centers. Hydroxylactam **2o**, accessed via maleimide alkylation, was also useful in this reaction, affording the synthetically versatile α,β-unsaturated adduct **3o** (entry 15).

In a straightforward demonstration of the applicability of this new methodology, we applied the enantioselective hydroxylactam cyclization to the total synthesis of (+)-harmicine (Scheme 1).[7] The cyclization to **3a** proceeded in 97% ee, with subsequent $LiAlH_4$ reduction affording the natural product in only four steps from tryptamine. The synthesis, which employs no protecting groups and generates only H_2O, $B(OH)_3$, and $Al(OH)_3$ as stoichiometric

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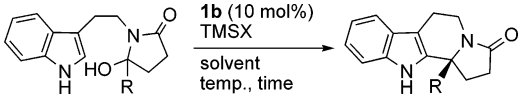
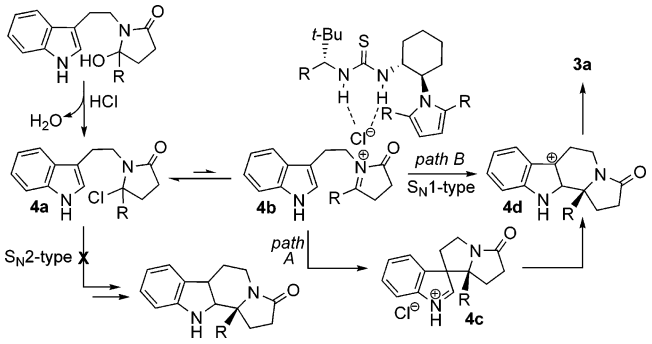
Table 2. Substituent, Counterion, and Solvent Effect Studies



entry	solvent	X	R	temp (°C)	time (h)	conv[a] (%)	ee[b] (%)
1	TBME	Cl	H	−78	8	12	99
2	TBME	Cl	CH_3	−78	8	94	96
3	TBME	Cl	H	−55	23	80	97
4	TBME	Br	H	−55	23	82	68
5	TBME	I	H	−55	23	75	<5
6	TBME	Cl	H	−55	8	65	97
7	THF	Cl	H	−55	8	>95	34
8	CH_2Cl_2	Cl	H	−55	8	>95	<5

[a] Determined by ^{1}H NMR. [b] Determined by chiral SFC analysis on commercial columns.

Scheme 2. Proposed Reaction Mechamism



byproducts,[8] allowed assignment of the absolute configuration of **3a** generated using **1b** as *R*.

Spectroscopic (variable temperature ^{1}H NMR) studies of reaction mixtures generated from hydroxylactam **2a** and TMSCl indicated that formal dehydration and formation of the corresponding chlorolactam[9] is rapid and irreversible.[6] Further, the observation of enhanced reactivity of alkylated versus reduced derivatives (Table 2, entries 1 and 2) suggests that an S_N2-type displacement of chloride is not operative in the cyclization reaction and points rather to an S_N1-type mechanism (eq 1).[1d] Since the enantioselectivity-determining step is likely, either the addition of the indole to the *N*-acyliminium ion (Scheme 2, Path A **4b**→**4c** or Path B **4b**→**4d**) or alkyl migration of the spiroindoline intermediate (Scheme 2, Path A **4c**→**4d**),[1c,10,11] catalyst interaction with at least one of these species is required. However, there is no viable Lewis basic site for *productive* catalyst binding to substrate in either **4b** or **4c**.[12,13]

We propose instead that the thiourea catalyst promotes enantioselective cyclization by inducing dissociation of the chloride counterion and forming a chiral *N*-acyliminium chloride−thiourea complex (Scheme 2). As would be expected within this model, pronounced halide counterion effects (Table 2, entries 3−5)[14] and solvent effects (entries 6−8) on enantioselectivity are observed. Catalysis and enantioinduction may thus result from initial abstraction of a chloride anion from **4a** by **1b** in an S_N1-type rate-determining step (**4a**→**4b**) and subsequent cyclization mediated by the resulting anion-bound thiourea.

Such a mode of catalytic generation of cationic intermediates finds support in the well-established anion-binding properties of ureas and thioureas.[15,16] Further, the possibility of high levels of enantioinduction induced through counterion interactions is well-precedented in chiral phase-transfer catalysis[17] and has recently been demonstrated in the context of asymmetric counterion-directed catalysis.[18] We anticipate that asymmetric catalysis via anion-binding mechanisms may be applicable to a wide variety of valuable transformations involving highly reactive cationic intermediates, and this is a focus of our current effort.

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Supporting Information Available: Complete experimental procedures and characterization data for products and all isolated intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews see: (a) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431−1628. (b) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311−2352. (c) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797−1842. (d) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367−4416.
(2) (a) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327−6328. (b) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 6801−6802. (c) Funabashi, K.; Ratni, H.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 10784−10785.
(3) (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558−10559. (b) Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 6700−6704.
(4) (a) Pan, S. C.; Zhou, J.; List, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 612−615. (b) Pan, S. C.; List, B. *Org. Lett.* **2007**, *9*, 1149−1151.
(5) (a) Hubert, J. C.; Speckamp, W. N.; Huisman, H. O. *Tetrahedron Lett.* **1972**, *13*, 4493−4496. (b) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437−1441.
(6) See Supporting Information for further details.
(7) Kam, T.-S.; Sim, K.-M. *Phytochemistry* **1998**, *47*, 145−147.
(8) For alternative synthetic approaches to harmicine, see: Szawkało, J.; Czarnocki, S. J.; Zawadzka, A.; Wojtasiewicz, K.; Leniewski, A.; Maurin, J. K.; Czarnockia, Z.; Drabowicz, J. *Tetrahedron: Asymmetry* **2007**, *18*, 406−413 and references cited therein.
(9) (a) Bose, A. K.; Spiegelman, G.; Manhas, M. S. *Tetrahedron Lett.* **1971,** 3167. (b) Nortey, S. O.; McComsey, D. F.; Maryanoff, B. E. *Heterocycles* **1993**, *35*, 1075−1088.
(10) (a) Bailey, P. D. *J. Chem. Res.* **1987**, 202−203. (b) Czerwiński, K. M.; Deng, L.; Cook, J. M. *Tetrahedron Lett.* **1992**, *33*, 4721−4724. (c) Bailey, P. D.; Hillinshead, S. P.; McLay, N. R.; Morgan, K.; Palmer, S. J.; Prince, S. N.; Reynolds, C. D.; Wood, S. D. *J. Chem. Soc., Perkin Trans. 1* **1993**, 431−439. (d) Kowalski, P.; Bojarski, A. J.; Mokrosz, J. L. *Tetrahedron* **1995**, *51*, 2737−2742.
(11) No KIE was observed in reactions in which the indole C2 position of **3a** was deuterated, ruling out the possibility of rate-limiting deprotonation/rearomatization step from **4d**.
(12) DFT calculations of fully ionized *N*-acyliminium ions interacting with thiourea derivatives failed to converge on any ground state bound structure. See Supporting Information.
(13) Similar reactivity and slightly diminished enantioselectivities are observed in reactions of urea analogues of catalyst **1** (e.g., 90% ee with **1a**, and 75% ee with the urea analogue) in the cyclization of **3a**. This appears to rule out a direct, productive interaction of the urea thiocarbonyl with the *N*-acyliminium ion.
(14) This effect may be ascribed to several factors, including a trend toward poorer ion pairing, weaker binding to the thiourea, or increased background reactivity with the increase and size and leaving group ability of the halide.
(15) (a) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609−1646. (b) Antonisse, M. M. G.; Reinhoudt, D. N. *Chem. Commun.* **1998**, 443−448. (c) Hisaki, I.; Sasaki, S.-I.; Hirose, K.; Tobe, Y. *Eur. J. Org. Chem.* **2007**, 607−615. (d) Jagessar, R. C.; Shang, M.; Scheidt, W. R.; Burns. D. H. *J. Am. Chem. Soc.* **1998**, *120*, 11684−11692.
(16) Analysis of ^{1}H NMR spectra of equimolar solutions of **1b** and tetrabutylammonium chloride revealed direct evidence for chloride binding to the thiourea. See Supporting Information.
(17) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013−3028 and references therein.
(18) (a) Mayer, S.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193−4195. (b) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496−499.

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