Asymmetric Synthesis

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Chiral Hypervalent Iodine Reagents in Asymmetric Reactions**

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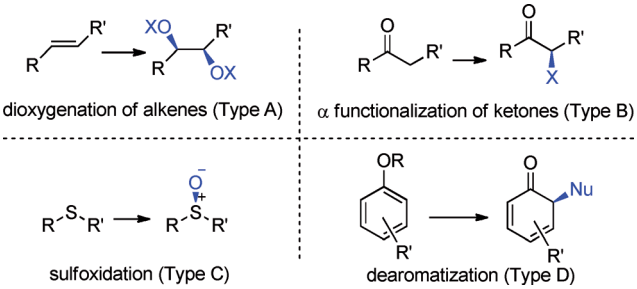
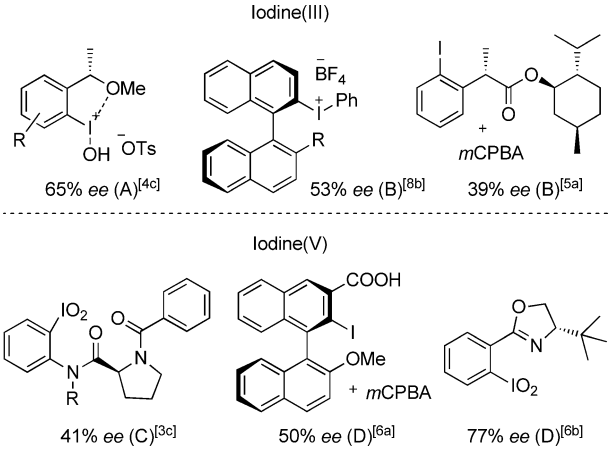
C_2 symmetry · dearomatization · hypervalent compounds · organocatalysis · spirolactonization

Hypervalent iodine reagents are unusually effective promoters of transformations that would be difficult, perhaps impossible, to accomplish otherwise. Low toxicity, a favorable safety profile, ease of handling, and an environmentally benign nature make them particularly attractive as agents for metal-free reactions.[1] Their unique reactivity inspires the exploration of powerful new strategies that simplify the synthesis of complex molecules, as apparent from an ever increasing number of papers and reviews.[2] A rapidly expanding area of research focuses on asymmetric transformations induced by chiral hypervalent iodine species. Activity in this field may be traced to a pioneering report on the enantioselective oxidation of sulfides to sulfoxides.[3] Notable asymmetric reactions developed since include alkene dioxygenation,[4] α oxygenation of ketones,[5] and oxidative dearomatization of phenols (Scheme 1).[6]

Chiral reagents based both on I^{III} (λ^3) and I^{V} (λ^5) have been described, some of which may be conveniently generated in situ by oxidation of appropriate iodoarenes and used in a catalytic,[7] substoichiometric, or excess amount. The chiral elements present in these agents are drawn either from the chiral pool or from scaffolds that have been extensively employed in transition-metal-catalyzed reactions (see examples in Scheme 2). The highest levels of asymmetric induction



Scheme 1. Asymmetric induction by chiral hypervalent iodine agents.



Scheme 2. Some recent chiral hypervalent λ^3- and λ^5-iodine reagents and precatalysts. The *ee* values are the highest achieved in reaction types A–D of Scheme 1 (letters in brackets). Ts = tosyl; *m*CPBA = *m*-chloroperoxybenzoic acid

achieved by the use of these reagents in reaction types A–D of Scheme 1 are in the range of 60–70% *ee*,[3–6,8] leaving much room for further research in the field.

A major breakthrough in this area is the advent of chiral species **4**, **6**, **15**, and **16**, which enable the conduct of highly enantioselective oxidative lactonization reactions, either through dearomatization of a phenol or by activation of a 2-alkenylbenzoic acid. Kita and co-workers developed C_2-symmetric iodine(III) reagent **4** for the oxidative dearomatization/spirolactonization reaction of naphthols (Scheme 3).[9] Thus, substrate **1** was oxidatively cyclized to **3** in up to 86% *ee*. By way of mechanism, the reaction could proceed through an "associative" pathway that forms intermediate **2**, which then undergoes intramolecular S_N2'-type displacement to afford product **3**, or by a "dissociative" one

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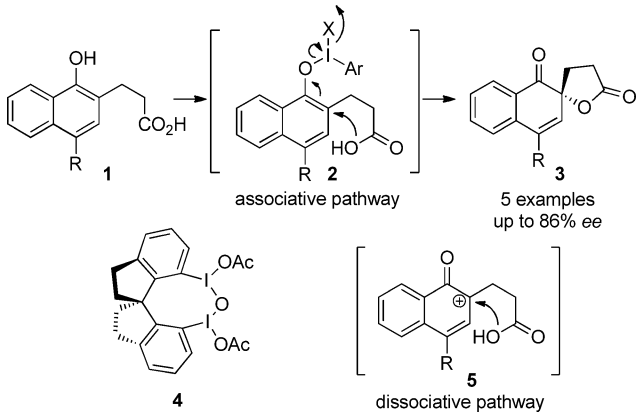
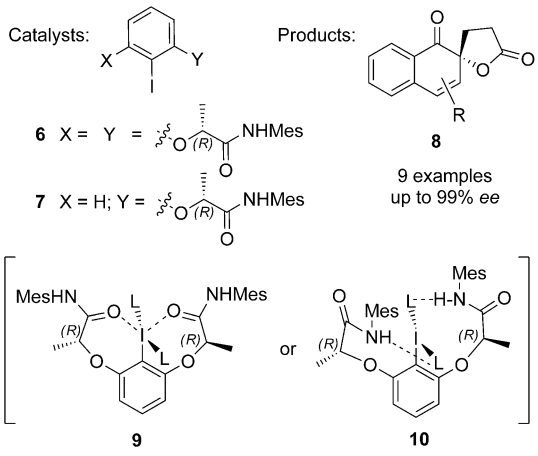


Scheme 3. Enantioselective spirolactonization and plausible reaction mechanisms, conditions: substrate (1 equiv), chiral λ^3-iodine (0.55 equiv), CH_2Cl_2 or $CHCl_3$, −50 °C or 0 °C.

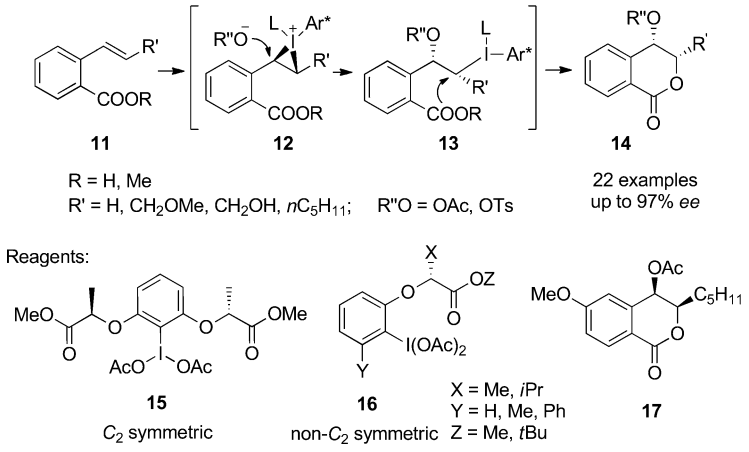


Scheme 4. Catalytic enantioselective spirolactonization by chiral hypervalent λ^3-iodines, conditions: substrate (1 equiv), precatalyst (10 mol%), *m*CPBA (1.3 equiv), CH_2Cl_2 or $CHCl_3$, −20 °C. Mes = mesityl

that generates a discrete phenoxenium ion such as **5**, which then collapses to **3**. The highest levels of asymmetric induction were observed for reactions carried out in nonpolar and moderately polar solvents such as CCl_4, CH_2Cl_2, and $CHCl_3$, rather than in polar ones such as $(CF_3)_3CHOH$, and with substrates carrying electron-withdrawing, rather than electron-donating substituents. These observations are consistent with an associative mechanism. A catalytic version of the same reaction afforded inferior enantiomeric excesses (up to only 69% *ee*).[9]

Compound **4** is conformationally rigid; however, such a molecular property appears not to be a sine qua non. To illustrate, Ishihara and co-workers discovered that a reactive iodine(III) species obtained in situ upon reaction of *m*CPBA with C_2-symmetric, conformationally flexible iodoarenes **6** induces similar spirolactonization reaction, but with a broader substrate scope (see Scheme 4).[10] In the presence of only 10 mol% of **6**, nine lactones **8** bearing electron-donating or -withdrawing groups were obtained in good to excellent yield and in up to 92% *ee* after isolation (99% *ee* after a single recrystallization). The active λ^3 catalyst may be stabilized by electron donation from the carbonyl groups of the lactic amides to the electron-deficient iodine(III) center, and/or may be activated by hydrogen bonding between the mesityl-protected NH groups and the oxygen ligands connected to the iodine atom (see structures **9** and **10**). Non-C_2-symmetric precatalysts such as **7** gave products with low *ee*.

A second class of chiral hypervalent iodine species developed in the Fujita group are effective promoters of the oxidative lactonization of 2-alkenyl benzoic acids and benzoates (Scheme 5).[11a] The new catalysts are also based on a lactate motif, and while some retain C_2 symmetry, others do not. An investigation of preparative and mechanistic aspects of the oxidative lactonization of substrates **11** has led to the mechanistic picture delineated below. Thus, an electrophilic iodine(III) species formed upon activation of **15** or **16** by *p*-toluenesulfonic acid (TsOH) or $BF_3{\cdot}OEt_2$ adds to the olefinic bond of **11** to give presumed intermediate **12**. Subsequent S_N2 displacement by acetate or tosylate affords λ^3-iodine complex **13**, which undergoes a second nucleophilic



Scheme 5. Oxylactonization of 2-alkenyl benzoate with a lactate-based hypervalent iodine, conditions: substrate (1 equiv), chiral λ^3-iodine (1.1–1.5 equiv), acid (0.7–1.5 equiv), CH_2Cl_2, −80 °C to −40 °C.

substitution to give product **14** with two *cis* substituents. Catalysts **15** or **16** afforded comparable extents of asymmetric induction, providing lactones **14** in 60–97% *ee*. As an application, an enantioselective synthesis of compound **17**, a naturally occurring aromatase inhibitor, was completed in 73% yield and 95% *ee* using a reagent of type *ent*-**16** (X = Z = Me, Y = H). This exercise, as well as the results obtained by the same research group in the area of asymmetric Prevost and Woodward diacetoxylation reactions,[11b] suggest that a lactate framework, rather than C_2-symmetry, is key to a high degree of asymmetric induction in the course of these transformations.

The examples presented herein illustrate the great potential of synthetic methods based on chiral hypervalent iodine reagents. Research is unveiling the structural requirements for a successful catalyst. Mastery of the factors that affect catalyst design, such as rigidity/flexibility and symmetry, along with mechanistic studies, will surely lead to exciting developments. The exploration of these reagents and their synthetic applications remains a fertile area of continuing research.[12]

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