RECENT DEVELOPMENTS IN THE ANTI-DIHYDROXYLATION OF ALKENES
Reported by Thomas Bearrood

October 4th, 2016

INTRODUCTION

Vicinal diols (1,2-diols) are a common motif found in many natural products ranging from simple sugars to complex polyketides. Given this, considerable effort has been directed towards dihydroxylation of readily available alkene precursors. Most of the work in this area has involved development of reagents for syn-dihydroxylation including notable metal oxide catalysts such as OsO$_4$ and RuO$_4$. These syn-dihydroxylation reagents afford selectivity between two potential diastereomers if control of E or Z alkene formation can be achieved. However, for cyclic alkenes and examples where alkene isomerization is impractical, controlled anti-dihydroxylation is needed. This demand has spurred the development of new methods for the selective production of anti-1,2-diols.

RECENT ADVANCES

1,3-Dioxan-2-ylum Ion Ring-opening

First reported by Prévost in 1933, one of the original approaches towards anti-dihydroxylation proceeds through of a 1,3-dioxan-2-ylum ion intermediate. Under wet conditions this reactive intermediate opens to yield the syn-diol, but under anhydrous conditions it can open to afford the anti-diol via nucleophilic attack by a carboxylate (Scheme 1). More recently, alternative conditions to generate the 1,3-dioxan-2-ylum ion intermediate have been reported using a reactive cyclopropyl malonyl peroxide, as well as (diacetoxyiodo)benzene with a Lewis acid catalyst. In both cases, the desired diol is generated after nucleophilic attack with a carboxylate and saponification. Using a chiral hypervalent iodine, Fujita demonstrated the enantioselective formation of the 1,3-dioxan-2-ylum ion on styrenes which ring-opens to an enantiomerically enriched anti-1,2-diol.

Radical-mediated Dihydroxylation

One of the least explored methods for anti-diol formation is radical dioxygenation. In this regard, Alexanian describes the hydroxamic acid directed dioxygenation of an alkene (Scheme 2). Early examples required an attached hydroxamic acid, but optimization enabled intermolecular reactions to take place. Starting from cyclic...
alkenes, anti-1,2-diols were achieved in diastereomeric ratios between 2:1 and 6:1. The use of atmospheric oxygen as a reagent is economical and convenient; however, this reaction exhibits poor stereocontrol.

**Asymmetric Epoxide Ring-opening**

Arguably, the most developed method for anti-dihydroxylation involves epoxide ring-opening. Recent examples include the enantioselective ring-opening of meso-epoxides. Numerous conditions have been explored, but the common mechanism involves activation of the epoxide by a chiral catalyst. For instance, Schneider employs a chiral scandium catalyst to achieve high selectivity on meso-stilbene oxide derivatives but only modest stereoselectivity for alkyl derivatives. 

Meanwhile, a chiral gallium catalyst enabled Shibasaki to achieve good to high enantioselectivity on numerous cyclic and acyclic meso-epoxide substrates. In addition to metal-catalyzed reactions, List developed a chiral phosphoric acid catalyst which facilitated consistently high enantioselectivity. Notably, in each of the aforementioned protocols, a different oxygen source was used – an aliphatic alcohol, a phenoxide, and a carboxylate, respectively – leading to monoprotected diols which could subsequently generate the desired diol upon deprotection.

**FUTURE DIRECTIONS**

Significant progress has been made in synthetically useful anti-dihydroxylations, but shortcomings still exist. General selectivity over side reactions remains a challenge for 1,3-dioxan-2-ylion ring-opening and radical anti-dihydroxylations. However, to maximize the synthetic utility of anti-dihydroxylation in complex molecule synthesis, selectivity in the ring-opening of asymmetric epoxides is necessary as well as demonstration of functional group tolerance.

**REFERENCES**