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Digest paper

# Mechanistic aspects of alkene oxidation using chiral hypervalent iodine reagents

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ABSTRACT

Recent progress in the area of hypervalent iodine-induced enantioselective oxidation is reviewed with emphasis from a mechanistic point of view. Chiral lactate and lactamide sidechains in hypervalent iodine reagents induce herical chirality around the iodine reaction site, which provides a chiral environment suitable for enantioselective transformations. The stereochemical outcomes of alkene oxidation are also compiled and used for systematically understanding the reaction mechanism of oxidative double bond difunctionalization.



**Contents**

Introduction . . . . 4409
Essentials of oxidative alkene difunctionalization using hypervalent iodine . . . . 4409
Chirality of hypervalent iodine induced by a lactate motif . . . . 4411
Oxidative difunctionalization with *syn*-selectivity . . . . 4412
Switchover between *syn*- and *anti*-difunctionalizations . . . . 4413
Stereochemical courses in *anti*-difunctionalization . . . . 4413
Rearrangement of aryl groups . . . . 4416
Oxidative cyclization of terminal alkenes . . . . 4417
Related reagents having the lactate motif . . . . 4418
Conclusion and outlook . . . . 4418
Acknowledgement . . . . 4418
References . . . . 4418

## Introduction

Hypervalent iodine compounds have been used for numerous chemical oxidations under mild conditions.[1] In particular, recent developments in chiral hypervalent iodine reagents for asymmetric oxidation has permitted highly stereocontrolled transformations,[2] including several types of alkene functionalizations.[3] This review summarizes recent advances in the field of enantioselective alkene oxidation from mechanistic point of views, including the origin of stereoinduction from a series of chiral hypervalent iodine reagents, and systematically compiling the stereochemical outcomes of alkene functionalization.

## Essentials of oxidative alkene difunctionalization using hypervalent iodine

Oxidative 1,2-difunctionalization of alkenes with hypervalent iodine reagents offers an attractive and powerful strategy for constructing diverse molecular complexity. The reaction can simultaneously introduce two vicinal functional groups in a stereoselective manner. A wide range of heteroatom functional groups, such as oxygen, nitrogen, halogen, and sulfur nucleophiles,

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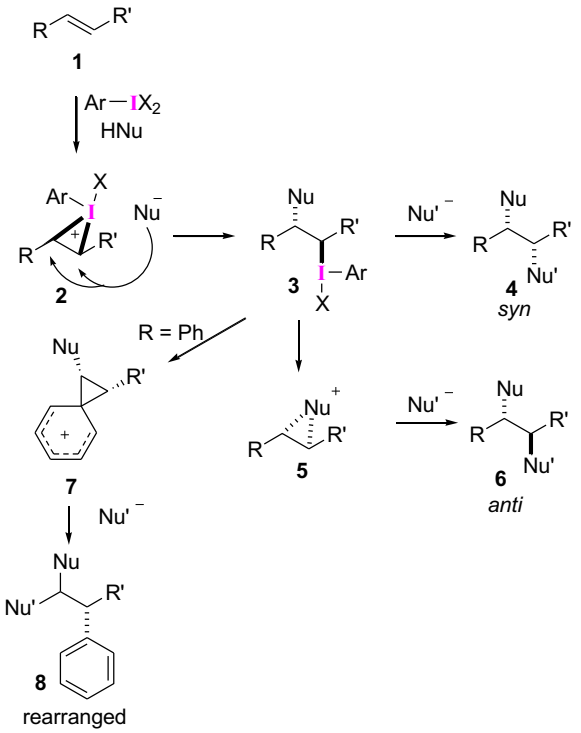
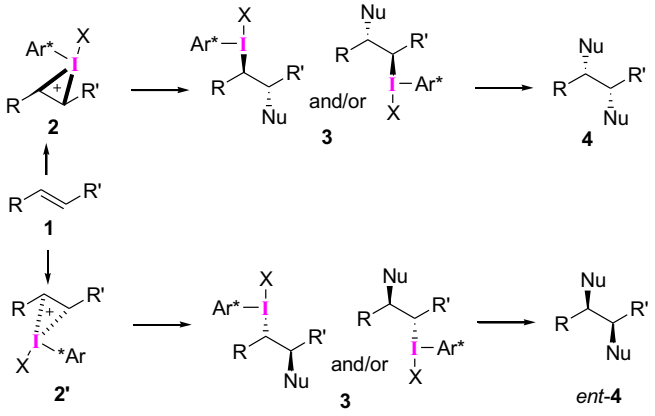


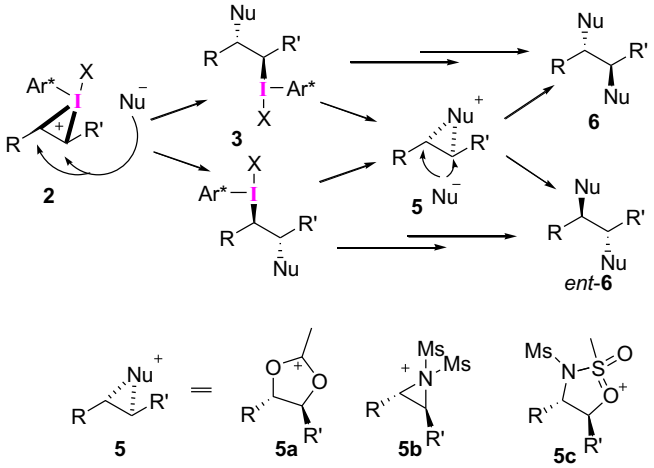

**Scheme 1.** Typical pathways of alkene oxidation with hypervalent iodine.

becomes attached to the carbon–carbon double bond. In addition to these heteroatom nucleophiles, the incorporation of a carbon nucleophile has recently been achieved. The combination of two nucleophiles leads to various kinds of difunctionalized products. As a further variation on this theme, an intramolecular nucleophile attached to the alkene substrate enables a cyclization transformation.

A typical reaction mechanism for oxidative functionalization of an alkene with hypervalent iodine(III) is shown in Scheme 1. The electrophilic reactivity of the hypervalent iodine compound can be enhanced by an acid additive. Shafir and coworkers have recently studied the phenomenon of (dicarboxyiodo)benzene acid-activation using NMR measurements, DFT calculations, and single crystal characterization.[4] The electron-deficient iodine reagent, which is activated by acid, makes a complex with the olefin's π-orbital. Complex **2** undergoes initial nucleophilic substitution with Nu at the carbon bearing the greater positive charge. In




**Scheme 2.** Facial selectivity in *syn*-difunctionalization.



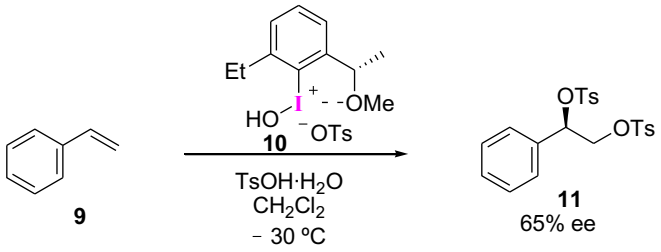

**Scheme 3.** Stereochemical course in *anti*-difunctionalization.

the case of styrene, as a typical example, the initial nucleophilic attack takes place at the benzylic position, where a positive charge may be localized. The iodane intermediate **3** readily receives nucleophilic substitution owing to its excellent leaving ability. The subsequent nucleophilic substitution with Nu' simply leads to the 1,2-difunctionalized product **4** with *syn*-selectivity.

In some cases, anchimeric assistance is provided during the subsequent nucleophilic substitution of **3**. In Scheme 1, the Nu functional group contributes to the assistance to yield an onium ion intermediate **5**. Inverted attack of a nucleophile, Nu', to intermediate **5** yields *anti*-product **6** as the result of double inversion. The other groups, R and R', can nucleophilically participate to the double inversion mechanism. If the phenyl group participates as a nucleophilic R group, rearrangement takes place via benzenium ion intermediate **7**.[5]

In an enantioselective variant of the oxidative difunctionalization of alkenes, facial-selective addition of the hypervalent iodine reagent to the olefin is one of the key steps that determine this enantioselectivity (Scheme 2). In the case of usual *syn*-selective difunctionalization, the order of the two subsequent nucleophilic substitution steps does not affect the stereochemical outcome.

On the other hand, the stereochemical outcome in *anti*-difunctionalization is affected by the double inversion position, as shown in Scheme 3. When *anti*-difunctionalized product **6** is obtained through symmetrical onium intermediates, such as 1,3-dioxolan-2-yl cation **5a**[6] and aziridinium **5b**,[7] the absolute configuration of the product is switched over depending on the position of nucleophilic ring-opening. The *anti*-product **6** can also be achieved via an unsymmetrical intermediate such as **5c**.[8] In this case, the ring opening position is fixed; thus, the initial position of nucleophilic attack on the iodine-olefin complex **2** determines the stereochemical outcome.




**Scheme 4.** Pioneering enantioselective dioxytosylation of styrene.