RECENT DEVELOPMENTS IN THE ANTI-DIHYDROXYLATION OF ALKENES

Reported by Thomas Bearrood October 4th, 2016

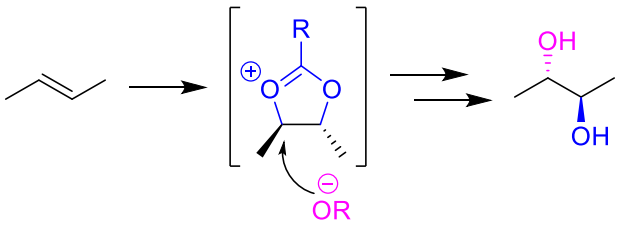
INTRODUCTION

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.[1] 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.[2] 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-ylium Ion Ring-opening

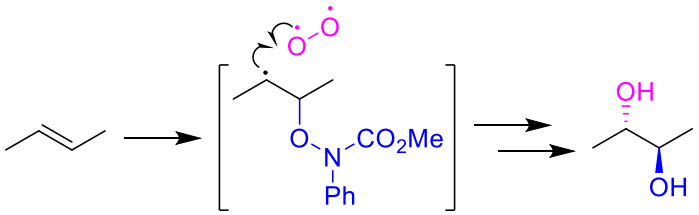
First reported by Prévost in 1933, one of the original approaches towards anti-dihydroxylation proceeds through of a 1,3-dioxan-2-ylium ion intermediate. Under wet conditions this reactive intermediate opens to yield the syn-diol, but under anhydrous conditions it can open to afford the anti-diol via nucleophilic attack by a carboxylate (Scheme 1). More recently, alternative conditions to generate the 1,3-dioxan-2-ylium ion intermediate have been reported using a reactive cyclopropyl malonyl peroxide, as well as (diacetoxyiodo)benzene with a Lewis acid catalyst.[3,4] 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-ylium ion on styrenes which ring-opens to an enantiomerically enriched anti-1,2-diol.[5]



Scheme 1. Anti-dihydroxylation through a 1,3-dioxan-2-ylium ion intermediate. R = acyl

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,[6] but optimization enabled intermolecular reactions to take place.[7] Starting from cyclic



Scheme 2. Radical anti-dihydroxylation with hydroxamic acid and molecular oxygen.

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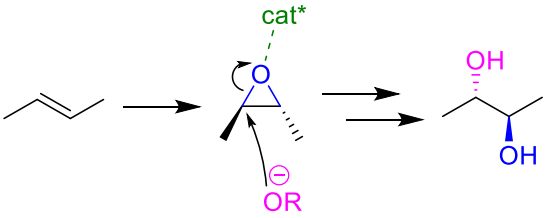
alkenes, anti-1,2-diols were achieved in diastereomeric ratios between 2:1 and 6:1. The use of atmospheric oxygen as a reagent is economical and convenient; however, this reaction exhibits poor stereocontrol.

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.[8] Meanwhile, a chiral gallium catalyst enabled Shibasaki to achieve good to high enantioselectivity on numerous cyclic and acyclic meso-epoxide substrates.[9] In addition to metal-catalyzed reactions, List developed a chiral phosphoric acid catalyst which facilitated consistently high enantioselectivity.[10] 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.



Scheme 3. Anti-dihydroxylation via epoxide ring-opening. cat* = chiral catalyst

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-ylium ion 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.

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