

PRF# 56852-UNI1

Development of a Novel and Versatile Method for the Synthesis of Substituted Cyclobutanes

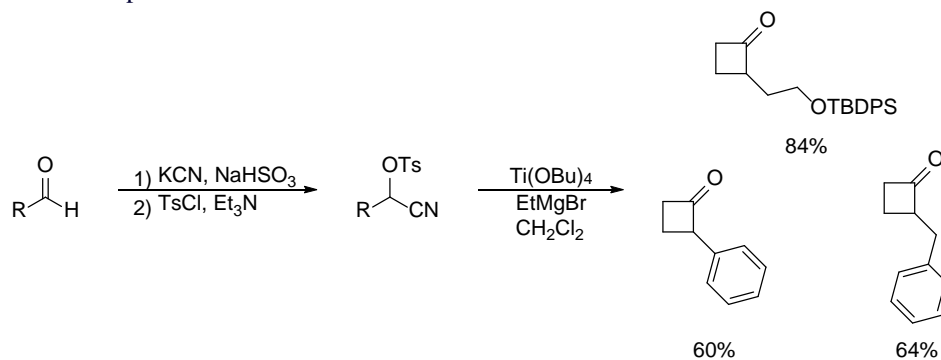
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Introduction

Substituted cyclobutanes have generated increasing interest in the fields of polymer, materials, and pharmaceutical sciences. For example, the strain associated with the reduced bond angle of cyclobutane rings make them useful reactive intermediates in organic synthesis and has served as active functional groups in stress-responsive polymers. In spite of this increasing interest, there is a paucity of methods for the synthesis of cyclobutanes, especially compared to other ring sizes. This grant has provided funding for research focused on the development of a novel method for the synthesis of substituted cyclobutanes using low-valent titanium (Kulinkovich) intermediates. Fortuitously, this project has resulted in a new application for these reagents. It has been discovered that these homogeneous low-valent titanium species can be used to synthesize valuable 1,4-diketones.

Synthesis of Cyclobutanones

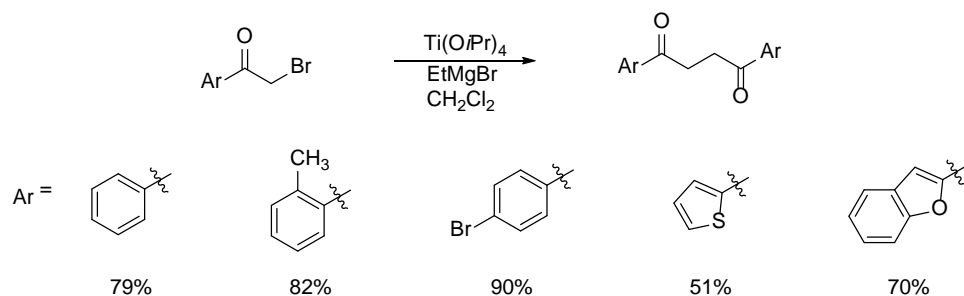
While many studies have explored the reaction of Kulinkovich reagents with esters, amides, and nitriles to form cyclopropanols, there have been no reports of reactions with dielectrophilic compounds. It was postulated that 1,2-dielectrophiles would react with these low-valent titanium species to afford substituted cyclobutane rings. To test this hypothesis, tosylated cyanohydrins were synthesized from commercially available aldehydes through a simple two-step process. When exposed to Kulinkovich conditions, the expected cyclobutanone was formed in 60% to 84% unoptimized yield, depending on the substrate. Significant optimization of this reaction was conducted. A variety of solvents and titanium(IV) reagents were explored; ultimately titanium(IV) butoxide in a solution of dichloromethane provided the optimal results. Currently, a variety of substrates, including enantioenriched cyanotosylates, are being explored to probe the scope of this reaction.



Synthesis of 1,4-Diketones

In an attempt to expand this methodology, 2-bromoacetophenone was subjected to Kulinkovich conditions. Surprisingly, the reaction resulted in a dimerization reaction that cleanly afforded a 1,4-diketone. These organic moieties are valuable building blocks for the synthesis of five-membered heterocyclic compounds, such as furans, thiophenes, and pyrroles. In a recent publication,¹ we disclosed the synthesis of eleven 1,4-diketones from α -haloketones indicating a large tolerance for a variety of functional groups, including heteroaromatics. Additionally, we have provided evidence that this reaction occurs through radical enolates that are formed by the generation of titanium(III) species. Further explorations to exploit this mode of reactivity has generated a new direction in the research of these low-valent titanium complexes.

¹ Le, N. N.; Rodriguez, A. M.; Alleyn, J. R.; Gesinski, M. R. "Synthesis of 1,4-Diketones via Titanium-Mediated Reductive Homocoupling of α -Haloketones." *Synlett*, **2018**, 29, 2195–2198.



Impacts of this Grant

This grant has had a profound positive effect on both the primary investigator and the students that have participated in this project. Through this funding program, five undergraduate students and the PI were able to completely immerse themselves in this research program during eight weeks over two summers. It has also led to a publication in a peer-reviewed journal that included three undergraduates as co-authors. Finally, the travel award in this grant has allowed the PI and students to travel to national meetings in San Francisco, CA, Davis, CA, and an upcoming meeting in Indianapolis, IN. These experiences are transformative for students conducting research at primarily undergraduate institutions as it allows them to interact with a wide variety of scientists at the forefront of their fields. Ultimately, this has laid the foundation for a sustainable research program in organic chemistry at Southwestern University and significantly contributed to the career of the PI. It is expected that this will lead to future successful grant applications from other funding organizations such as the National Science Foundation and the National Institute of Health.