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Regio- and Enantioselective Catalytic Cyclization of Pyrroles onto *N*-Acyliminium Ions

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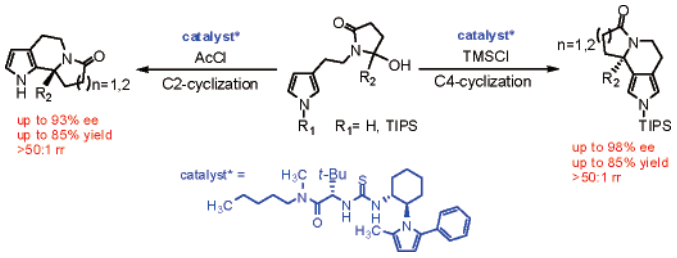
ABSTRACT



The regio- and enantioselective cyclization of pyrroles onto *N*-acyliminium ions generated in situ from hydroxylactams is reported. Modest to excellent ee's and yields are obtained in these novel Pictet–Spengler-type reactions with a chiral thiourea-pyrrole catalyst. Useful synthetic transformations of the versatile pyrroloindolizidinone and pyrroloquinolizidinone products are presented.

Our group has recently developed thiourea-catalyzed *N*-acyl-Pictet−Spengler-type reactions involving intramolecular addition of indoles onto in situ-generated *N*-acyliminium ions, affording enantioenriched tetrahydro-β-carboline frameworks (Figure 1).[1,2] These methodologies incorporate either acylative or dehydrative approaches to *N*-acyliminium ion generation. To date, only indole frameworks have been utilized as the reactive aromatic nucleophile. In an effort to broaden the scope of this reaction class, we sought to identify other viable β-aryl ethyl substrates that may provide access to novel, alkaloid-like skeletal frameworks. Herein, we report the discovery that pyrrole nucleophiles engage successfully in hydroxylactam-based *N*-acyl-Pictet−Spengler methodology and that high levels of enantio- and regioselectivity are attainable in these reactions.

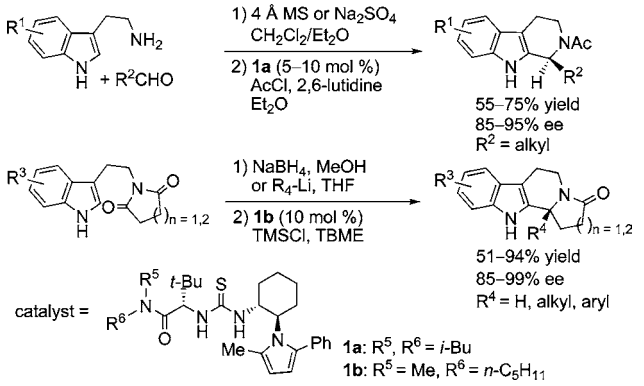


Figure 1. Catalytic asymmetric acylative and dehydrative *N*-acyl-Pictet−Spengler reactions of indole derivatives.

Our preliminary investigations focused on extending the β-indole ethyl hydroxylactam cyclization methodology to other aromatic substrates. Our initial survey identified pyrrole as a promising lead (Figure 2). However, no significant

(1) (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558−10559. (b) Raheem, I.; Thiara, P.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404−13405.

(2) For other approaches to asymmetric catalysis of the Pictet−Spengler reaction, see: (a) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086−1087. (b) Wanner, M. J.; van der Haas, R. N. S.; de Cuba, K. R.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7485−7487.

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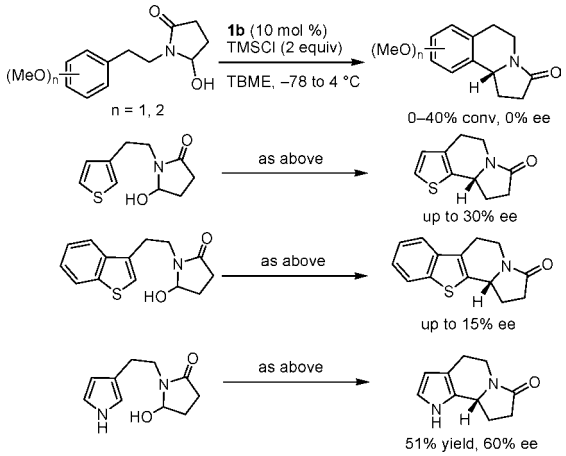


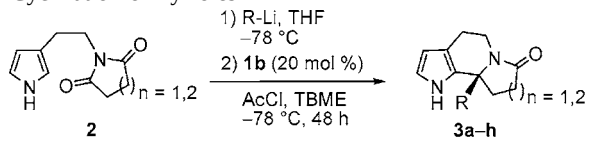
Figure 2. Preliminary screen of aromatic cyclization candidates.

improvements in enantioselectivity were achieved after exhaustive optimization of catalyst structure and reaction conditions, including examination of solvent, temperature, acidic additive, and reaction concentration. Ultimately, the best results were obtained under conditions nearly identical to those identified for indole cyclization.[1b]

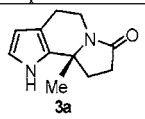
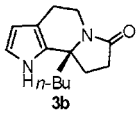
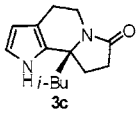
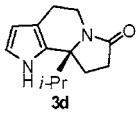
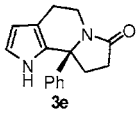
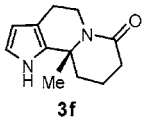
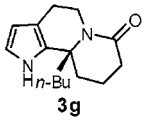
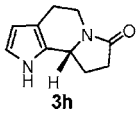
Significant rate accelerations due to increased substitution at the reactive electrophilic center were seen in the asymmetric dehydrative *N*-acyl Pictet−Spengler cyclization of indole substrates,[1b] consistent with an S_N1-type mechanism. We reasoned that improved reactivity might also result in the pyrrole cyclization chemistry. Indeed, higher levels of substrate conversion were obtained in pyrrole cyclization reactions using hydroxylactam substrates prepared by imide alkylation. In addition, an unexpected improvement in enantioselectivity was also observed. Reinvestigation of the experimental parameters resulted in identification of the optimal reaction conditions outlined in Table 1. Hydroxylactams prepared by alkylation of β-pyrrolo-ethylsuccinimide afforded cyclization products in good-to-excellent yields and high enantioselectivies (Table 1, entries 1−4). However, only modest ee's were obtained in the cyclization of glutarimide-derived substrates (Table 1 entries 6−7), a limitation that is observed to a lesser extent in the indole cyclizations.[1b] The reductively prepared hydroxylactam (Table 1, entry 8) afforded the cyclization product with only moderate (65%) ee under these conditions.

Despite the structural and electronic similarities between pyrroles and indoles, well-known reactivity differences exist with respect to *inter*molecular electrophilic aromatic substitution reactions. While the C3 position of indole is generally the most nucleophilic site, pyrroles undergo kinetic substitution selectively at the C2 (or C5) position.[4] However, strategies have been devised to direct electrophilic substitution to the C3 (or C4) position, including pre-functionalization of the C2 position with a labile, deactivating substituent,[5] product isomerization from the C2 position to the C3 position,[6] and protection of the pyrrole with an *N*-(phenylsulfonyl) group.[7] However, the most commonly used approach employs a sterically demanding protecting group, in particular the bulky triisoproylsilyl (TIPS) group, on the pyrrole nitrogen, effectively shielding the N1, C2, and C5 postions.[4]

Table 1. Representative Substrate Scope for Regioselective C2-Cyclization of Pyrroles[a]



2 3a–h

entry	product	yield (%)[b]	ee (%)[c]
1	 **3a**	77	90
2	 **3b**	84	91
3	 **3c**	57	88
4	 **3d**	86	93
5	 **3e**	51	60
6	 **3f**	64	52
7	 **3g**	54	61
8[d]	 **3h**	71	65

[a] Absolute configuration assigned by analogy (see ref 3). [b] Isolated yield after flash chromatography on SiO_2. [c] Determined by chiral SFC using commercial chiral columns. [d] Corresponding hydroxylactam was prepared by imide reduction. See Supporting Information.

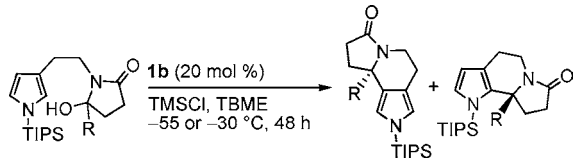
(3) Attempts to determine absolute configuration by X-ray crystallographic analysis of heavy-atom derivatives (e.g., **6**, **8**, or **9**) were unsuccessful. The absolute configuration was assigned as *R* by analogy to the face selectivity oserved in both the indole cyclizations (ref 1b) and the regioisomeric pyrrole C4 cyclizations (vide infra).

(4) (a) Bray, B.; Mathies, P.; Naef, R.; Solas, D.; Tidwell, T.; Artis, D.; Muchowski, J. *J. Org. Chem.* **1990**, *55*, 6317, and references therein. (b) Gilchrist, T. *Heterocyclic Chemistry*, 3rd ed; Addison Wesley Longman, Ltd.: Harlow, 1997; pp 193 and 231, and references therein. (c) Rücker, C. *Chem. Rev.* **1995**, *95*, 1009.

(5) Loader, C.; Anderson, H. *Can. J. Chem.* **1981**, *59*, 2673.

(6) DeSales, J.; Greenhouse, R.; Muchowski, J. *J. Org. Chem.* **1982**, *47*, 3668.

Table 2. Regioselectivities in Catalyzed and Uncatalyzed Cyclizations of *N*-TIPS-Protected Pyrrole Substrates



entry	R	catalyst **1b** (mol %)	conversion (%)[a]	regioisomeric ratio (C4:C2)[a]
1	H	0	60	1:4.4
2	H	20	>95	1.7:1
3	CH_3	0	40	3:1
4	CH_3	20	>95	>50:1

[a] Determined by ^{1}H NMR analysis of unpurified reaction mixtures.

We sought to take advantage of the versatile reactivity of the pyrrole moiety in the context of the asymmetric Pictet–Spengler-type cyclization chemistry, hoping to utilize the aforementioned steric directing properties imparted by large protecting groups on the pyrrole nitrogen to influence the regioselectivity. Whereas *N*-TIPS-protected pyrrolohydroxylactams prepared by reduction underwent cyclization with only moderate regioselectivity under both catalzyed and uncatalyzed conditions (Table 2, entries 1−2), substrates prepared by alkylation provided the regioisomer of C4 cyclization exclusively in the presence of **1b** (entry 4). In the absence of catalyst, much lower regioisomeric ratios were observed (entry 3), highlighting the dual role of catalyst in imparting both enantioselectivity and regiocontrol.

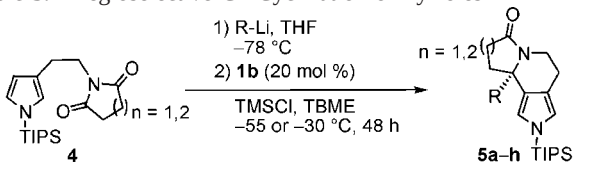
Under slightly modified optimal reaction conditions, a variety of products bearing fully substituted stereogenic centers were accessed in good yields and excellent ee's (Table 3, entries 1−7), employing both succinimide and glutarimide-derived hydroxylactams. As in the C2-selective cyclizations, substrates prepared by imide alkylation provided highest enantioselectivities, whereas those prepared by reduction underwent cyclization with only modest ee (Table 3, entry 8).

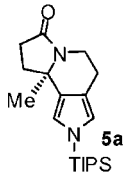
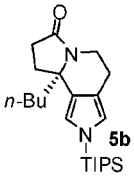
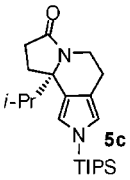
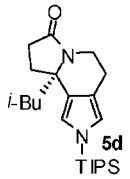
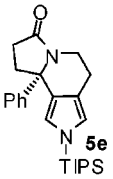
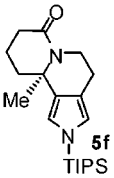
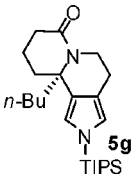
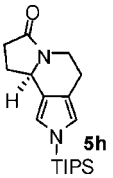
The products of the cyclization reactions are synthetically versatile chiral intermediates thanks to the numerous strategies available for elaboration of the pyrrole nucleus (Schemes 1 and 2). The products of C2-cylization (**3**) can be induced to undergo monobromination regioselectively at either the C2 or C3 position (**3** → **6** or **3** → **7** → **8**), as well as dibromination (**3** → **9**), by judicious choice of brominating reagent and reaction conditions. The resulting halogenated pyrroles are versatile intermediates for further transformations, including selective lithiation and cross-coupling reactions.[4,8] Other potentially useful synthetic transformations include reduction (**3** → **10**), diastereoselective alkylation (**3** → **11**), and Ciamician-Dennstedt-type rearrangement[9] to the

(7) Anderson, H.; Loader, C.; Xu, R.; Le, N.; Gogan, N.; McDonald, R.; Edwards, L. *Can. J. Chem.* **1985**, *63*, 896.

(8) For a review see: Banwell, M.; Goodwin, T.; Ng, S.; Smith, J.; Wong, D. *Eur. J. Org. Chem.* **2006**, 3043.

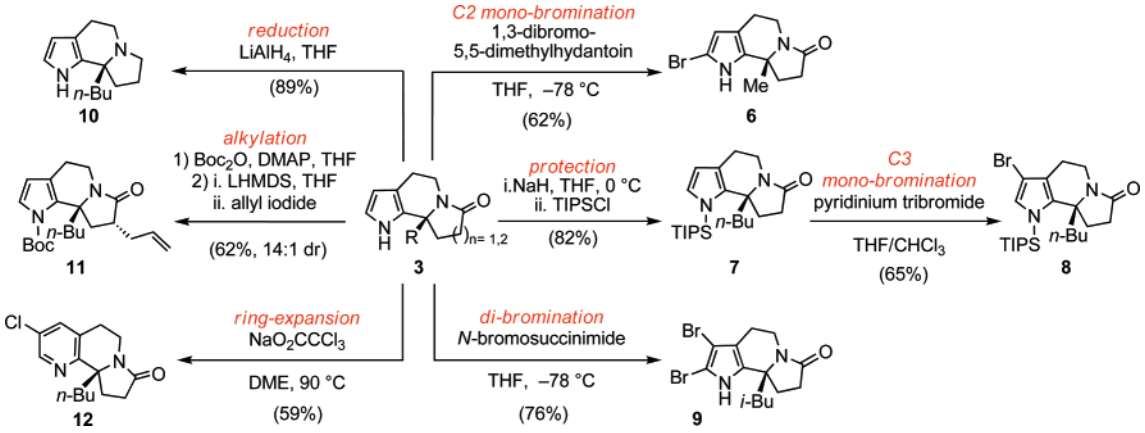
Table 3. Regioselective C4-Cyclization of Pyrroles[a]



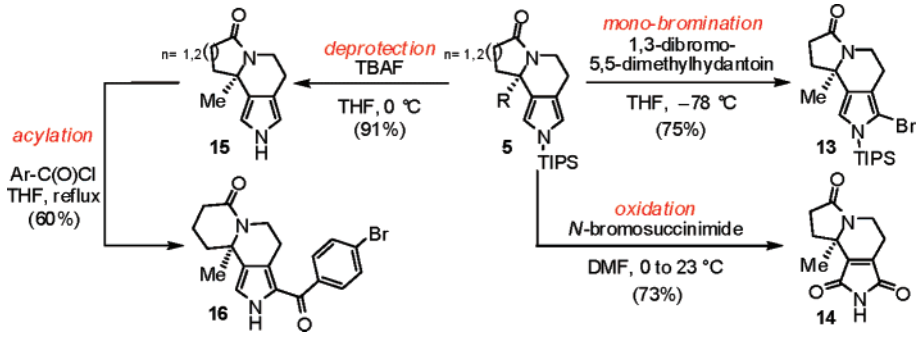
entry	product[b]	yield (%)[c]	ee (%)[d]
1	 **5a**	77	92
2	 **5b**	69	96
3	 **5c**	49	93
4	 **5d**	68	96
5	 **5e**	63	92
6	 **5f**	75	93
7	 **5g**	70	97
8[e]	 **5h**	76	70[f]

[a] Absolute configuration determined by X-ray crystallographic analysis of **16** (see Scheme 2). See Supporting Information. [b] In each case except entry 8, the product indicated was the only regioisomer detected. [c] Isolated yield after flash chromatography on SiO_2. [d] Determined by SFC analysis using commercial chiral columns. [e] Corresponding hydroxylactam was prepared by imide reduction. [f] Product was formed as a 1.7:1 mixture of regioisomers, favoring C4-cyclization.

Scheme 1. Synthetic Transformations of C2-Cyclization Products



Scheme 2. Synthetic Transformations of C4-Cyclization Products



enantioenriched tetrahydronaphthyridine framework (**3** → **12**). The products of C4 cyclization (**5**) are equally versatile, being amenable to selective mono-bromination (**5** → **13**), direct acylation (**5** → **15** → **16**) and oxidation to the corresponding maleimide (**5** → **14**). To the best of our knowledge, the latter mild oxidation protocol is heretofore unknown. Unfortunately, selective bromination of the C5 position in these products was not realized.

Thiourea-catalyzed reactions of *N*-acyliminium ions have thus been extended to the regio- and enantioselective cyclization of pyrrolohydroxylactams. The observation of enhanced reactivity and enantioselectivity with alkylatively prepared hydroxylactams suggest an S_N1-type mechanism of cyclization, and lend further support to a mechanism of catalysis and enantioinduction involving anion binding by the thiourea catalyst. We are currently exploring other synthetically valuable transformations involving cationic intermediates that may be amenable to asymmetric catalysis.

Acknowledgment. This work was supported by the NIGMS (P50 GM-69721). I.T.R. gratefully acknowledges the ACS, Pfizer, Inc., and the Bristol-Myers Squibb Co. for fellowship support.

Supporting Information Available: Complete experimental procedures and full spectroscopic and X-ray crystallographic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Dhanak, D.; Reese, C.; *J. Chem. Soc., Perkin Trans. 1* **1987**, 2829.