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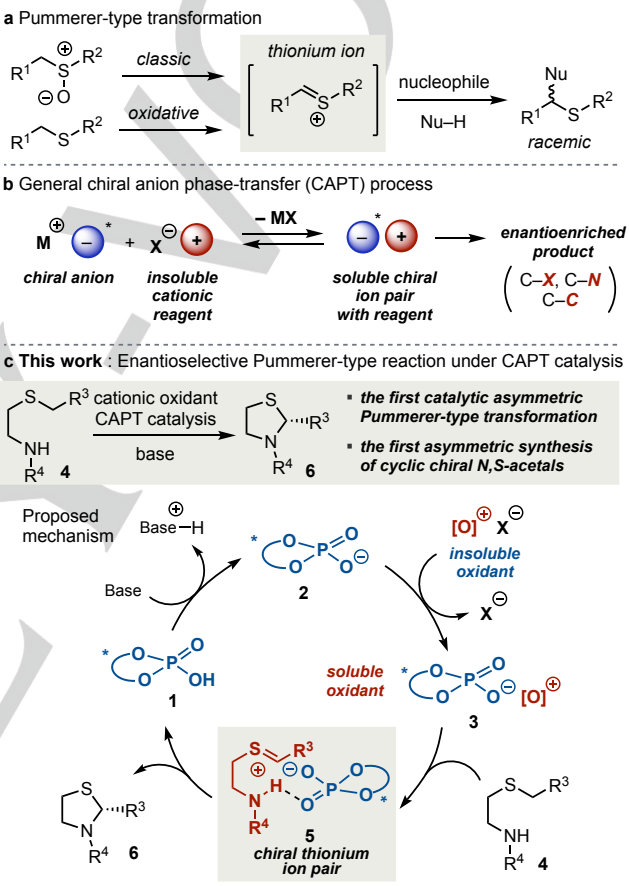
# Enantioselective Synthesis of *N,S*-Acetals by an Oxidative Pummerer Type Transformation Using Anionic Phase-Transfer Catalysis

Souvagya Biswas,[a], [b] Koji Kubota,[a], [b] Manuel Orlandi,[c] Mathias Turberg,[a] Dillon H. Miles,[a] Matthew S. Sigman,* [c] and F. Dean Toste* [a]

***Abstract:*** *We report the first enantioselective oxidative Pummerer-type transformation using anionic phase-transfer catalysis, resulting in the formation of enantioenriched sulfur bearing heterocycles. This reaction includes the direct oxidation of sulfides to the thionium intermediate, followed by an asymmetric intramolecular nucleophilic addition to form the chiral cyclic N,S-acetals with moderate to high enantioselectivites. Deuterium labelling experiments were performed to identify the stereodiscrimination step of this process. Further analysis of the reaction transition states by means of multidimensional correlations and DFT computations highlight the existence of a set of weak noncovalent interactions between the catalyst and substrate that governed the enantioselectivity of the reaction.*

Since its discovery in 1909, the Pummerer reaction and related thionium chemistry have been successfully applied to the synthesis of a variety of synthetically and biologically useful compounds and natural products.[1,2] Mechanistically, Pummerer-type reactions are proposed to proceed via nucleophilic addition to an *in situ* generated thionium species to form sulfur containing motifs (Scheme 1a). Despite significant investigation of this transformation, there have been no reports to date describing catalytic enantioselective variants.[3] Development of this transformation would provide an enantioselective entry into sulfur containing carbon stereocenters previously deemed challenging or inaccessible.[4,5]

Given our recent success in applying chiral anion phase-transfer (CAPT) catalysis to various challenges in asymmetric synthesis (Scheme 1b),[6,7] we envisioned that this strategy may be applied to the enantioselective construction of stereogenic C–S bonds through a Pummerer-type reaction (Scheme 1c). In this scenario, under basic conditions chiral phosphoric acid **1** generates chiral phosphate anion **2**, which participates in a salt metathesis with an appropriately identified insoluble cationic oxidant to form soluble ion pair **3** in a non-polar solvent. Species **3** presumably reacts with sulfide **4** to generate chiral thionium ion pair **5**[8] that undergoes a nucleophilic attack to provide the enantioenriched product, cyclic *N,S*-acetal (**6**), and release the chiral phosphate. This strategy would enable the first enantioselective construction of cyclic *N,S*-acetal skeletons.[9]




***Scheme 1.*** Application of CAPT catalysis to the oxidative Pummerer-type C–N bond forming reaction for the synthesis of enantioenriched *N,S*-acetals.

To initiate this study, we first tested Bobbitt's salt **7a**,[10,11] as this reagent was successfully applied to produce an iminium ion pair using CAPT catalysis in an enantioselective cross-dehydrogenative coupling.[7] It should be noted that direct oxidation of sulfides to thionium species using this class of oxidant has not been reported to date.[12] Encouragingly, the reaction of **4a** in the presence of 10 mol % (*R*)-TRIP (**1a**) catalyst, the oxidant **7a** (3.0 equiv) and $Na_3PO_4$ (3.0 equiv) in toluene under air at room temperature gave the desired cyclic *N,S*-acetal **6a** in good yield (62%) and promising enantioselectivity (62% *ee*, entry 1, Table 1).[13] Introducing alkyl chains onto the binaphthyl backbone of the phosphoric acid (**1b**) to enhance catalyst solubility marginally improved the enantioselectivity of the reaction (64% *ee*, entry 2). Unfortunately, the use of another conventional phosphoric acid

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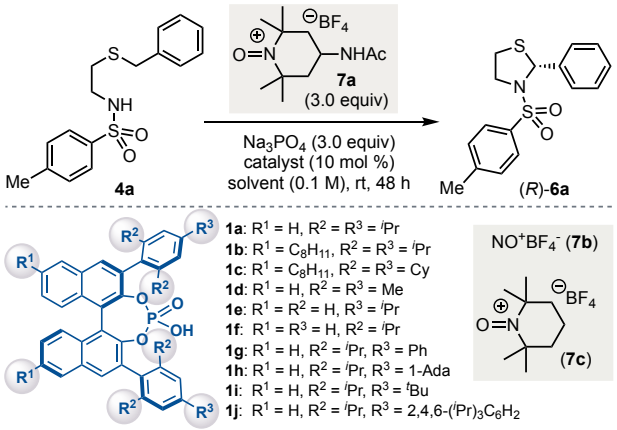
***Table 1.*** Optimization of Reaction Conditions for the Enantioselective Oxidative Pummerer-Type Cyclization.[a]



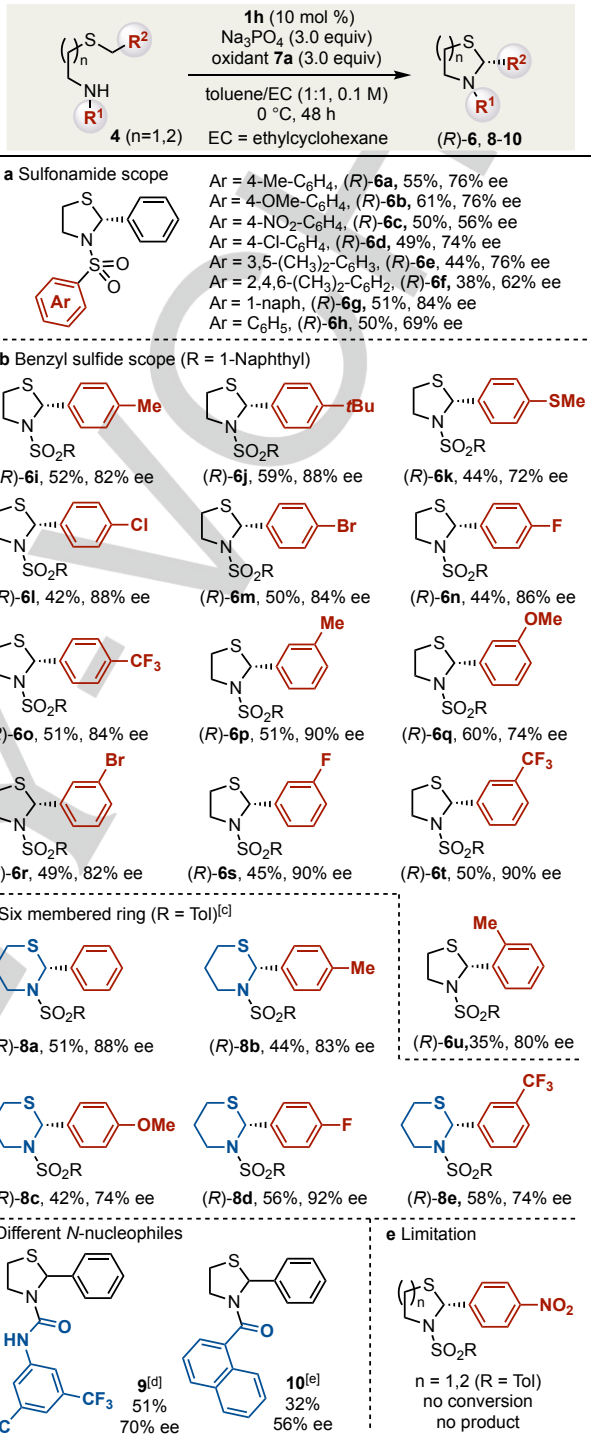

| Entry | Catalyst | Solvent | Yield(%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | **1a** | toluene | 62 | 62 |
| 2 | **1b** | toluene | 60 | 64 |
| 3 | **1c** | toluene | 64 | 52 |
| 4 | **1d** | toluene | 61 | 49 |
| 5 | **1e** | toluene | 62 | 26 |
| 6 | **1f** | toluene | 59 | 56 |
| 7 | **1g** | toluene | 58 | 60 |
| 8 | **1h** | toluene | 56 | 68 |
| 9 | **1i** | toluene | 50 | 62 |
| 10 | **1j** | toluene | 44 | 62 |
| 11[d] | **1h** | toluene | <5 | – |
| 12[e] | **1h** | toluene | 22 | 77 |
| 13 | **1h** | toluene/EC[f] | 60 | 68 |
| 14[g] | **1h** | toluene/EC[f] | 55 | 76 |

[a] See the Supporting Information for complete optimization data. [b] Isolated yield after silica gel column chromatography. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Reaction was carried out with nitrosyl tetrafluoroborate salt (**7b**) as oxidant, gave complex mixture of products. [e] Reaction was carried out with 2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate salt (**7c**) as oxidant. [f] EC = ethylcyclohexane. [g] Reaction was carried out at 0 °C.

(TCYP) (**1c,** entry 3) resulted in lower enantioselectivity. In order to probe steric effects, various other phosphates displaying unique substitution patterns were examined. This systematic investigation (entries 4–10, Table 1) revealed that the substituent at the $R^2$ position on the 3,3'-phenyl ring is crucial (entry 6) and that a bulky substituent at $R^3$ further improved the enantioselectivity (entry 8-10). To further explore improvements to the reaction, a stronger cationic oxidant, nitrosyl tetrafluoroborate salt (**7b**), was evaluated but unfortunately gave a complex mixture of products (entry 11). Interestingly, the structurally analogous oxidant, 2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate salt (**7c**), improved the enantioselectivity significantly (77% *ee*), although a poor yield was observed (22%, entry 12).[14] Finally, we found that the use of toluene/ethylcyclohexane (EC) as a co-solvent system at 0 °C resulted in formation of the product in improved enantioselectivity (76% *ee*, entry 14).

Using this set of conditions, the scope of this process was explored as depicted in Table 2. Aryl sulfonamides bearing both electron-rich and electron-poor groups at the *para* position were tolerated, resulting in moderate to good enantioselectivities (**6e**–**6f**, 62-72% *ee*). While methyl substituents on the sulfonamide backbone (**6a**–**6d**, 56–76% *ee*, Table 2a). did not improve the enantioselectivities, the 1-naphthyl substrate **4g** afforded the

***Table 2***. Scope and Limitations of the Enantioselective Oxidative Pummerer-Type Cyclization.[a,b]




[a] Isolated yields are shown. Remainder of the mass balance is starting material and products derived from oxidative debenzylation of the sulfide. [b] The *ee* values were determined by HPLC analysis using a chiral stationary phase, the absolute configuration of the product **6a** was established by the comparison of the retention time of the HPLC analysis of the optically active authentic sample. The structures of other products were assigned by analogy. [c] **1c** was used as a catalyst. [d] $H_8$-TCYP was used as a catalyst at -30 °C. [e] **1b** was used as a catalyst.

product (*R*)-**6g** in high enantiomeric excess (84% *ee*). We next turned our attention to the scope of the benzyl sulfide moiety using the 1-naphthyl sulfonamide backbone (Table 2b). Benzylic groups bearing both electron-rich (**6i–6k**, **6u**) and electron-poor groups (**6l**–**6o**, **6r**–**6t**) were tolerated to furnish the

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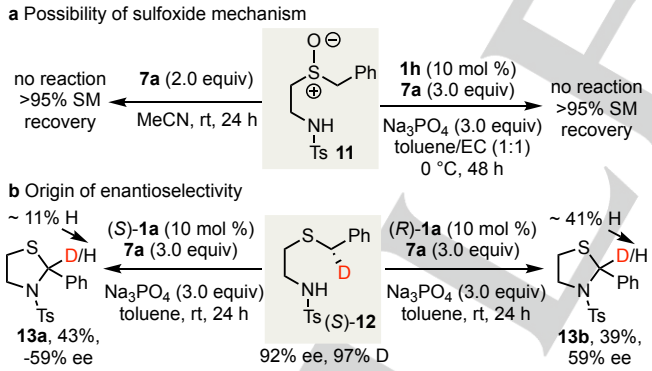
corresponding *N,S*-acetal products with good to high enantioselectivities (72-90% *ee*). Notably, substrates having a sterically hindered-substituent (**6j**) and *meta* substituents (**6p**, **6r**–**6t**) were prone to give higher ee (82–90% *ee*). Moreover, the developed reaction conditions were readily applicable to the enantioselective synthesis of six-membered *N,S*-acetals (**8a**–**8e**, 74-92% *ee,* Table 2c) and substrates bearing different *N*-nucleophiles (**9**, **10**, Table 2d). Unfortunately, substrates bearing an electron-deficient 4-nitrobenzyl group were not oxidized under the reaction conditions.

A series of experiments were conducted in order to gain insight into the reaction mechanism. Reaction of the sulfoxide **11** under both the optimized phase-transfer and non-enantioselective conditions resulted in no observed product, discounting a sulfoxide-mediated mechanism (Scheme 2a). These results are consistent with the proposed phase-transfer mechanism that includes direct oxidation of a sulfide to a thionium cation using an oxoammoium-phosphate chiral ion-pair (Scheme 1c). We sought to establish whether the enantioselectivity was determined during substrate oxidation or the cyclization of the oxidized intermediate. Although the stereogenic center of the product (Scheme 1c, **6**) is formally set in the cyclization of the oxidized intermediate (Scheme 1c, **5**), substrate-catalyst interactions during the oxidation event may preorganize the system for the enantioselective cyclization. In order to examine these possibilities, enantiopure substrate (*S*)-**12** (92% *ee*, 97% D incorporation) was subjected to the oxidative Pummerer-type cyclization (Scheme 2b). The observation that the isolated products (Scheme 2b, **13a** and **13b**) exhibited equal but opposite levels of enantioselectivity, with different levels of H-incorporation, is consistent with a mechanism in which the chiral phosphate is involved in substrate oxidation, but the redox event is decoupled from the enantiodetermining cyclization.




***Scheme 2***. Mechanistic Investigations.

Multidimensional correlation analysis was performed to gain additional information about the features of the catalyst that contribute to the stereoselectivity.[15] A set of parameters for several phosphates **1a-1h** (see SI for full set of catalysts) was computed using the molecular model in Figure 1a.[16] This parameter set included IR vibrational frequencies (***ν***) and intensities (***i***),[17] NBO charges, and Sterimol steric descriptors (***B1***, ***B5*** and ***L***).[18] When the parameters acquired were correlated with the measured *ee* expressed as $\Delta\Delta G^{\ddagger}$, the multidimensional model in Figure 1a was obtained. This model presented a good correlation ($R^2$=0.96, intercept=0.03) and was statistically validated leave-one-out cross validation (L1O=0.89). Three Sterimol parameters appeared in the equation: ***B5***, maximum width of the entire catalysts' aryl substituent; ***B1₂*** and ***B1₄***, minimum width of the substituents in the 2,6-positions and of the substituent in the 4-position of the aryl group respectively. ***B1₂*** presented the largest coefficient and accounted for the necessity of large groups in the 2,6-positions. However, despite enhancements provided by bulky 2,6-groups, increasing their length negatively impact the *ee* as highlighted by the presence of parameter ***B5*** with a negative coefficient. Finally, the smallest coefficient was associated to ***B1₄***, which accounted for fine tuning resulting from the presence of substituents with increasing size at the 4-position of the phosphate aryl group (compare catalysts **1a** with **1g-1j**).[19]

Further information about the interaction mode between the catalyst and the substrate was gained by transition state (TS) analysis of the reaction between (*R*)-TRIP **1a** and substrate **4h**. As the D-labelling experiments suggested that the thionium ring closure is stereodetermining, computations were focused on this reaction step. The low-lying TSs leading to the (*R*)- and (*S*)-products (**TS-*R*** and **TS-*S***) are depicted in Figure 1c (see SI for computational details). **TS-*R*** is favored consistent with the experimentally observed product configuration, and the relative energy of **TS-*S*** (1.03 kcal/mol) matched with the selectivity measured experimentally (56% ee, 0.75 kcal/mol). The two TSs showed several NCIs between the phosphate and the substrate.[20] However, **TS-*R*** displayed a better accommodation of the benzenesulfonamide group via a plethora of CH-π interactions that involved the *i*Pr substituents and the binaphthyl backbone of the catalyst.[17b, 21] This provides an interpretation for the statistical model in Figure 1a (*vide infra*). Additionally, a stronger CH-π interaction between the catalysts aryl substituent ($i$Pr$_3$Ph) and the substrate's electron-deficient alkyl chain was present in **TS-*R*** (three CH-π contacts, while **TS- *S*** presents only one CH-π contact).

The importance of this interaction in the stereochemical recognition was also highlighted by multidimensional analysis of the substrate's arylsulfonylamide group. Descriptors for compounds **4a-4h** (for a full set of substrates, see Supporting Information) were calculated from the uncatalyzed cyclization TS of the corresponding thionium cation.[22] Comparison of the enantioselectivity and the corresponding parameters resulted in the statistical model in Figure 1b ($R^2$=0.86, intercept=0.13, L1O=0.81), which contains two parameters condensed in only one term. The simple equation obtained can be readily interpreted. as ***B5$_{Ar}$*** accounts for the steric hindrance or the shape of the aryl substituent, and while ***NBO$_{AlkH}$*** describes the average charge of the thionium alkyl chain. The presence of this latter descriptor in the model supports the importance of the interaction highlighted in **TS-*R***. Moreover, calculation of the electron density map of the uncatalyzed TS for the benchmark substrate **6d**, showed that the acidic N–H proton and the alkyl chain close to the thionium cation were the most electron-poor regions of the cyclizing substrate (Figure 1d). Thus, the TS computational analysis and the multidimensional correlation analyses agree as a mutual validation of the presented results.

In summary, we have developed an oxidative Pummerer-type cyclization for the synthesis of cyclic *N,S* acetals from readily available starting materials. This operationally simple and mild protocol provides a powerful means to access a broad range of enantioenriched cyclic *N,S*-acetals using an anionic phase transfer catalyst. Deuterium labelling experiments were performed to identify the stereodiscrimination step of this process. Additionally, the origin of the enantioselectivity was investigated by means of DFT TS analysis and of

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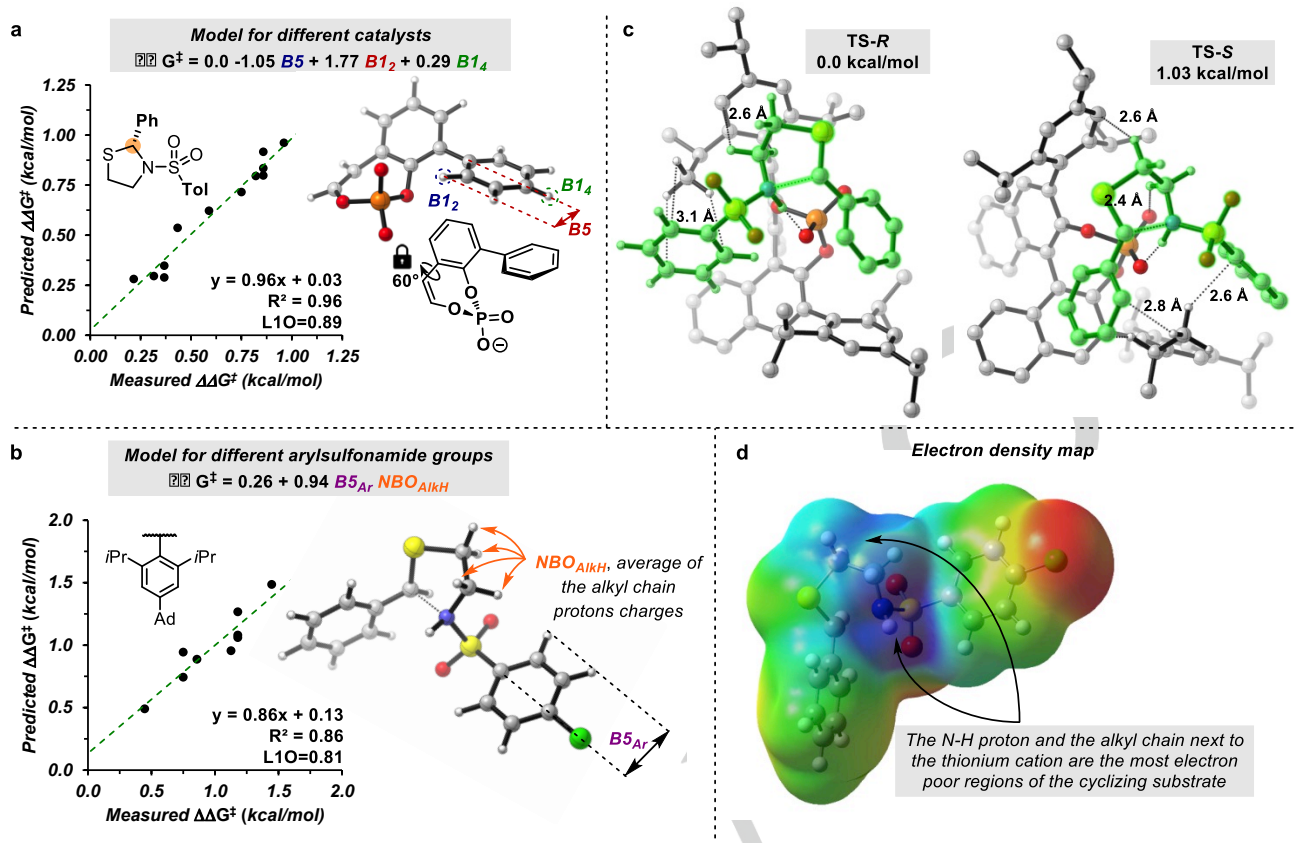


***Figure 1***. [a] Multidimensional correlation analysis for the set of catalysts **1a**-**1h** and [b] for the set of substrates **4a**-**4h**. [c] TS-R and TS-S computed at the wB97XD/6-31G(d) level of theory. wB97XD/6-311+G(2d,p)[PCM=Tol] energies are reported. The substrate is highlighted in green and interatomic distances are shown as dashed lines. [d] electron density map of the uncatalyzed TS of **6d**.

multidimensional correlation techniques, which revealed that a set of subtle yet important NCIs are responsible for the observed level of enantioselectivity (up to 92% ee).

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**Keywords:** phase-transfer catalysis • chiral anions • Pummerer reaction • *N,S*-acetal • synthetic method • theoretical study

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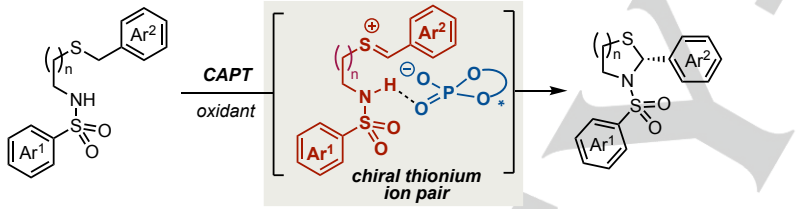


**The first catalytic enantioselective Pummerer type transformation** has been developed employing chiral anion phase-transfer catalysis. This chemical transformation allows the facile construction of a wide variety of enantioenriched cyclic *N,S*-acetal motifs that were previously difficult to access.

*Souvagya Biswas, Koji Kubota, Manuel Orlandi, Mathias Turberg, Dillon H. Miles, Matthew S. Sigman, F. Dean Toste*

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**Enantioselective Synthesis of *N,S*-Acetals by an Oxidative Pummerer Type Transformation Using Anionic Phase-Transfer Catalysis**