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

Yongho Park, Corinna S. Schindler[†], and Eric N. Jacobsen^{*}

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138, United States

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.

Graphical Abstract

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, asymmetric anion-binding catalysis has been utilized successfully to effect enantioselective additions to *N*-acyliminium ions⁶ 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

Corresponding Author: jacobsen@chemistry.harvard.edu.

[†]Current Addresses: Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109, United States

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Supporting Information

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>.

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 obtained with phenylpyrrolidinoamido thiourea catalyst **3b** (Table 1, entry 2). As has been observed in a wide variety of 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 **2** (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 oxidation¹⁵ 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 cyclization. Combining the inherent Lewis basicity of chiral thioureas with their anion-binding ability could enable the use of relatively weak nucleophiles 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 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 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 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. For a review, see: Michael JP. Nat Prod Rep. 2008; 25:139. [PubMed: 18250900]
2. For examples of recent efforts directed toward the synthesis of Indolizidines and quinolizidine motifs, see: Miasiewicz S, Gaillard B, Kern N, Weibel JM, Pale P, Blanc A. Angew Chem Int Ed. 2016; 55:9088. Day J, McKeever-Abbas B, Dowden J. Angew Chem Int Ed. 2016; 55:5809. Kalaitzakis D, Triantafyllakis M, Sofiadis M, Noutsias D, Vassilikogiannakis G. Angew Chem Int Ed. 2016; 55:4605. Yang ZP, Wu QF, Shao W, You SL. J Am Chem Soc. 2015;137, 15899. Donets PA, Cramer N. Angew Chem Int Ed. 2015; 54:633. Koley D, Krishna Y, Srinivas K,

- Khan AA, Kant R. *Angew Chem Int Ed.* 2014; 53:13196. Ortega N, Tang DTD, Urban S, Zhao D, Glorius F. *Angew Chem Int Ed.* 2013; 52:9500. Xu X, Zavalij PY, Doyle MP. *J Am Chem Soc.* 2013; 135:12439. [PubMed: 23889041] Brimiouille R, Bach T. *Science.* 2013; 342:840. [PubMed: 24233720] Pronin SV, Tabor MG, Jansen DJ, Shenvi RA. *J Am Chem Soc.* 2012; 134, 2012. [PubMed: 22148883] Wong H, Garnier-Amblard EC, Liebeskind LS. *J Am Chem Soc.* 2011; 133:7517. [PubMed: 21513336] Seki H, Georg GI. *J Am Chem Soc.* 2010; 132:15512. [PubMed: 20958040] Yang D, Micalizio GC. *J Am Chem Soc.* 2009; 131:17548. [PubMed: 19950989] Dalton DM, Oberg KM, Yu RT, Lee EE, Perreault S, Oinen ME, Pease ML, Malik G, Rovis T. *J Am Chem Soc.* 2009; 131:15717. [PubMed: 19817441]
3. For pioneering work, see Overman LE, Malone TC, Meier GP. *J Am Chem Soc.* 1983; 105:6993. Overman LE, Bell KL, Ito F. *J Am Chem Soc.* 1984; 106:4192. Overman LE, Goldstein SW. *J Am Chem Soc.* 1984; 106:5360. Overman LE, Robichaud AJ. *J Am Chem Soc.* 1989; 111:300.
 4. Selected total syntheses using the aza-Sakurai cyclization: Grieco PA, Fobare WF. *J Chem Soc, Chem Commun.* 1987:185. Hong CY, Kado N, Overman LE. *J Am Chem Soc.* 1993; 115:11028. He F, Bo Y, Altom JD, Corey EJ. *J Am Chem Soc.* 1999; 121:6771. Sun P, Sun C, Weinreb SM. *Org Lett.* 2001; 3:3507. [PubMed: 11678694] Wang Y, Zhu L, Hong R. *Angew Chem Int Ed.* 2011; 50:2787. Yang D, Micalizio GC. *J Am Chem Soc.* 2012; 134:15237. [PubMed: 22957796] Nocket AJ, Weinreb SM. *Angew Chem Int Ed.* 2014; 53:14162. Liu H, Yu J, Li X, Yan R, Xiao JC, Hong R. *Org Lett.* 2015; 17:4444. [PubMed: 26332648]
 5. For reviews on the use of allylsilanes in allylation of carbonyl compounds, see: Yus M, González-Gómez JC, Foubelo F. *Chem Rev.* 2011; 111:7774. [PubMed: 21923136] Chabaud L, James P, Landais Y. *Eur J Org Chem.* 2004:3173. Langkopf E, Schinzer D. *Chem Rev.* 1995; 95:1375. Masse CE, Panek JS. *Chem Rev.* 1995; 95:1293–1316.
 6. For reviews on reactions involving N-acyliminium intermediates, see: Maryanoff BE, Zhang HC, Cohen JH, Turchi II, Maryanoff CA. *Chem Rev.* 2004; 104:1431. [PubMed: 15008627] Royer J, Bonin M, Micouin L. *Chem Rev.* 2004; 104:2311. [PubMed: 15137793] Speckamp WN, Moolenaar MJ. *Tetrahedron.* 2000; 56:3817.
 7. (a) Taylor MS, Jacobsen EN. *J Am Chem Soc.* 2004; 126:10558. [PubMed: 15327311] (b) Taylor MS, Jacobsen EN. *Angew Chem Int Ed.* 2005; 44:6700. (c) Raheem IT, Thiara PV, Peterson EA, Jacobsen EN. *J Am Chem Soc.* 2007; 129:13404. [PubMed: 17941641] (d) Knowles RR, Lin S, Jacobsen EN. *J Am Chem Soc.* 2010; 132:5030. [PubMed: 20369901]
 8. For a review, see: Brak K, Jacobsen EN. *Angew Chem Int Ed.* 2013; 52:534.
 9. Hiemstra H, Sno MHAM, Vijn RJ, Speckamp WN. *J Org Chem.* 1985; 50:4014.
 10. For a review on organocatalytic cyclizations, see: Moyano A, Rios R. *Chem Rev.* 2011; 111:4703. [PubMed: 21615119]
 11. No reactions were observed with analogs of **1** bearing unactivated alkenes.
 12. See the Supporting Information for details. For illustrative examples of the importance of arylpyrrolidinoamido components in thiourea-based chiral catalysts, see ref. 7d, 14b, and Brown AR, Uyeda C, Brotherton CA, Jacobsen EN. *J Am Chem Soc.* 2013; 135:6747. [PubMed: 23597402] Bergonzini G, Schindler CS, Wallentin CJ, Jacobsen EN, Stephenson CRJ. *Chem Sci.* 2014; 5:112.
 13. Jakab G, Tancon C, Zhang Z, Lippert KM, Schreiner PR. *Org Lett.* 2012; 14:1724. [PubMed: 22435999]
 14. (a) Zhang H, Lin S, Jacobsen EN. *J Am Chem Soc.* 2014; 136:16485. [PubMed: 25380129] (b) Yeung CS, Ziegler RE, Porco JA Jr. *J Am Chem Soc.* 2014; 136:13614. [PubMed: 25213353] (c) Lin S, Jacobsen EN. *Nature Chem.* 2012; 4:817. [PubMed: 23000995]
 15. Poppo R, Allen DS Jr, Lemieux RU, Johnson WS. *J Org Chem.* 1956; 21:478.
 16. Ent-**2** was obtained using ent-**3e**.
 17. Cutter AC, Miller IR, Kelly JF, Bellingham RK, Light ME, Brown RCD. *Org Lett.* 2011; 13:3988. [PubMed: 21744783]
 18. The absolute stereochemistry of ent-**2** and **6** was assigned by comparing the optical rotation of synthetic tashiromine and epi-lupinine to their values in the literature. The stereochemistry of all other products was assigned by analogy.

19. Denmark SE, Burk MT. *Proc Natl Acad Sci.* 2010; 107:20655. [PubMed: 20705900]
20. For selected examples of using thiourea as a chiral Lewis base: Zhou L, Tan CK, Jiang X, Chen F, Yeung YY. *J Am Chem Soc.* 2010; 132:15474. [PubMed: 20945837] Zhou L, Chen J, Tan CK, Yeung YY. *J Am Chem Soc.* 2011; 133:9164. [PubMed: 21539367] Jiang X, Tan CK, Zhou L, Yeung YY. *Angew Chem Int Ed.* 2012; 51:7771. Zhao Y, Jiang X, Yeung YY. *Angew Chem Int Ed.* 2013; 52:8597.
21. For a recent review on catalytic, asymmetric halofunctionlization, see: Denmark SE, Kuester WE, Burk MT. *Angew Chem Int Ed.* 2012; 51:10938. Cheng YA, Yu WZ, Yeung YY. *Org Biol Chem.* 2014; 12:2333.
22. (a) Mayr H, Hagen G. *J Chem Soc, Chem Commun.* 1989:91–92. (b) Hagen G, Mayr H. *J Am Chem Soc.* 1991; 113:4954.
23. The sizeable 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.

Figure 1.
Examples of natural products synthesized previously using the aza-Sakai cyclization.^{4b,c,e}

Scheme 1.
Initial Reaction Design

Scheme 2.

Total synthesis of (-)-tashiromine and (+)-epi-lupinine

Table 1

Catalyst Optimization^a

^aReactions run on a 0.05 mmol scale. Enantiomeric excess determined by GC or HPLC analysis on commercial chiral columns. Yields determined by GC analysis relative to dodecane as an internal standard.

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

entry	substrate	product	yield ^b	ee ^c
6 ^g	 13	 14	83	92
7 ^h	 15	 16	85	88

^aReactions run on a 0.2 mmol scale.

^bIsolated yields.

^cEnantiomeric excess determined by GC or HPLC analysis on commercial chiral columns.

^dReaction run using 20 mol% thiourea catalyst.

^eReaction run for 3 days.

^fReaction run for 1 day.

^gReactions run at −30 °C.

^hCatalyst **3g** used instead of **3e**.

Table 3Effect of silicon Lewis acidity on reaction rate^a

Relative rates of consumption

entry	substrate	thiourea (3e)	urea (4)
1	1	1 (defined) 92% ee	0.13 28% ee
2	17	0.14 33% ee	0.27 41% ee
3	18	1.79 89% ee	0.09 26% ee

^aRelative rates were assigned by comparing the initial rates of each system. See the Supporting Information for details.