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Xanthene-4,5-diamine derivatives: a study of anion-binding catalysis

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ABSTRACT

This study describes the synthesis of a class of anion-binding catalysts based on a xanthene scaffold. Both unsymmetrical catalysts and C_2 -symmetrical catalysts were generated, and were examined in the cyclization of 3- and 2-substituted furans onto *N*-acyliminium ions. Good conversion for each reaction was observed with a variety of anion-binding catalysts (42–76%).

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Introduction

Ion-pairing chemistry has emerged as a useful form of catalysis and relies on electrostatic interactions.^{1,2} There are two methods of anion-pairing catalysis that have been utilized in the literature (Fig. 1). The first is anion-binding catalysis, which is explored in this paper. The second is chiral anion-directed catalysis and it varies from the former by having the chiral center attached to the anion rather than non-covalently bound to it. These catalyst types are still in their early stages of development and relatively few types have been explored.

Jacobsen and Seidel have been the leading pioneers in the field of organocatalysis involving anion-binding catalysis.^{3,4} The work in this paper was inspired by Jacobsen's Pictet–Spengler-type reaction of hydroxylactams (Scheme 1). Here Jacobsen was able to effect indole addition into *N*-acyliminium ions in good yield (97%) and good enantiomeric excess (97%) using a thiourea catalyst (TBME = *tert*-butyl methyl ether).^{4a} A variety of experiments were carried out to support this mechanism. Not only was a pronounced anion effect on enantioselectivity observed but also rate enhancement was detected when *tertiary* alcohols are utilized. Jacobsen extended this chemistry to an *intermolecular* reaction^{4b} and an *intramolecular* version with pyrroles.^{4c} The exceptional anion-binding properties of thioureas have been known for quite some time.⁵ Because of this feature, they are the

primary functional group found in organocatalysts used for counteranion binding.

We hypothesized that other types of known anion receptors should have the ability to form good anion-binding catalysts.⁶ Acridones and similar anthracenyl scaffolds are well known in the literature for their ability to bind to anions. Xanthene-derived compounds have been used as hydrogen-bonding catalysts to promote the addition of 2-acetylcyclopentanone into α,β -unsaturated nitroalkenes.⁷ This paper describes the investigation of xanthene-derived compounds as anion-binding catalysts.

Results and discussion

4,5-Diaminoxanthene **3** was accessed in straightforward manner requiring three steps with a high overall yield (75%, Scheme 2).⁸ Additionally, compound **3** can be mono-Boc protected or coupled to one amino acid to yield compound **5**. This reactivity enables unsymmetrical catalysts to be made.

Using these conditions, various catalysts could be made expediently, including unsymmetrical catalysts **6–8** and C_2 -symmetrical catalysts **9** and **10** (Fig. 2). C_2 -Symmetrical catalysts are beneficial because of the smaller number of possible diastereomeric transition states available.⁹ Although urea compounds are less acidic and therefore weaker hydrogen-bond donors, they have been found to give a greater amount of enantioinduction in certain systems.⁷ As such, both urea **7** and thiourea (**6** and **8**) were made. A greater variety of amides are accessible using commercially available amino acids **4**, but sulfonyl amides were hypothesized to be better hydrogen-bond donors (again due to their increased acidity).¹⁰ Thus, amides (**6** and **7**) and sulfonyl amide **8** were formed.

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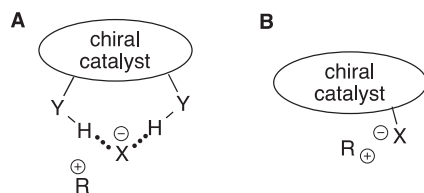
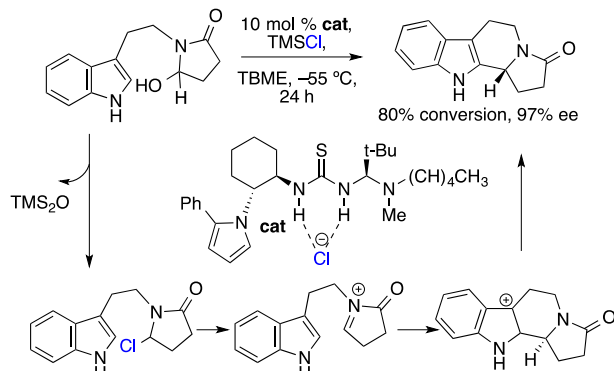
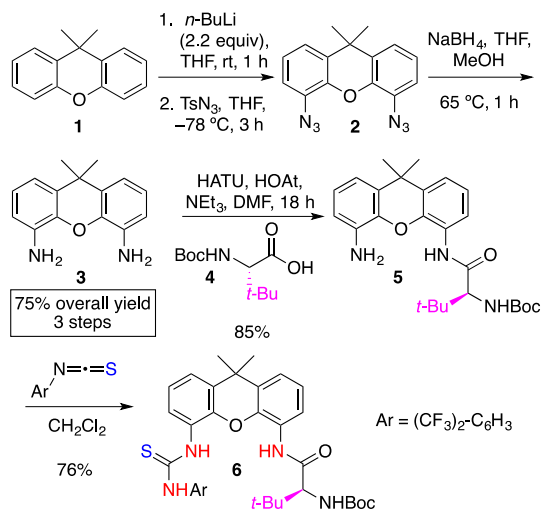


Figure 1. Two methods of anion-pairing catalysis. (A) Anion-binding catalysis. (B) Chiral anion-directed catalysis.



Scheme 1. Jacobsen's Pictet–Spengler-type reaction of hydroxylactams and proposed mechanism.



Scheme 2. Summary of route to 4,5-diaminoxanthene followed by peptide coupling and thiourea formation.

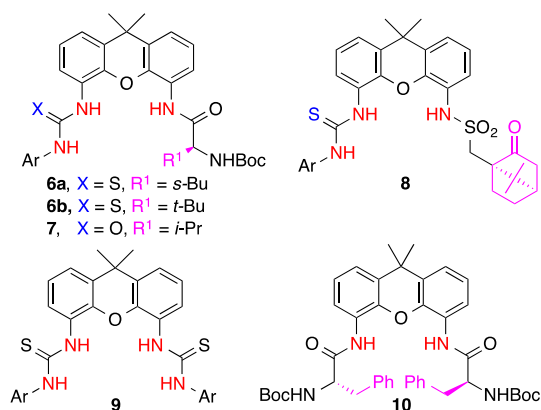


Figure 2. Anion-binding compounds used in this study. Ar = (CF₃)₂-C₆H₃.

With structurally different compounds in hand, their catalytic activity was evaluated using Jacobsen's Pictet–Spengler-type reaction (refer to [Supporting information](#) for further details). In this study, thiourea **6a** and urea **7** performed similarly. Literature supports that N-alkyl, N-aryl thioureas and ureas have a very similar affinity for a chloride anion ($K_{\text{eq}} = 22$ and 21 in DMSO, respectively) indicating the activity of these catalysts is a function of their affinity for a chloride anion *rather* than their $\text{p}K_{\text{a}}$ (13 and 19 , respectively).¹¹ Bisthiourea **9** and thiourea **6a** performed better than a simple thiourea, 1-(3,5-bis(trifluoromethyl)phenyl)-3-phenylthiourea. These experiments suggest that four and three hydrogen bonds, respectively, are superior for catalysis. Since high selectivities have been reported for this reaction in the literature, this substrate was not tested for enantiomeric excess.

To determine the basis of the increased catalytic activity of the xanthene-derived compounds relative to simple thioureas in the Jacobsen's Pictet–Spengler-type reaction, their binding constants to chloride were measured. Binding studies on similar compounds have been performed.⁶ Although xanthenyl diamide **10** was found to have the lowest equilibrium constant of the compounds measured for a chloride binding, it is still favorable in less polar solvents such as pyridine. [Figure 3](#) shows the change in chemical shift of the NH protons for **10** (0.272 M in py-d₅) in the ¹H NMR spectrum with increasing equivalents of chloride anion. [Figure 4](#) displays the corresponding binding curve. Since only one peak is observed, this system is undergoing fast exchange between **10** and complex **10**·Cl⁻*n*-Bu₄⁺; an average of the bound NH protons and unbound NH protons is observed rather than two distinct peaks. The immediate change in chemical shift after addition of chloride anion ($t = 1$ h) indicates equilibrium has been reached before data collection ($t = 1$ – 24 h).

These data allowed calculation of $K_{\text{eq}} = 56$ for binding of **10** to chloride in pyridine ([Table 1](#)). This equilibrium constant corresponds to a $\Delta G = -2.39$ kcal/mol. The equilibrium constant of this reaction was too low to be measured in DMSO. Next, analysis was performed on **6b** and **7** since they were predicted to be the next strongest anion-binders. In line with other literature reports,¹¹ these two catalysts have very similar binding constants, $K_{\text{eq}} = 127$ versus 159 for **6b** and **7** respectively ($\Delta G = -2.87$ and -3.00 kcal/mol) in DMSO ([Table 1](#)). This similarity is supported by the reactivity that we observed in Jacobsen's Pictet–Spengler-type reaction (refer to [Supporting information](#) for details). The steric hindrance of the *tert*-leucine may decrease the affinity of compound **6b** toward chloride.

Finally, analysis was performed on **9**. As predicted, this catalyst has the highest affinity for a chloride anion of the compounds studied ($K_{\text{eq}} = 1517$, $\Delta G = -4.34$ kcal/mol) in DMSO. A summary of these binding constants compared to other neutral, organic, anion binders can be found in [Table 1](#).¹² The NH groups responsible for chloride binding are highlighted in red.

Given the good binding affinity of the xanthene-based catalysts to chloride, we wanted to expand this Pictet–Spengler-type reaction to more challenging substrates. We decided to investigate the cyclization of 2 and 3-substituted furans (**25** and **23**, respectively) onto *N*-acyliminium ions. To the best of our knowledge, there are no reported enantioselective or organocatalytic methods for these transformations.¹³

The cyclization of 3-substituted furans is slower (entry 4, 42% conversion after 7 h at -42 °C) than the corresponding indole (44% conversion after 1.5 h at -55 °C). This difference arises from the lower nucleophilicity of the furan relative to indole. Unsymmetrical sulfonamide thiourea **8** performs better than amide urea **7** (entries 3 and 4, 60% vs 42% conversion) and this result is proposed to be a consequence of sulfonamides being more acidic than amides ($\text{p}K_{\text{a}}$ 16 vs 23 in DMSO, respectively).¹⁰ *tert*-Leucine-derived catalyst **6b** showed small but significant

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