

RECENT ADVANCES IN ASYMMETRIC BAEYER-VILLIGER OXIDATIONS

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INTRODUCTION

Discovered in 1899, the Baeyer Villiger (BV) reaction has been widely used in natural product and pharmaceutical synthesis to transform ketones into esters or lactones.¹ This is achieved through nucleophilic attack of the carbonyl by a peroxide to form a “Criegee intermediate” followed by rearrangement to the ester or lactone. Asymmetric BV oxidation is especially useful in the synthesis of chiral lactones to produce enantioenriched products. However, the regioselectivity of these reactions is often challenging to control. The first examples of asymmetric BV were reported independently in 1994 by Bolm and Strukul utilizing copper and platinum complexes, respectively.¹ In the past decade, many advances have been made using metal catalysts and organocatalysts to increase enantio- and regioselectivity.

METAL CATALYST-MEDIATED ASYMMETRIC BV

In order to increase enantioselectivity in the BV oxidation of 3-arylcyclobutanones, Sandaroos and coworkers utilized a Co(salen) catalyst (Figure 1).² This catalyst provides two coordinating sites to form a chelated Criegee intermediate. The γ -lactones were obtained with good enantioselectivities (up to 80% ee); however, the differing substituents on the substrate had a pronounced influence on these values. In addition, Sandaroos synthesized a polymer-supported version of the same catalyst, which gave high catalytic efficiency without the loss of enantioselectivity.

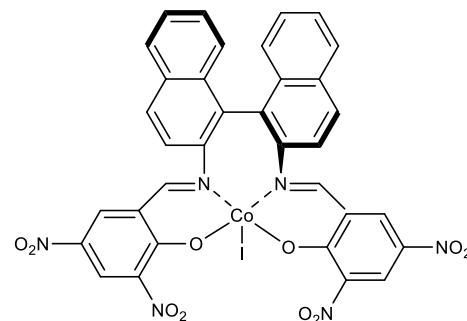


Figure 1. Sandaroos' Co(salen) catalyst

In 2012, Feng and coworkers harnessed the catalytic ability of *N,N'*-dioxide-Sc(III) complexes to perform BV oxidations on a number of substrates (Figure 2).³ For prochiral cyclobutanones and cyclohexanones, the steric bulk of the Sc(III) ligands proved crucial in producing highly enantioenriched products. Both aryl and alkyl substituents were well-tolerated with good yields (up to 90%) and high enantioselectivities (up to 95% ee). Feng further expanded this methodology towards kinetic resolution of various cyclic ketones.^{4,5} Notably, the BV reaction with 2-substituted cyclohexanones resulted in formation of the abnormal lactones produced with excellent enantioselectivities

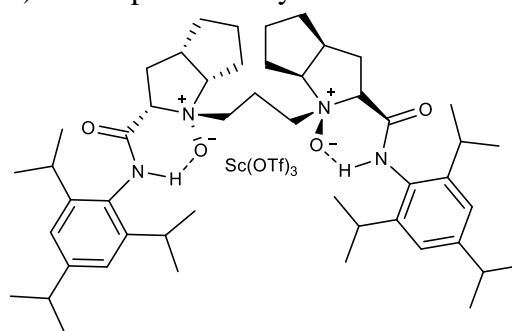


Figure 2. Feng's *N,N'*-Dioxide-Sc(III) catalyst

(up to 99%) as the major product due to steric reasons. This same reversal of migratory aptitude was not seen with cyclobutanones or cyclopentanones, suggesting that both ring strain and steric interactions between substrate and catalyst play important roles in regioselectivity.

ORGANOCATALYST-MEDIATED ASYMMETRIC BV

Organocatalytic BV oxidations are much less explored as compared to metal catalysts. The first example was reported by Ding and coworkers in 2008 using a chiral Bronsted acid, specifically a chiral phosphoric acid, in the BV reaction with prochiral cyclobutanones.⁶ Ding and coworkers later expanded their work to include tricyclic and bicyclic cyclobutanones as substrates.⁷ Initial testing showed low enantiocontrol; however, the catalytic performance and enantioselectivity were both significantly improved by fine-tuning the chiral environment around the phosphoric acid (Figure 2). Mechanistic studies supported Ding's hypothesis that phosphoric acid functions as a bifunctional catalyst activating the reactants and the Criegee intermediate. Inspired by this work, Miller and coworkers developed a phosphothreonine-based chiral peptide for use in the BV reaction of cyclobutanones.⁸ This peptide was specifically designed to interact with substrates through numerous noncovalent interactions, thereby increasing enantioselectivity (up to 94% ee).

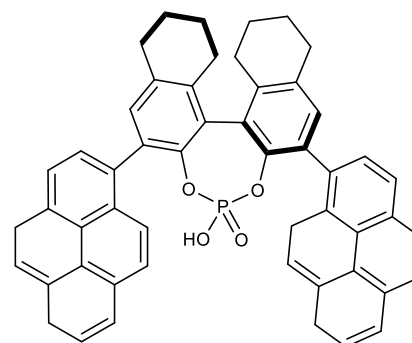


Figure 2. Ding's chiral phosphoric acid catalyst

SUMMARY AND OUTLOOK

Even though the Baeyer-Villiger reaction of ketones was discovered over 120 years ago, a highly enantioselective version has proven difficult to achieve. In the past decade, significant progress has been made in the BV oxidation of cyclic ketones utilizing both metal and organocatalysts. The resultant lactones can be produced in high yield with moderate to high enantioselectivity. Despite this progress, there is still much research to be explored. Currently, catalysts must be fine-tuned for each specific substrate, and the overall substrate scope is still fairly limited.

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