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New Reactivity Mediated by Trimethylsilyl Trifluoromethanesulfonate

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The common goal of the projects described below is to discover new reactivity mediated by trimethylsilyl trifluoromethanesulfonate (TMSOTf) through its ability to react both as a Lewis acid and as a thermodynamic silylating agent. Over the past twelve months, significant progress has been made on a variety of fronts as summarized below.

A. Addition of Nitriles to Aldehydes

Nitriles are common laboratory solvents and often function as masked carboxylic acid derivatives. The ability of (trimethylsilyl)acetone nitrile (TMSACN) to act as a mild nucleophile in the presence of a nucleophilic catalyst has been adequately investigated, but the reactivity of α -silylnitriles under Lewis acidic catalysis is virtually unknown. We recently discovered the ability of TMSACN to efficiently add to aldehydes. Several aldehydes have been reacted with TMSACN under similar conditions, and further expansion of the reaction scope is ongoing (eq 1). Most aromatic aldehydes tested so far react with good yields, especially electron-poor aromatics. This family of projects has importance for the career of the PI because it is the first example of TMSOTf-catalyzed reaction to

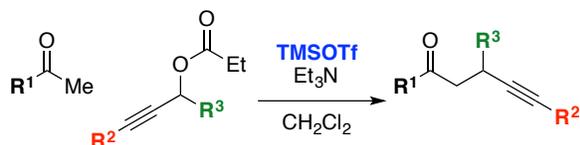


appear from the group that does not require an amine base as co-catalyst. Two student summer stipends funded by ACS have supported 1) a current senior who is applying to chemistry graduate school, and 2) a current junior who plans to apply to medical school.

B. Reactivity of Propargyl Alcohols and Propargyl Carboxylates

An early attempt to synthesize propargyl silanes involved the activation of propargyl acetates with silyl

Table 1. Reaction scope for alkylation with propargyl carboxylates: selected reactions

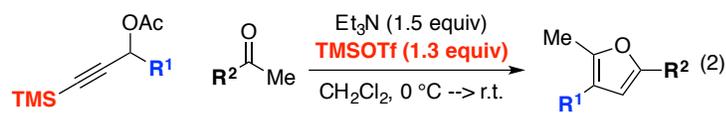


R ¹	R ²	R ³	yield (%)
4-(MeO)Ph	Ph	Ph	97
1-naphthyl	Ph	Ph	87
PhS	Ph	Ph	76
<i>n</i> -Bu	4-ClPh	Ph	84
TES	<i>n</i> -Bu	Ph	94
Ph	TES	Ph	39
Ph	Ph	4-(MeO)Ph	84
Ph	Ph	4-(CF ₃)Ph	71

triflates. Although attempts to trap the resultant propargyl cations with silyl anions failed, ionization of the substrate was very successful under our conditions and the cation could be easily trapped by an enol silane formed in situ from TMSOTf and Et₃N. The reaction yielded primarily the β -alkynyl ketone (Table 1). Minor amounts (typically <5%) of the allene product were sometimes observed.

A survey of reactivity across a range of ketones proceeded with good results (Table 1), including the reaction of a thioester substrate. In general, more consistent results were observed if the acetate leaving group was replaced by a propionate, which slows the ionization step somewhat and helps to prevent rapid decomposition of the propargyl substrate. Our current results show a wide range of substitution is tolerated at the alkynyl position (R¹), including aryl, alkyl, and silyl components. Substitution at the propargyl position (R²) showed considerable tolerance, but electron-rich aryl substituents and secondary alkyl substituents at that position resulted in undesired decomposition.

Close study of the reactivity of the triethylsilyl-substituted substrate revealed that an alternative reaction path sometimes occurs. Under very mild reaction conditions, the alkylation product undergoes spontaneous cyclization, aromatization, and desilylation to yield 2-methylfurans (eq 2). Investigation of the reaction scope and mechanism of this reaction is ongoing. Yields observed so far have ranged from 78-83% for various aryl methyl ketones. This reaction marks the first heterocycle synthesis achieved in our group achieved through the action of

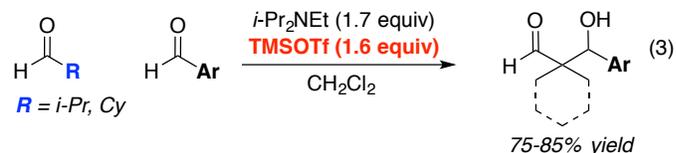


TMSOTf. The enol silane formation-alkylation portion of the project is now complete, and a manuscript has been submitted for publication. The student primarily developed this project is now a chemistry graduate student at Yale University. Of the other other two students who worked on this project, one enrolled in Fall 2018 in chemistry

graduate school at Northwestern University, and the plans to apply to chemistry graduate schools in the fall of 2018. The furan synthesis project has been studied by a current junior who now plans to attend graduate school, and her summer stipend in 2017 was paid by ACS-PRF funds. This alkylation chemistry is the basis for a pending grant proposal at the National Science Foundation, which if awarded would stabilize the funding of the PI's laboratories for the next four years.

C. One-Pot Enol Silane Formation-Mukaiyama Aldol Couplings of Aldehydes

Controlling crossed aldol reactions between two different aldehydes, where one aldehyde generates the enolate and the other acts as the electrophile, is complicated by the possibility of role reversal, which can generate competing aldol addition products. We have discovered that the use of hindered aldehydes (e.g., *i*-PrCHO or CyCHO) with our TMSOTf/R₃N system allows ready enol silane formation at -78 or 0 °C. This stable enol silane

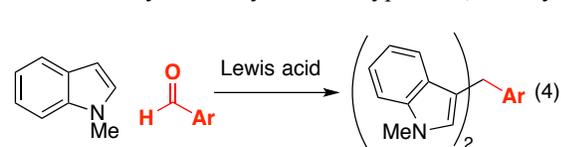


can then be treated with a second aldehyde, which leads to crossed Mukaiyama aldol addition through catalysis by residual TMSOTf to yield α,α -disubstituted aldehydes (eq 3). Notably, these hindered aldehyde products do *not* act as electrophiles with any remaining enol silane,

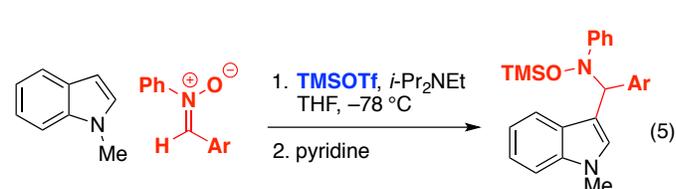
making this reaction extremely chemoselective. This project has been spearheaded by a current senior whose summer stipend in 2017 was funded by ACS-PRF. He plans to apply to graduate school in chemistry following a gap year. This project is slated for publication within the year.

D. Addition of N-Alkylated Indoles to α -Aryl Nitrones

The Friedel-Crafts addition of indoles to aryl aldehydes has traditionally been hampered by the generation of a thermodynamically favored byproduct, a triarylmethane derived from two indoles and one aldehyde (eq 4). The



identical byproduct also typically prevails during the related Friedel-Crafts addition of indoles to nitrones derived from those same aryl aldehydes. Very recently, we have discovered that the use of a TMSOTf/R₃N system to promote this transformation leads to the selective formation of 1:1



indole:nitron adducts, a product type not currently known in the literature (eq 5). It is speculated that the bulk of the trimethylsilyl group slows coordination of acidic species to the hydroxylamino group, which in turns slows ionization of the desired product and downstream production of the undesired byproduct. Several

examples of this reaction have now been achieved, and the scope of the reaction is currently under study in our laboratory. This project is the responsibility of a current senior at the University of Richmond who is in the process of applying to chemistry graduate school. His summer stipend in 2018 was funded by ACS-PRF. The reaction was discovered by another student who is now a chemistry graduate student at Emory University. This project is an important example of the importance of the PI's program because it shows that the TMSOTf/R₃N system is capable of achieving reactivity unknown with other systems.