FINAL REPORT

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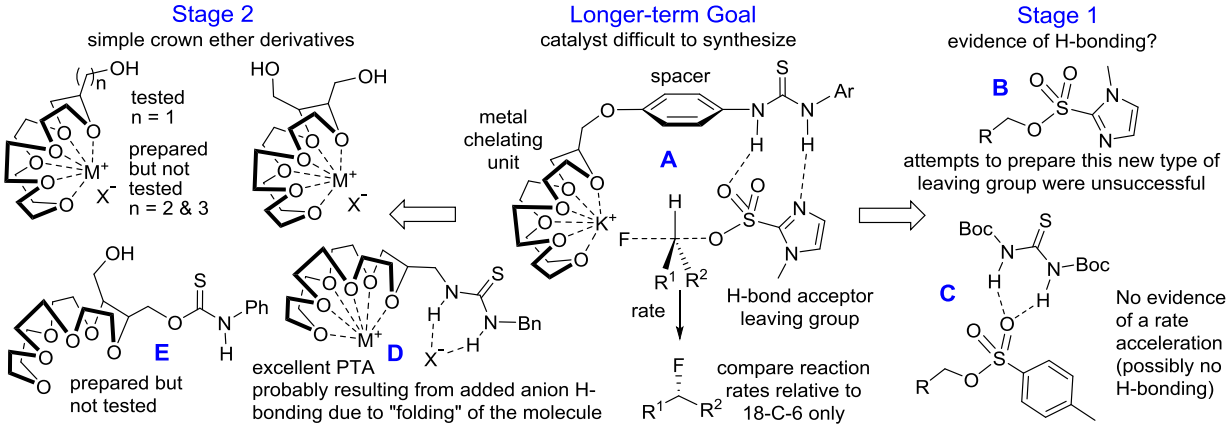
Long-term Goal. The Lepore group is interested in the development of improved reactions to facilitate the preparation of radioactive compounds (radiotracers) required for medical imaging, specifically positron emission tomography (PET).[1] An important strategy often used to develop ultrafast radiolabeling reactions is the design of more efficient phase transfer agents (PTAs). To function properly, these agents must bind to radioactive salts (e.g. $K^{18}F$) used to label radiotracers. The host research group has a long record of accomplishment in the development of agents able to bind selectively to salts leading to reaction acceleration.[2] Working together, the two research groups seek to create a new class of PTAs based on new design concepts. Ultimately, these new agents are expected to improve markedly the synthesis of radiotracers for more widespread use of PET.

Strategy of STM Study. Our working hypothesis for this project is that phase transfer agents can be modified to contain a unit that promotes nucleophilic substitution (acting as a bifunctional catalyst).[3] In this period, we sought to explore several key aspects of this idea to determine feasibility for long-term development. In the first stage, we sought to determine if a relatively simple hydrogen-bond donor could affect the leaving group properties of an aryl sulfonate in a nucleophilic displacement reaction. We then tested a variety of relatively simple macrocyclic metal chelating agents (specifically containing the 18-crown-6 unit) that also contained a hydrogen-bond donor to see if rate acceleration was possible.

Experimental Findings. Our longer-term goal is to construct a catalyst that contains a spacer unit capable of separating the metal chelating unit from the hydrogen bond donor unit (see structure **A** in figure). However, before investing considerable effort to prepare these types of compounds, we sought to examine if a reaction rate enhancement would be possible with more simple constituents. In Stage 1, attempts were made to prepare a novel imidazolyl sulfonate leaving group (compound **B**).[4] These attempts were unsuccessful and thus we turned to a more conventional leaving group (tosylate) for these feasibility studies. Using an excellent hydrogen bond (H-bond) donor (diBoc-thiourea), we performed a series of aliphatic nucleophilic bromination reactions in the presence of 18-crown-6 and KBr. Based on these experiments, it does not appear that added thiourea enhances the reaction rate; this may suggest that H-bonding does not occur (as in structure **C**). In Stage 2, we examined the same bromination reaction as in Stage 1 in the presence of a series of relatively simple mono- and di-substituted crown ethers.[5] These reactions were compared to those performed in the presence of 18-crown-6. In most cases, the substituted crown ethers were more efficient in dissolving the metal salts used as nucleophiles; however, substitution reactions (using KBr, $BaBr_2$, or NH_4Br) were slower compared to simple 18-crown-6. For example, the thiourea resulting from 18-crown-6-CH_2NH_2 (see structure **D**) was a superior PTA relative to 18-crown-6 for the salts examined; nevertheless, bromination reactions occurred more rapidly with 18-crown-6. We also prepared a tri-functional agent (structure **E**) with the expectation that an additional H-bonding unit would be capable of interacting with (and activating) the leaving group. This experiment will be performed as part of our future collaborative efforts.

Future Directions. Based on these results (especially those involving structure **D**), it seems that a more rigid spacer is needed between the crown ether and H-bond donating unit (as in structure **A**). These will be created (by the Lepore group) and examined as potential catalysts. In addition, researchers in the Mandolini group will attempt to directly examine potential H-bonding interactions in these catalyst systems using instrumental techniques such as NMR.



[1] (a) Al-huniti, M. H.; Lu, S.-Y.; Pike, V. W.; Lepore, S. D. Enhanced Nucleophilic Fluorination and Radiofluorination of Organosilanes Appended with Potassium-Chelating Leaving Groups, J. Fluor. Chem. 2014, 158, 48; (b) Lu, S.-Y.; Lepore, S. D.; Li, S. Y.; Mondal, D.; Cohn, P. C.; Bhunia, A. K.; Pike, V. W. Nucleophile Assisting Leaving Groups: A Strategy for Aliphatic ^{18}F-Fluorination *J. Org. Chem.* **2009**, *74*, 5290.

[2] For their more recent work see: (a) Salvio, R.; Cacciapaglia, R.; Mandolini, L. General Base Guanidinium Cooperation in Bifunctional Artificial Phosphodiesterases. *J. Org. Chem.* **2011**, *76*, 5438–5443; (b) Baldini, L.; Cacciapaglia, R.; Casnati, A.; Mandolini, L.; Salvio, R.; Sansone, F.; Ungaro, R. Upper Rim Guanidinocalix[4]arenes as Artificial Phosphodiesterases. *J. Org. Chem.* **2012**, *77*, 3381−3389.

[3] This idea was inspired in part by: Pliego, J. R.; Pilo-Veloso, D. Chemoselective Nucleophilic Fluorination Induced by Selective Solvation of the S_N2 Transition State. *J. Phys. Chem. B* **2007**, *111*, 1752-1758.

[4] Lepore, S.D.; Mondal, D. Recent Advances in Heterolytic Nucleofugal Leaving Groups *Tetrahedron* **2007**, *63*, 5103-5122.

[5] These compounds are not commercially available and were prepared by the Lepore group prior to the STM research period following our recently published methods: Jana, S.; Suresh, V.; Lepore, S. D. Synthesis of Novel C-Pivot Lariat 18-Crown-6 Ethers and their Efficient Purification. *Synlett* **2015**, *26*, 1977.