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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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1. 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 (Figure 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.

Figure 1. Two methods of anion-pairing catalysis. **A:** Anion-Binding Catalysis. **B:** Chiral Anion-Directed Catalysis.

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 affect 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.

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

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 addition of 2-acetylcyclopentanone into α , β -unsaturated

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nitroalkenes.⁷ This paper describes the investigation of xanthene-derived compounds as anion-binding catalysts.

2. 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.

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

Using these conditions, various catalysts could be made expeditiously, including unsymmetrical catalysts **6–8** and C_2 -symmetrical catalysts **9** and **10** (Figure 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.

Figure 2. Anion-binding compounds used in this study. Ar = $(CF_3)_2-C_6H_3$

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 ($K_{eq} = 22$ and 21 in DMSO, respectively) indicating the activity of these catalysts is a function of their affinity for a chloride anion *rather* than their pK_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** (0.0272 M in $py-d_5$) 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^- • $n-Bu_4N^+$; 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).

Figure 3. Change in NH protons of **10**, 0.0272 M, by 1H NMR with increasing equivalents of chloride anion, Cl^- • $n-Bu_4N^+$, in $py-d_5$.

Figure 4. Binding curve for **10**, 0.0272 M, with increasing equivalents of chloride anion, Cl^- • $n-Bu_4N^+$ in $py-d_5$.

These data allowed calculation of $K_{eq} = 56$ for binding of **10** to chloride in pyridine (Table 1). This equilibrium constant corresponds to a $\Delta G = -3.00$ 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, $K_{eq} = 127$ vs. 159 for **6b** and **7** respectively ($\Delta G = -3.00$ and -2.87 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 ($K_{eq} = 1517$, $\Delta G = -4.34$ 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.

Table 1
Summary of binding constants in this study and the literature

Compounds	K_{eq}	solvent	Ref.
10	56	py-d ₅	this work
7	159	DMSO-d ₆	
6b	127		
9	1517		
11	840		6b
12	1000		
13	1930		14d
14	>10,000		14a
15	<10	DMSO-d ₆ /0.5% water	11a
16	10		
17	21		
18	22		
19	96		
20	28		
21	273		6a
22	53		

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 furan relative to indole. Unsymmetrical sulfonamide thiourea **8** performs better than amide urea **7** (entry 3 and 4, 60% vs. 42% conversion) and this result is proposed to be a consequence of sulfonamides being more acidic than amides (pK_a 16 vs. 23 in DMSO, respectively).¹⁰ *tert*-Leucine-derived catalyst **6** showed small but significant levels of enantioinduction (entry 5, 70% conversion and 17% ee). Bisamide **10** (entry 6) did not promote the cyclization, in line with its low affinity for a chloride anion.

We were uncertain if furan **25** would undergo cyclization given the decreased stability of the positive charge in its non-

aromatic intermediate relative to furan **23**. Cyclization does occur with addition of catalyst (Table 3), albeit with higher temperatures (0 °C) and longer reaction times (17 h). Surprisingly, bisamide **10** (entry 4) performs well for this reaction (60% conversion) despite its failure to promote the previous two reactions (0% conversion). This observation suggests π -stacking with **25** promotes reactivity of this substrate. Unfortunately, no significant enantioselectivity was observed.

Table 2
The cyclization of 3-substituted furans into *N*-acyliminium ions

entry	catalyst	time (h)	conversion ^a (%)
1	none	1, 7	< 5
2	9	1	76
3	8	7	60 (0)
4	7	7	42 (10)
5	6b	7	70 (17)
6	10	7	0

^a Determined by ¹H NMR relative to an IS, butylated hydroxytoluene (BHT). Numbers in parentheses refer to enantiomeric excess (%).

Table 3
The cyclization of 2-substituted furans into *N*-acyliminium ions

entry	catalyst	time (h)	conversion ^a (%)
1	none	17	< 5
2	8	17	60 ^b
3	7	17	57 ^b
4	10	17	60 ^b

^a Determined by ¹H NMR relative to an IS, butylated hydroxytoluene (BHT).

^b Significant enantioselectivity was not observed.

To gain a deeper understanding of the mechanism, DFT calculations were undertaken on a model system using a truncated version of the anion-binding catalyst (Figure 5). These calculations support chloride as the deprotonating agent rather than water or the sulfur moiety of the catalyst. They also support direct cyclization to form a six-membered ring (Figure 6).¹⁴ This same trend was observed in the absence of catalyst and for the corresponding indole system of Scheme 1 (see SI for further details). Similar reports are known in the literature.¹⁵ However, formation of a spirocyclic intermediate has not been ruled out experimentally.

Additional screening was done around 3-substituted furans in attempt to optimize the best yielding catalyst in Table 2 (entry 5). Yields and enantiomeric excess were measured using several solvents and varied temperatures (Table 4). Etheral solvents (entry 1 and 5) give good conversion and small but significant amounts of enantiomeric excess, whereas more polar solvents¹⁶ such as CH₂Cl₂ tend to give good conversion and no enantioinduction (entry 3). Aromatic solvents decrease the conversion and enantioselectivity, presumably due to decreased solubility of the catalysts (entry 2 and 4). Additional experiments around etheral solvents (entry 6–9, CPME = cyclopentyl methyl ether) support that polar solvents¹⁷ decrease

Figure 5. Deprotonation with chloride, achiral catalyst **27** or water [B3LYP/6-31G(d)], in diethyl ether using a CPCM model for solvation.

enantioselectivity, possibly due to increased reaction rates (entry 6 vs. 7, THF vs. CPME, 14% vs. 24% ee). Also, it was determined that higher reaction concentrations (0.1 M versus 0.01 M) increase the rate of reaction, subsequently lowering enantioselectivity (entry 9 vs. 5, 6% vs. 22% ee). In an attempt to increase the enantioselectivity, the temperature was lowered to -78°C . However, this change inhibited reaction progression (entry 11–13, <5% conversion). Decreased solubility of the

AcCl or TMSBr). Additional efforts are aimed toward validating the computational model of the cyclization of furans onto *N*-acyliminium ions with the goal of designing catalysts to achieve higher enantioinduction

Table 4
Additional
around

entry	solvent	temp ($^{\circ}\text{C}$)	time (h)	conversion ^a (%)
1	TBME	-42	5	71 (16)
2	toluene	-42	5	65 (0)
3	CH_2Cl_2	-42	5	75 (< 5)
4	$\text{CF}_3\text{C}_6\text{H}_5$	-23	5	55 (< 5)
5	ether	-42	5	73 (22)
6	THF	-42	7	67 (14)
7	CPME	-42	7	42 (24)
8	ether (no cat)	-42	7	< 10 (N/A)
9	ether (0.1 M)	-42	7	97 (6)
10	diglyme	-42	5	98 (< 5)
11	THF	-78	15	0
12	ether	-78	15	< 5
13	CPME	-78	15	< 5

^a Determined by ^1H NMR relative to an IS, butylated hydroxytoluene (BHT). Numbers in parentheses refer to enantiomeric excess (%).

Figure 6. Six- vs. five-membered ring formation with achiral catalyst **27** [B3LYP/6-31G(d)], in diethyl ether using a CPCM model for solvation.

catalyst at these temperatures is most likely the cause for the low conversions (reaction mixtures appeared cloudy as opposed to clear). Following the hypothesis that more polar linear ethereal solvents may increase enantioselectivity (entry 1 vs. 5, TBME vs. ether, 16% vs. 22% ee), diglyme was tested.¹⁸ However, this solvent provided no benefit (entry 10, <5% ee). An intermediate temperature was also attempted (-60°C). In CPME, little to no catalyzed reaction was observed (about 12% conversion) and there was not sufficient product to determine accurately the enantiomeric excess. The reactions in CPME were still cloudy indicating potential catalyst precipitation. In ether, the reaction did progress, but no increase in enantioselectivity was observed at -60°C . From these results the optimal reaction conditions remain CPME, at -42°C for 7 h. Future efforts are focused on catalyst modification or altering the halogenating reagent (i.e.

In summary, this paper discusses the effect of anion-binding interactions on reaction catalysis. Anion-binding compounds based on a xanthene scaffold are described. They are distinct from the thiourea hydrogen-bonding catalysts currently in the literature, because they are more effective in promoting Pictet-Spengler-type reactions of hydroxylactams. These potent anion-binders have the potential to pave the way for a new reaction development focused on anion-binding catalysis.

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Supporting Information

Supplementary data (complete computational details, complete ref 14 for Gaussian09, experimental procedures, full characterization, including ¹H NMR and ¹³C NMR spectra, for all new compounds, HPLC chromatograms) associated with this article can be found, in the online version.

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