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Enantioselective Aza-Sakurai Cyclizations: Dual Role of Thiourea as H-Bond Donor and Lewis Base

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Supporting Information

ABSTRACT: An enantioselective, catalytic aza-Sakurai cyclization of chlorolactams has been developed as an efficient entry into indolizidine and quinolizidine frameworks. Structure–enantioselectivity relationship studies and mechanistic analysis point to a dual role of the catalyst wherein the thiourea moiety of the catalyst is engaged in both anion binding and Lewis base activation of a substrate.

Indolizidines and quinolizidines are common *N*-heterocyclic motifs present in biologically active molecules, and the development of efficient methods for their synthesis has accordingly attracted considerable attention from synthetic chemists.[1,2] The aza-Sakurai cyclization, which involves the intramolecular reaction of an iminium ion with an allylsilane, represents a powerful method for constructing these heterocycles,[3] and diastereoselective variants of this transformation have enabled the efficient synthesis of naturally occurring alkaloids in this and related classes (Figure 1).[4,5] Recently,

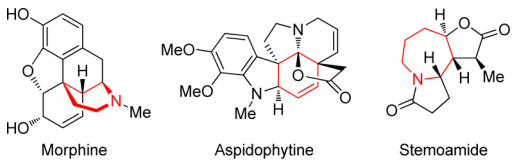


Figure 1. Examples of natural products synthesized previously using the aza-Sakurai cyclization.[4b,c,e]

asymmetric anion-binding catalysis has been utilized successfully to effect enantioselective additions to *N*-acyliminium ions[6] with a variety of nucleophiles, such as silyl ketene acetals, indoles, and polyenes.[7,8] Drawing from the precedents, we envisioned that the thiourea-assisted ionization of chlorolactam **1-Cl** would generate a chiral ion pair that might undergo an enantioselective aza-Sakurai cyclization, thereby providing an efficient route to bicyclic lactam **2** (Scheme 1).[9,10] We report here the successful development of this reactivity principle, together with the unexpected revelation of a new mode of substrate activation involving a dual role for the thiourea catalysts as H-bond donors and Lewis bases.

Our initial studies focused on model substrate **1-OH**, which contains a hydroxylactam as a latent *N*-acyliminium precursor and a pendant allyltrimethylsilane as a potential nucleophile (Table 1).[11] With generation of chlorolactam **1-Cl** accomplished in situ with TMSCl, a promising lead result was

Scheme 1. Initial Reaction Design

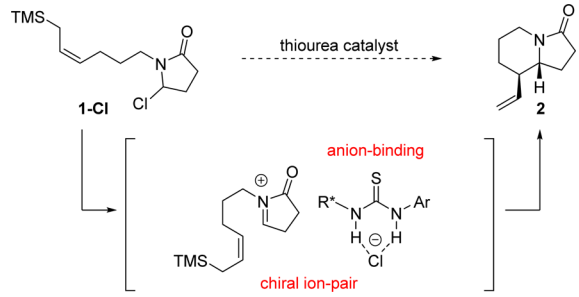
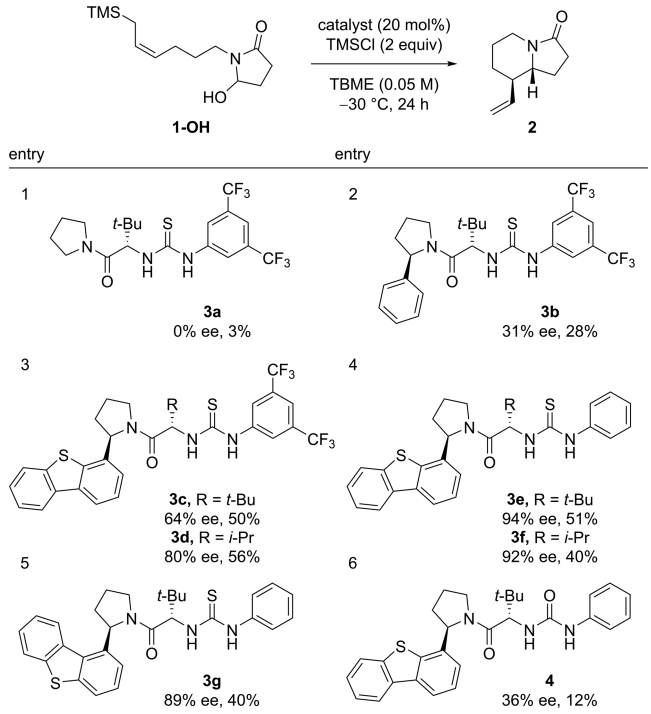


Table 1. Catalyst Optimization[a]



[a]Reactions run on a 0.05 mmol scale. Enantiomeric excess determined by GC analysis on commercial chiral columns. Yields determined by GC analysis relative to dodecane as an internal standard.

obtained with phenylpyrrolidinoamido thiourea catalyst **3b** (Table 1, entry 2). As has been observed in a wide variety of

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other transformations involving anion-abstraction catalysis, the arylpyrrolidino unit proved to be an important handle for catalyst optimization, and the dibenzothiophene derivative **3c** was identified to possess the optimal arene component (**3c**, Table 1, entry 3).[12] A significant improvement in enantioselectivity was obtained with phenylthiourea **3e**, which is a significantly weaker H-bond donor than the bis(trifluoromethyl) analog **3c**.[13] This observation was highly unexpected, as bis(trifluoromethyl) anilide-derived thioureas are generally observed to display superior reactivity and enantioselectivity in anion-binding reactions.[14] The excellent performance of valine-derived catalysts **3d** and **3f** relative to *tert*-leucine-derived analogs **3c** and **3e** is also highly atypical in asymmetric catalysis with this family of catalysts. Taken together, these results suggested that the Lewis basicity of the thiourea moiety was critical to catalyst performance in the model aza-Sakurai reaction. The marked difference in reactivity and enantioselectivity between thiourea **3e** and urea **4** (Table 1, entry 6) also supported this hypothesis.

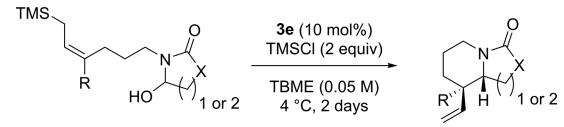
The scope of the cyclization reaction was investigated with optimal catalyst **3e** (Table 2). Carbamate-derivative **5** underwent cyclization with similar enantioselectivity to the structurally analogous lactam **6** (Table 2, entry 2). From hydantoin-derived **7**, the cyclization was achieved at a sterically hindered carbon adjacent to a quaternary center in good yield and enantioselectivity (Table 2, entry 3). The reaction scope was extended to access 6,6-fused bicyclic systems (Table 2, entries 4–6). Substrates derived from glutarimide **9** and dihydrouracils bearing different *N*-substituents (**11**, **13**) afforded the corresponding bicycles (**10**, **12**, **14**) in excellent yield and enantioselectivity. Use of the trisubstituted allylsilane **15** allowed enantioselective construction of a quaternary stereocenter (Table 2, entry 7). In this instance, thiourea **3g** afforded improved enantioselectivity relative to **3e** (88 vs 75% ee).

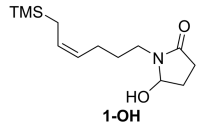
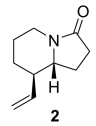
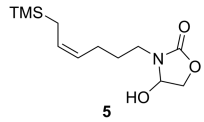
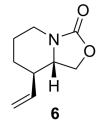
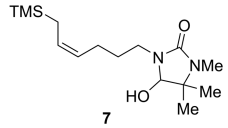
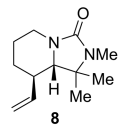
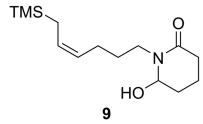
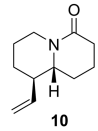
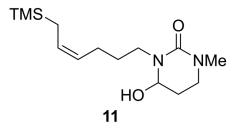
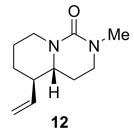
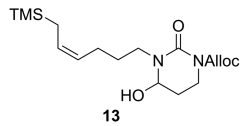
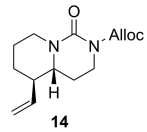
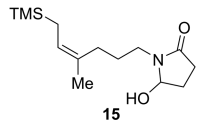
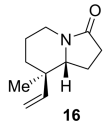
The absolute stereochemistry of the products was assigned through the synthesis of two alkaloid natural products (Scheme 2). Lemieux–Johnson oxidation[15] of *ent*-**2**,[16] followed by a global reduction gave (−)-tashiromine in 90% yield over two steps.[17] The same two-step sequence from **10** afforded (+)-*epi*-lupinine in 72% yield.[18]

As noted above, the catalyst structure–enantioselectivity relationships observed during the catalyst optimization studies point to a critical role for the nucleophilicity of the thiourea sulfur in enantioinduction. Following Denmark's report that sulfur-based Lewis bases such as tetramethylthiourea can serve as efficient halocyclization catalysts,[19] various thiourea derivatives have been developed as chiral Lewis-base catalysts to achieve enantioselective reactions such as halofunctionalizations.[20,21] We considered whether the combination of thiourea Lewis basicity with its well-established H-bond donor properties might underlie a dual mechanistic function of the catalyst in the aza-Sakurai cyclizaton. Combining the inherent Lewis basicity of chiral thioureas with their anion-binding ability could enable the use of relatively weak nucleophile species in the reactions with chiral electrophilic ion pairs.

The importance of the putative Lewis acid–base interaction was evaluated by studying the aza-Sakurai reaction of a series of substrates containing differently substituted silyl groups (Table 3). In experiments with thiourea **3e**, substrates containing more electron-rich allylsilane were consumed more slowly despite being more inherently nucleophilic (k_{rel}: **18** > **1** > **17**).[22] With urea **4**, however, faster rates were observed with intrinsically more nucleophilic substrates (k_{rel}: **17** > **1** > **18**). The reversal of the relative reactivity due to *S* vs *O* substitution in the catalyst

Table 2. Substrate Scope[a]



entry	substrate	product	yield[b]	ee[c]
1	 **1-OH**	 **2**	85	91
2[d]	 **5**	 **6**	72	90
3[e]	 **7**	 **8**	82	94
4[d,f]	 **9**	 **10**	90	90
5[g]	 **11**	 **12**	93	94
6[g]	 **13**	 **14**	83	92
7[h]	 **15**	 **16**	85	88

[a]Reactions run on a 0.2 mmol scale. [b]Isolated yields. [c]Enantiomeric excess determined by GC or HPLC analysis on commercial chiral columns. [d]Reaction run using 20 mol % thiourea catalyst. [e]Reaction run for 3 days. [f]Reaction run for 1 day. [g]Reactions run at −30 °C. [h]Catalyst **3g** used instead of **3e**.

Scheme 2. Total Synthesis of (−)-Tashiromine and (+)-*epi*-Lupinine

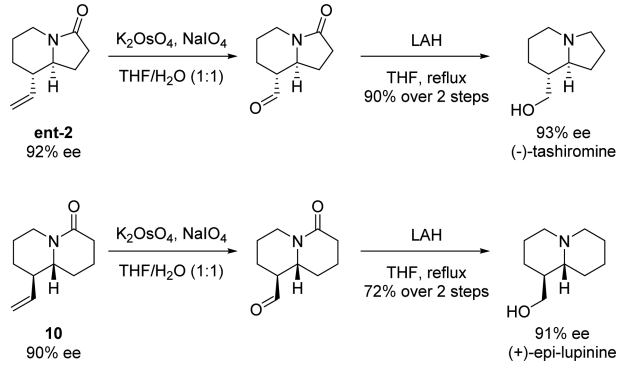


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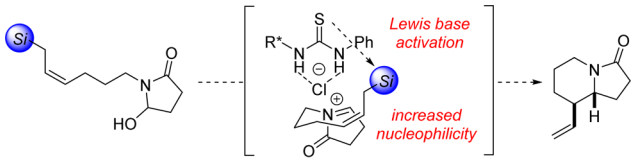
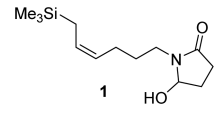
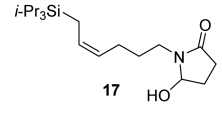
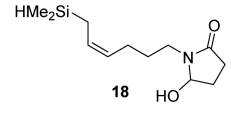
Table 3. Effect of Silicon Lewis Acidity on Reaction Rate[a]



Relative rates of consumption

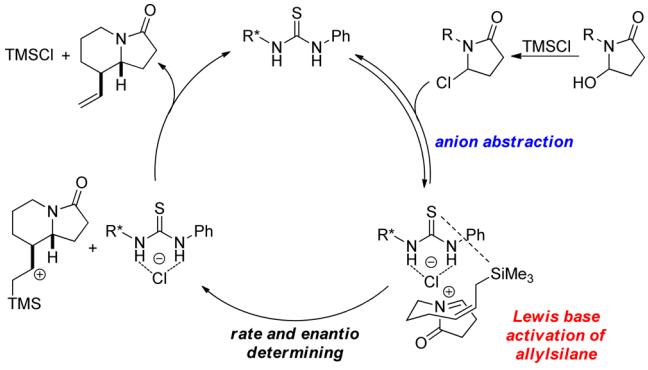
entry	substrate	thiourea (**3e**)	urea (**4**)
1		1 (defined) 92% ee	0.13 28% ee
2		0.14 33% ee	0.27 41% ee
3		1.79 89% ee	0.09 26% ee

[a]Relative rates were assigned by comparing the initial rates of each system. See the Supporting Information for details.

lends definitive support to the proposal of nucleophilic activation of allylsilane by the thiourea moiety in **3e**.[23]

Based upon these observations, the catalytic cycle outlined in Scheme 3 is proposed. Ionization of chlorolactam is induced by

Scheme 3. Proposed Catalytic Cycle



the thiourea catalyst to generate an *N*-acyliminium thiourea-bound chloride ion pair. The Lewis basicity of the thiourea should be enhanced by the anion binding, and this charged moiety is proposed to activate the allylsilane in the cyclization event. Elimination of the β-silyl cation from the resulting cyclic intermediate would generate the lactam product.

In summary, we have developed a catalytic enantioselective aza-Sakurai cyclization with *N*-acyliminium ions as a route to various indolizidine, quinolizidine, and related bicyclic frameworks. The catalyst structure−enantioselectivity relationship and substrate studies point toward a previously unrecognized mechanism for thiourea catalysis in which the thiourea is not only involved in the generation of the reactive cationic electrophile through anion abstraction but also engaged in the Lewis base activation of the allylsilane nucleophile. We anticipate this dual activation strategy will be valuable in other transformations involving relatively weak nucleophiles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b09736.

Complete experimental procedures and characterization data for products and all isolated intermediates (PDF)

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Notes

The authors declare no competing financial interest.

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(21) For reviews on catalytic, asymmetric halofunctionalization, see: (a) Denmark, S. E.; Kuester, W. E.; Burk, M. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10938. (b) Cheng, Y. A.; Yu, W. Z.; Yeung, Y.-Y. *Org. Biomol. Chem.* **2014**, *12*, 2333.
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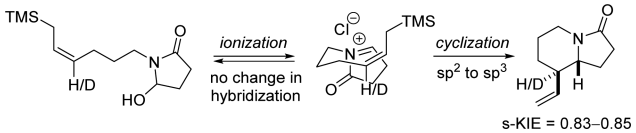
(23) The sizable inverse secondary KIE (0.83−0.85) measured in the system shown below is consistent with rate-limiting cyclization. See the Supporting Information for details.



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