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Enantioselective Thiourea-Catalyzed Additions to Oxocarbenium Ions

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Small-molecule chiral hydrogen-bond donors have emerged as important organocatalysts for the activation of Lewis basic electrophiles—such as imines, nitroolefins, and carbonyl compounds—toward nucleophilic addition.[1] In this context, we recently discovered that pyrrole-bearing thiourea derivatives (e.g., **1**) catalyze highly enantioselective *N*-acyl-Pictet−Spengler and Mannich-type reactions to provide products in high ee's.[2] Reactivity patterns in these additions were found to be consistent with an S_N1 pathway, and we proposed a mechanism involving thiourea-assisted chloride dissociation from a transient α-chloroamide (**2**) to generate a reactive *N*-acyliminium chloride−thiourea complex **1**•Cl^-•**3** (Scheme 1).[2c] The ability to engage highly reactive cationic species in this manner presents exciting new possibilities for asymmetric catalysis. Herein we report the successful application of this mode of activation to catalyst-controlled enantioselective additions to oxocarbenium ions.

The reactions of oxocarbenium ions play an important role in the synthesis of complex natural products and in the chemistry of carbohydrates in particular. Numerous methods for Lewis acid mediated *substrate*-controlled diastereoselective additions to substituted oxocarbenium ions have been identified.[3,4] On the other hand, enantioselective addition reactions to prochiral oxocarbenium ions are almost completely undeveloped.[5,6] A catalyst system capable of inducing stereocontrol in nucleophilic additions to cyclic oxocarbenium ions would be of considerable significance. With the goal of applying the principle of H-bond donor catalysis by anion binding to transformations involving oxocarbenium ions, we targeted the addition of carbon-centered nucleophiles to cyclic glycosyl donors.[7] Whereas α-chloroamides (e.g., **2**) are generally unstable, glycosyl chlorides (e.g., **4**) are often isolable and more easily manipulated. Under the thiourea-catalyzed reaction conditions, use of glycosyl chlorides would allow direct access to putative intermediate ion pair **5**.

For exploratory studies, 1-chloroisochroman **7** was selected as a model substrate and prepared by treatment of known methyl acetal **6**[8] with BCl_3 (0.33−0.4 equiv), followed by purification by vacuum distillation.[9,10] At −78 °C in TBME, conditions under which **7** does not undergo spontaneous reaction with silyl ketene acetal **8a**, catalyst **10**[11] was found to promote clean substitution to generate ester **9a** in 63% ee (Table 1, entry 1).

Systematic evaluation of a variety of thioureas revealed that both the bis(trifluoromethyl)aniline and the tertiary benzyl amide components were important for achieving useful reaction rates at low temperatures.[12] Incorporation of an additional stereogenic center within the benzyl amide imparted a measurable detrimental (mismatched) or complementary (matched) influence on enantioselectivity: (*S*,*S*)-**11** induced reaction with diminished (54%) ee and lower conversion, while (*R*,*S*)-**12** afforded **9a** in 73% ee (Table 1, entries 2 and 3). Reasoning that the conformations available to the benzyl amide may be tied closely to reaction enantioselectivity, we hypothesized that appropriately constrained amide components might prove advantageous. Indeed, 2-phenylpyrrolidine-derived thiourea (*R*,*S*)-**14** provided ester **9a** in 81% ee.[13] Catalysts lacking an aryl group in the amide component (e.g., **16**, entry 7) induced slower reaction rates and diminished enantioselectivity. This observation, taken together with the relative rates and enantioselectivities of catalysts **11**/**12** and **13**/**14**, suggests

Scheme 1. Enantioselective Addition to Reactive Cationic Species: Hydrogen-Bond Catalysis by Anion Binding

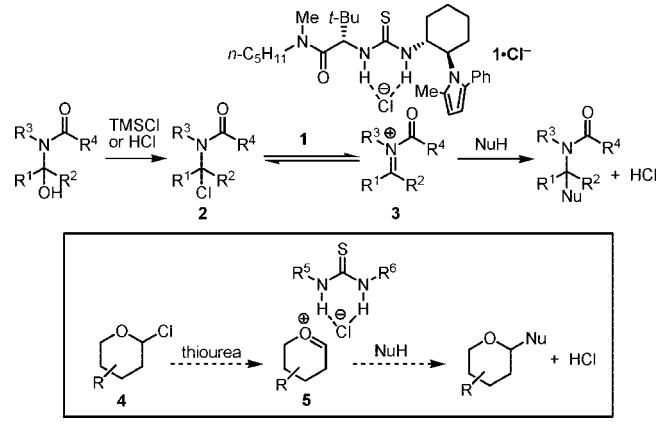
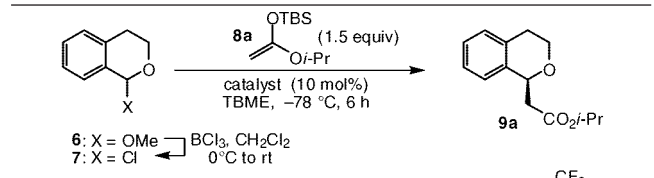
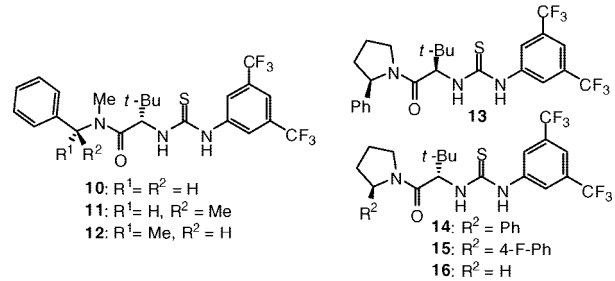


Table 1. Thiourea-Catalyzed Addition of **8a** to 1-Chloroisochroman (**7**) To Give Ester **9a**





entry	catalyst	conversion (%)[a]	ee (%)[b]
1	**10**	88	63
2	**11**	69	54
3	**12**	97	73
4	**13**	78	–41
5	**14**	96	81
6	**15**	98	85
7	**16**	59	42

[a] Determined by ^{1}H NMR analysis of crude reaction mixtures relative to an internal quantitative standard. [b] Determined by HPLC analysis using commercial chiral columns.

that the aromatic group may engage in stabilizing interactions between the catalyst and oxocarbenium ion or silyl ketene acetal in the rate-determining transition state. Pursuant to this possibility, evaluation of several catalysts with varying aryl substitution led to the identification of fluoroaryl catalyst **15** as optimal.[12]

With the identification of a suitable catalyst, the substrate scope of this transformation was explored (Table 2 and Figure 1). Thiourea **15** induced high ee's in additions of the commercially available methyl acetate derived silyl ketene acetal **8b** to a variety of isochroman

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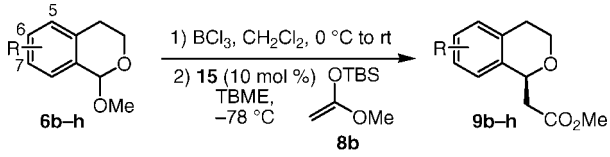
Table 2. Enantioselective Addition of Silyl Ketene Acetal **8b** To Provide Substituted Isochromans



entry	R	time (h)	product	yield (%)[a]	ee (%)[b]
1	H	6	**9b**	87	85
2	5-Me	7.5	**9c**	71	90
3	6-Me	7.5	**9d**	82	84
4	7-Me	7.5	**9e**	82	87
5	6-F	21	**9f**	70	90
6	6-OMe	22	**9g**	96	74

[a] Isolated yield (based on **6**) after silica gel chromatography. [b] Determined by HPLC analysis using commercial chiral columns.

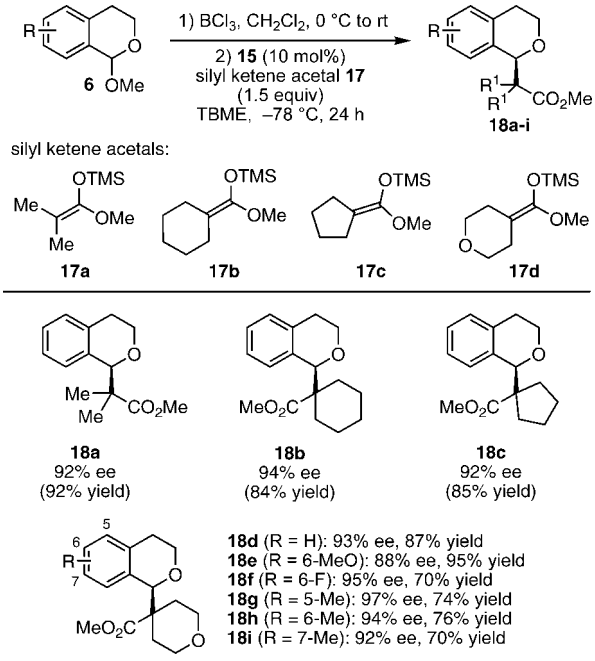


Figure 1. Addition of tetrasubstituted silyl ketene acetals to provide substituted isochromans.

derivatives. The substituted chloroisochromans were prepared from the corresponding methyl acetals and used directly without purification in a one-pot, two-stage procedure. Saponification of ester **9a** provided the corresponding carboxylic acid, which was found to be levorotatory, and therefore assigned as the *S*-enantiomer by comparison to previously published data.[14] Symmetric tetrasubstituted silyl ketene acetals afforded addition products with uniformly high enantioselectivities (Figure 1). When conducted on a 5 mmol scale using 5 mol % of catalyst **15**, ester **18a** was produced in 95% yield (1.1 g) and 91% ee (TON = 19, TOF > 3 h^{-1}).

The successful enantioselective catalysis of silyl ketene acetal addition to racemic 1-chloroisochromans raises interesting mechanistic questions. The products are isolated in >50% yield in good-to-excellent ee's that were found to remain constant over the course of the reaction. These data indicate that the described reaction is a dynamic kinetic resolution, with racemization of **7** being either spontaneous or catalyst-induced.[15] Addition of 10 mol % of *n*-Bu_4NCl resulted in complete inhibition of the reaction, as would be expected in the context of a chloride-binding mode of action of **15** in these substitutions.[16] Reaction rates and enantioselectivities were observed to be dependent on the concentration and nature of the silyl ketene acetal. While the observation of S_N2 kinetics requires that the nuceophile is engaged in the rate-determining step, it is consistent with an oxocarbenium chloride−thiourea complex as the reactive electrophilic species.[17,18]

This work brings oxocarbenium ions into the realm of viable electrophilic substrates for asymmetric catalysis. Taken together with our previously described reactions of *N*-acyliminium ions, thiourea catalysis by anion binding provides a general mechanism for enantioselective additions to cationic intermediates. We anticipate that this mode of catalysis will find use in related reactions of oxocarbenium ions, such as diastereoselective glycosyl bond formation, and this is the focus of ongoing research.[19]

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews, see: (a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743. (b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543. (c) Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1758–1763. (d) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062–2064. (e) Oestreich, M. *Nachr. Chem.* **2004**, *52*, 35–38. (f) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289–296.

(2) (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. (c) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404–13405. See also: (d) Pan, S. C.; Zhou, J.; List, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 2971–2973.

(3) For a reviews of *C*- and *O*-glycoside formation within total synthesis, see: (a) Du, Y. G.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913–9959. (b) Pellissier, H. *Tetrahedron* **2005**, *61*, 2947–2993.

(4) For systematic studies of substituent effects on the nucleophilic addition to five- and six-membered oxocarbenium ions, see: (a) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521. (b) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10879–10884.

(5) Braun, M.; Kotter, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 514–517.

(6) For additions of catalytically-generated chiral metal enolates to symmetric oxocarbenium ions, see: Evans, D. A.; Thomson, R. J. *J. Am. Chem. Soc.* **2005**, *127*, 10506–10507.

(7) For ketalizations catalyzed by achiral thioureas, see: (a) Kotke, M.; Schreiner, P. R. *Tetrahedron* **2006**, *62*, 434–439. (b) Kotke, M.; Schreiner, P. R. *Synthesis* **2007**, 779–790.

(8) Xu, Y. C.; Lebeau, E.; Gillard, J. W.; Attardo, G. *Tetrahedron Lett.* **1993**, *34*, 3841–3844.

(9) For BCl_3-mediated preparation of α-chloroethers, see: Berger, D.; Overman, L. E.; Renhowe, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 2446–2452.

(10) Although 1-chloroisochroman (**7**) undergoes hydrolysis when exposed to moist air, it can be distilled and is stable indefinitely when stored under nitrogen in a−78 °C freezer.

(11) (a) Wenzel, A. G.; Lalonde, M. P.; Jacobsen, E. N. *Synlett* **2003**, 1919–1922. The utility of bis(trifluoromethyl)aniline-derived thioureas in catalysis via H-bonding was established by Schreiner. (b) Wittkopp, A.; Schreiner, P. R. *Chem., Eur. J.* **2003**, *9*, 407–414.

(12) See Supporting Information for details.

(13) Preparation of enantioenriched 2-arylpyrrolidines: Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C. Y. *J. Am. Chem. Soc.* **2006**, *128*, 3538–3539.

(14) TenBrink, R. E.; Bergh, C. L.; Duncan, J. N.; Harris, D. W.; Huff, R. M.; Lahti, R. A.; Lawson, C. F.; Lutzke, B. S.; Martin, I. J.; Rees, S. A.; Schlachter, S. K.; Sih, J. C.; Smith, M. W. *J. Med. Chem.* **1996**, *39*, 2435–2437.

(15) A titanium-catalyzed dynamic kinetic resolution of configurationally stable indanols via ion-paired carbocationic intermediates has been reported. See ref 5.

(16) (a) Antonisse, M. M. G.; Reinhoudt, D. N. *Chem. Commun.* **1998**, 443–448. (b) Hisaki, I.; Sasaki, S. I.; Hirose, K.; Tobe, Y. *Eur. J. Org. Chem.* **2007**, 607–615. (c) Jagessar, R. C.; Shang, M. Y.; Scheidt, W. R.; Burns, D. H. *J. Am. Chem. Soc.* **1998**, *120*, 11684–11692. (d) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609–1646.

(17) Similar reactivity and slightly diminished enantioselectivity is observed using urea analogues of catalyst **15** for the addition of **17a** to **7** (i.e., 84 versus 92% ee with **15**). This renders highly unlikely any mechanism involving a direct, productive interaction of the the thiocarbonyl with either the 1-chloroisochroman or oxocarbenium intermediate.

(18) For mechanistic studies on the addition of silyl ketene acetals to carbenium ions, see: Burfeindt, J.; Patz, M.; Muller, M.; Mayr, H. *J. Am. Chem. Soc.* **1998**, *120*, 3629–3634.

(19) Preliminary results obtained in additions to both simple and stereochemically complex tetrahydropyranyl derivatives are included in the Supporting Information.

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