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α -Functionalization of Carbonyl Compounds using Hypervalent Iodine Reagents

Eleanor A. Merritt, Berit Olofsson*

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden.

Fax: +46-8-154908.

E-mail: berit@organ.su.se.

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Key words: catalysis, asymmetric synthesis, oxidation, hypervalent iodine, C-C bond formation.

1 Introduction

α -Functionalized carbonyl compounds are versatile intermediates for the synthesis of a variety of heterocyclic compounds of medicinal interest, as well as natural products and related compounds. Many fields of organic chemistry provide elegant solutions to the challenges of α -functionalization of carbonyl compounds. In recent years, organocatalysis has become a versatile tool in this area, enabling the incorporation of a vast range of carbon and heteroatom electrophiles in an asymmetric fashion.^[1] Despite the success of organocatalysis in α -heterofunctionalization, α -arylation of carbonyl compounds is dominated by transition metal catalysis.^[2]

Hypervalent iodine compounds have recently received considerable attention as mild, non-toxic and selective reagents in organic synthesis.^[3] They are efficient alternatives to toxic heavy metal-based oxidants and expensive organometallic catalysts in many organic transformations. Several comprehensive reviews^[4] and books^[5] have been published on the topic of hypervalent iodine chemistry.

Iodine(V) reagents, such as Dess-Martin periodinane (DMP) and 2-iodoxybenzoic acid (IBX), are frequently used as mild oxidants of alcohol moieties in total syntheses of natural products. IBX can also effect oxidative transformations of a variety of other functional groups.^[6] Iodine(III) compounds with two heteroatom ligands, *e.g.* (diacetoxyiodo)benzene (PIDA), [bis(trifluoroacetoxy)]iodobenzene (PIFA) and iodosylbenzene, are employed in oxidations of

alcohols and alkenes, as well as in α -functionalization of carbonyl compounds.^[3] Figure 1 illustrates some of the common hypervalent iodine reagents that will be referred to throughout this review article. For the preparation of these reagents, the reader is referred to reviews on that topic.^[4]

Iodine(III) reagents with two carbon ligands have also been widely used in the α -functionalization of carbonyl compounds. Diaryliodonium salts are the most well known compounds in this class. Due to their highly electron deficient nature and hyperleaving group ability, they serve as versatile electrophilic arylating agents with a variety of nucleophiles.^[7]

Alkynyl(aryl)iodonium salts display somewhat similar properties, although the comparative lack of facile synthetic routes to this class of compounds has limited their use in synthetic chemistry.^[8]

Figure 1 Commonly used hypervalent iodine reagents.

Recent progress in hypervalent iodine chemistry involves the development of catalytic systems, thereby obviating the stoichiometric amount of iodoarene generally formed as a byproduct in these

reactions.^[3b, 9] After more than a decade of research into asymmetric reactions with hypervalent iodine reagents, a number of highly enantioselective reactions have recently been developed.^[10] With these breakthroughs in mind, hypervalent iodine compounds show great potential as environmentally benign and selective reagents in many, yet undiscovered transformations to come.

This review provides an overview of the use of hypervalent iodine reagents to α -functionalize carbonyl compounds, with focus on recent improvements, catalytic and asymmetric reactions. Moriarty and Prakash reviewed this topic in 1995 and 1999,^[11] since then the area has been covered only in general reviews on hypervalent iodine chemistry.

The article is divided into sections according to the group being introduced into the α -position, and each section is ordered with the catalytic and asymmetric variants of the transformation at the end. Reactions that deliver α -substituted carbonyl compounds from starting materials not containing this functional group are generally not covered. However, the use of silyl enol ethers is included in sections containing only few reports using carbonyl compounds. Likewise, reactions where the carbonyl group is present in the hypervalent iodine reagent, *e.g.* in iodonium ylides, are outside the scope of this review. Oxidative dearomatization of phenols, which can be considered as a special type of α -functionalization, has recently been reviewed and is therefore omitted.^[12]

2 Oxygenation

The α -hydroxycarbonyl group is of interest to synthetic chemists owing to its ubiquity in nature, occurring in polyketide, terpenoid and alkaloid natural products. The most widely used direct approach to α -oxycarbonyl compounds is *via* oxidation of an enolate, although metal-free organocatalytic methods are becoming more widespread.^{[13],[14]} Hypervalent iodine reagents provide a route to a range of α -oxygenated carbonyl compounds, obviating the need for anhydrous and anaerobic reaction conditions used in enolate reactions. Herein we shall discuss the major developments in hypervalent iodine-mediated α -oxygenation chemistry from its inception in the late 1970s to present day development of catalytic and asymmetric variants of these transformations.

2.1 Sulfonyloxylation

2.1.1 α -Sulfonyloxylation using HTIB and related reagents

The most numerous examples of α -oxygenation of carbonyl compounds are tosyloxylation reactions using [hydroxy(tosyloxy)iodo]benzene (HTIB). First

prepared in 1970 by Neilands and Karele,^[15] this versatile reagent was studied in detail by Koser and co-workers and is thus frequently referred to as Koser's reagent.^[16] Indeed Koser *et al.* were first to report the use of HTIB as an α -oxytosylating agent (Scheme 1).^[17]

Scheme 1 Koser's α -tosyloxylation of ketones using HTIB.

This work was subsequently extended by Lodaya and Koser to include α -mesyloxylation of ketones using [hydroxy(mesyloxy)iodo]benzene (HMIB).^[18] In 1990 Varvoglis *et al.* successfully prepared [hydroxy((+)-10-camphorsulfonyloxy)iodo]benzene and used this reagent in the α -(10-camphorsulfonyl)oxylation of a range of substrates including ketones, β -dicarbonyls and other carbonyls bearing an activated methylene group (Scheme 2).^[19]

Scheme 2 α -(10-Camphorsulfonyl)oxylation of carbonyls.

Over the years there have been many developments and modifications of the reaction, such as solvent-free α -sulfonyloxylation of ketones by grinding HTIB with a ketone using a pestle and mortar,^[20] and use of ultrasound.^[21] Nabana and Togo investigated the use of a range of [hydroxy(tosyloxy)iodo]arenes and [hydroxy(phosphoryloxy)iodo]arenes in the α -tosyloxylation and α -phosphoryloxylation of ketones respectively (Scheme 3).^[22] It was found that the incorporation of trifluoromethyl substituents *meta* to the iodine greatly enhanced the reactivity over the parent reagents.

Scheme 3 Novel [hydroxy(tosyloxy)iodo]arenes used by Nabana and Togo.

Lee and co-workers developed a rapid microwave-assisted method for the preparation of α -sulfonyloxyated carbonyl compounds using [hydroxy(2,4-dinitrobenzenesulfonyloxy)iodo]benzene.^[23] This methodology was subsequently extended to provide a route to α -hydroxyketones by forming [hydroxy(2,4-dinitrobenzenesulfonyloxy)iodo]benzene *in situ* from PIDA and 2,4-dinitrobenzenesulfonic acid using water as the solvent (Scheme 4).^[24] A similar method had been reported previously by Xie and Chen in which Koser's reagent was used in place of the more electron-deficient nitro-substituted reagent.^[25]

Scheme 4 2,4-Dinitrobenzenesulfonic acid in α -oxygenation of ketones. DNs = 2,4-Dinitrobenzenesulfonyl.

A recent application of the α -tosyloxylation reaction using Koser's reagent was reported in 2009 by Karade *et al.* in which addition of sodium sulfide nonahydrate to the reaction mixture resulted in formation of symmetrical ketodisulfides (Scheme 5).^[26]

Scheme 5 Synthesis of symmetrical ketodisulfides from enolizable ketones.

2.1.2 *In situ* Formation of HTIB

In situ formation of HTIB from various precursors is an increasingly common strategy in the preparation of α -tosyloxycarbonyl compounds. Tanaka and Togo recently reported an iodine(III)-mediated α -tosyloxylation of ketones in which a stoichiometric amount of 4-iodotoluene was oxidized using Oxone[®] in the presence of tosic acid (Scheme 6).^[27]

Scheme 6 4-MeC₆H₄I-mediated α -tosyloxylation of ketones.

More widespread is the use of iodine(III) precursors to HTIB, such as PIDA, 4-iodotoluene difluoride (TollIF₂), and iodosylbenzene. A solvent-free method for α -sulfonyloxylation of ketones was reported by Yusubov and Wirth in 2005 in which PIDA, a sulfonic acid and a ketone were ground together using a pestle and mortar.^[28] A microwave-assisted variant of this procedure has also been reported.^[29]

Zhang and co-workers recently published a detailed study on the α -oxygenation of β -dicarbonyls mediated by TollIF₂ using a range of oxygen-containing nucleophiles, including TsOH, MsOH, AcOH, diphenyl phosphate, MeOH, EtOH and ^tPrOH.^[30] A ligand exchange mechanism to form the necessary iodine(III) species *in situ* was postulated (Scheme 7), supported by NMR evidence. It is noteworthy that in most cases, these reactions proceed at room temperature in dichloromethane, as opposed to the standard conditions of reflux in acetonitrile.

Scheme 7 α -Oxygenation using TollIF₂.

Iodosylbenzene was used as the HTIB precursor by Togo and co-workers for both α -tosyloxylation of ketones and an oxidative α -tosyloxylation of alcohols (Scheme 8).^[31]

Scheme 8 Use of iodosylbenzene in α -tosyloxylation reactions.

Wirth and co-workers have reported the use of iodoxolone-based hypervalent iodine reagents in a number of transformations, including the preparation of α -tosyloxyketones.^[32] Novel fluorinated iodoxolones were demonstrated to enhance the rate of tosyloxylation reactions amongst others (Scheme 9).^[33]

Scheme 9 Wirth's use of iodoxolone-based reagents.

Karade *et al.* prepared an iodoxolone reagent similar to those used above by reacting DMP and TsOH. The resulting product **1** was found to be an efficient α -oxtosylating agent (Scheme 10).^[34]

Scheme 10 Karade's DMP-derived α -tosyloxylation reagent.

Although almost exclusively the domain of iodine(III) reagents, there are some examples of iodine(V) and even iodine(VII) reagents in α -tosyloxylation of carbonyl compounds. Mahajan *et al.* reported the use of reagents such as DMP, IBX, HIO₃ and HIO₄ in conjunction with TsOH or MsOH. DMP was found to be most effective under the conditions shown in Scheme 11.^[35]

Scheme 11 Iodine(V) in α -sulfonyloxylation reactions.

2.1.3 Recyclable Reagents

Over the past decade, several studies have been conducted in which various polymer-bound or other recyclable forms of hypervalent iodine reagents were used in the preparation of α -tosyloxyketones. In 2001, Togo and co-workers investigated the α -tosyloxylation of ketones using two poly[4-(hydroxy)(tosyloxy)iido]styrenes.^[36] Both reagents were able to α -oxtosylate ketones, in some cases more efficiently than HTIB (Scheme 12). These reagents can also be employed in the oxidative α -tosyloxylation of alcohols, forming α -tosyloxyketones directly.^[37]

Scheme 12 Polymer bound HTIBs. PS = polystyrene, average molecular weight 45,000; PMS = poly(α -methylstyrene), average molecular weight 6,200.

Nicolaou *et al.* prepared another polymer-bound variant of HTIB by treating a polystyrenesulfonic acid resin with PIDA. This enabled the preparation of resins loaded with α -sulfonyloxy ketones, which could subsequently be used to generate heterocycle and enediyne libraries (Scheme 13).^[38]

Scheme 13 Polystyrenesulfonic acid resin-based HTIB derivative.

Many recyclable HTIB-type reagents have been developed in recent years, examples of which are illustrated in Figure 2. An adamantane-based PIDA reagent was reported by Kita and co-workers in 2004.^[39] This reagent could be readily converted to a HTIB derivative (Figure 2) by reaction with TsOH, and then used in the tosyloxylation of propiophenone. The aryl iodide could be recovered almost quantitatively. Recyclable tetraphenylmethane-based reagents were subsequently developed by the same research group, and also proved useful in the α -sulfonyloxylation of ketones.^[40] Biphenyl and terphenyl-based HTIB reagents were reported by Moroda and Togo in 2006.^[41] These reagents demonstrated comparable reactivity to 4-(diacetoxyiodo)toluene and 4-[(hydroxy)(tosyloxy)iido]toluene, but with the benefit of being easily recovered by filtration of the reaction mixture.

Figure 2 Recyclable HTIB reagents used in α -tosyloxylation reactions.

In 2005, Handy and Okello prepared an ionic liquid variant of Koser's reagent that was successfully employed in the α -tosyloxylation of ketones (Scheme 14).^[42]

Scheme 14 Ionic liquid-supported Koser's reagent.

2.1.4 Catalytic and/or Asymmetric Reactions

In recent years, the focus of research in this area has shifted towards the development of catalytic protocols for the preparation of α -tosyloxyketones. Particularly prominent is the research of Togo and co-workers, who in 2006 developed an iodobenzene-catalyzed α -tosyloxylation reaction using *m*CPBA as the stoichiometric oxidant (Scheme 15).^[43]

Scheme 15 PhI-catalyzed α -tosyloxylation.

The scope of this work was later extended to include polymer-supported iodobenzene, and to enable the preparation of α -tosyloxyketones directly from alcohols,^[44] as well as ionic liquid-supported iodobenzene.^[45]

The development of an asymmetric variant of the iodine(III)-mediated α -tosyloxylation reaction has been ongoing for more than a decade. In 1997, Wirth and Hirt published the synthesis of several chiral HTIBs, together with the first application of such reagents in the asymmetric α -tosyloxylation of ketones (Scheme 16, compounds **2** and **3**).^[46]

Scheme 16 Asymmetric α -tosyloxylation of propiophenone.

Optimization of the chiral reagents by varying the substituents on the aromatic ring led to *ees* up to 28% (Scheme 16, compounds **4–6**).^[47] Further investigations showed that increased steric bulk of the ortho substituent improved the enantioselectivity. Compound **7**, bearing an ethyl substituent in the ortho position furnished α -tosylpropiophenone in 40% *ee*.^[48] In 2007 a catalytic asymmetric version of this reaction was reported using 10 mol% enantiopure iodoarene in conjunction with *m*CPBA as the stoichiometric oxidant (Scheme 17).^[49] With compound **7** as the catalytically active species, the product was obtained in 59% yield and 27% *ee* as the (*R*)-enantiomer.

Scheme 17 Catalytic asymmetric α -sulfonyloxylation of ketones.

It was proposed that Path B operates in this reaction, as in Path A, the stereocenter is distant from the α -carbon, thus enantio-induction would be unlikely. The use of enantiomerically pure esters as catalysts for this process was also investigated with menthyl- and fenchyl esters proving most successful (compounds **8** and **9** respectively; Figure 3), giving *ees* up to 39%.^{[50][51]}

Figure 3 Enantiomerically pure esters used in the asymmetric α -tosyloxylation of propiophenone.

2.2 Hydroxylation

As with α -tosyloxylation of ketones, the α -hydroxylation of carbonyl compounds using hypervalent iodine reagents has been known for a considerable length of time. Indeed, the first reported direct α -hydroxylation of ketones was published by Moriarty *et al.* in 1981 (Scheme 18).^[52]

Scheme 18 α -Hydroxylation of ketones using iodosylbenzene.

In the same year, Moriarty and co-workers also reported a PIDA-mediated conversion of carboxylate esters into either α -hydroxycarboxylic acids or α -alkoxyesters, the product depending on choice of solvent and base (Scheme 19).^[53] A multigram-scale variant of this reaction was also devised using 2-iodosylbenzoic acid.^[54]

Scheme 19 Preparation of α -hydroxycarboxylic acids or α -alkoxyesters from esters using PIDA.

In a departure from the more common use of basic reaction conditions, Moriarty subsequently developed a protocol for the α -hydroxylation of ketones under acidic conditions using PIFA and trifluoroacetic acid in acetonitrile-water (Scheme 20).^[55]

Scheme 20 α -Hydroxylation of ketones under acidic conditions.

For a more comprehensive discussion of the numerous significant contributions made to this field by Moriarty's group, including α -hydroxylation of acetals, which falls outside the scope of this article, the 2005 review article is referred to.^[56]

Polymer-supported hypervalent iodine reagents have also found application in the α -hydroxylation of ketones. Togo *et al.* reported a method similar to Moriarty's PIDA-mediated hydroxylation reaction using poly[4-(diacetoxyiodo)styrene] under basic conditions.^[57] The same reagent was also used by Ley and co-workers under acidic conditions to prepare α -hydroxyketones from aromatic ketones in quantitative yields (Scheme 21).^[58]

Scheme 21 Polymer-supported PIDA in the synthesis of α -hydroxyketones.

Kirsch successfully utilized IBX in the synthesis of α -hydroxyketones from α -alkynyl carbonyl compounds (Scheme 22).^[59] This unusual iodine(V)-mediated reaction was investigated further, and the substrate scope expanded to include β -ketoesters, β -ketoamides and β -ketothioamides.^[60]

Scheme 22 Examples of IBX-mediated α -hydroxylation reactions.

In 2008, Huang and co-workers published an iodobenzene-catalyzed protocol for the preparation of aromatic α -hydroxyketones using Oxone[®] as the stoichiometric oxidant. A diverse range of α -hydroxyketones could be prepared in moderate to good yields (Scheme 23).^[61]

Scheme 23 PhI-catalyzed α -hydroxylation of ketones.

To date, only one catalytic asymmetric α -hydroxylation using hypervalent iodine has been published.^[62] Using L-proline as catalyst and iodosylbenzene as oxidant, α -hydroxyketones were prepared with *ees* up to 77% (Scheme 24).

Scheme 24 Organocatalytic asymmetric α -hydroxylation of ketones.

2.3 Acyloxylation

α -Acetoxylation of ketones is the oldest of the hypervalent iodine-mediated α -oxygenation reactions. It is also one of the least reported α -oxygenations, with tosylation and hydroxylations being far more numerous. In 1978, Mizukami *et al.* reported the α -acetoxylation of acetophenones and β -diketones using PIDA (Scheme 25).^[63]

Scheme 25 Acetoxylation of acetophenones using PIDA.

Some years later, Podolešov reported a similar method, in which a 9:1 mixture of acetic acid-water was used as solvent, and the sulfuric acid catalyst omitted.^[64]

Two decades after Podolešov's publication, Ochiai and co-workers reported an iodobenzene-catalyzed α -acetoxylation of ketones using *m*CPBA and $\text{BF}_3 \cdot \text{OEt}_2$.^[9a] The proposed catalytic cycle is illustrated in Scheme 26. A noteworthy feature of this protocol is that it is not limited to the use of acetophenones.

Scheme 26 Ochiai's PhI-catalyzed α -acetoxylation of ketones.

Huang and co-workers subsequently reported a similar protocol in which 30% aqueous hydrogen peroxide and acetic anhydride were used to generate PIDA *in situ*.^[65] Recently, a protocol for the formyloxylation of ketones was reported.^[66] Initial α -tosyloxylation using HTIB was followed by reaction with DMF, then subsequent hydrolysis of the resulting iminium ion to yield the product (Scheme 27). Dimethylacetamide could be used in place of dimethylformamide to prepare α -acetoxyketones.

Scheme 27 α -Acyloxylation of ketones.

2.4 Other α -Oxygenations

In addition to the α -oxygenation categories discussed above, there are a number of reports on the use of other oxygen nucleophiles. α -Phosphorylation of ketones was reported by Koser *et al.* using [hydroxy(bis(phenyloxy)phosphoryl)oxy]iodobenzene, prepared by reaction of PIDA with diphenyl hydrogen phosphate (Scheme 28).^[67] Moriarty prepared similar reagents for the α -methylphosphonylation of ketones, as well as for α -diphenyl and α -dimethylphosphinylation reactions.^[68]

Scheme 28 α -Phosphorylation of ketones.

Liang and co-workers used IBX in the presence of potassium iodide in order to prepare a range of α -(2-iodobenzoyloxy)ketones (Scheme 29).^[69]

Scheme 29 Synthesis of α -(2-iodobenzoyloxy)ketones.

Moriarty used iodosylbenzene in conjunction with boron trifluoride etherate to perform a range of different α -functionalizations of β -diketones and β -ketoesters, including α -mesyloxylation and alkoxylation.^[70]

2.5 Intramolecular α -Oxygenations

Iodine(III) reagents have found numerous applications in the synthesis of lactones and many other oxygen-containing heterocycles. A review from 1994 covers the earlier developments in this field,^[71] while other aspects of hypervalent iodine-mediated cyclization reactions were reviewed in 2004.^[72] The examples presented herein are predominantly, although not entirely, drawn from more recent literature.

A common approach to the preparation of oxygen-containing heterocycles using iodine(III) reagent involves the initial formation of an α -tosyloxyketone. Subsequent intramolecular attack of an oxygen nucleophile gives the product, as exemplified by the aroylcoumaranone synthesis shown in Scheme 30.^[73]

Scheme 30 Synthesis of aroylcoumaranones.

Alternatively, reaction with a nucleophile such as potassium methyl malonate followed by cyclization provides furanones (Scheme 31).^[74]

Scheme 31 Synthesis of arylfuranones.

Murphy and West demonstrated the use of iodonium ylides, formed *in situ* from PIDA, in the synthesis of furanones under rhodium catalysis.^[75] In this reaction, the iodonium ylide behaves as a diazoketone surrogate, permitting direct conversion of activated methylene-containing compounds to the corresponding 2-substituted heterocycles (Scheme 32).

Scheme 32 Synthesis of furanones *via* iodonium ylides.

The HTIB-mediated synthesis of keto- γ -lactones from 5-ketoacids was reported by Moriarty *et al.* in 1990. This reaction proved applicable to a wide range of substrates, some of which are highlighted in Scheme 33.^[76]

Scheme 33 Preparation of lactones from 5-ketoacids.

Recently an iodobenzene-catalyzed version of this transformation was reported by Ishihara *et al.*^[77] based on Ochiai's α -acetoxylation protocol.^[9a] HTIB was formed *in situ* from iodobenzene and TsOH, with *m*CPBA as the oxidant (Scheme 34). HTIB reacts with the enol to form intermediate **10**, which is in equilibrium with iodonium carboxylate **11** and/or iodonium tosylate **12**. Reductive elimination from **10**, or S_N2 substitution on **11** or **12** then affords the product, together with the iodoarene catalyst.

Scheme 34 PhI-catalyzed lactonization reaction.

Wirth and co-workers recently reported a catalytic lactonization using chiral iodoarenes under similar conditions. The products were obtained in moderate yields with <5% *ee*, indicating that no tosyloxylated intermediate was formed and the products were instead formed via a substrate-iodoarene complex.^[51]

Fused dihydrofurans can be prepared from tricarbonyl precursors using iodosylbenzene (Scheme 35a).^[78] Using this [1,5]-oxidative cyclization, a structurally diverse range of dihydrofurans was produced in up to 90% yield and with high diastereoselectivity. The proposed mechanism for the above reaction is illustrated in Scheme 35b.^[78]

Scheme 35 a) Synthesis of fused dihydrofurans. b) Proposed mechanism for the [1,5] oxidative cyclization of Michael adducts.

The use of hypervalent iodine reagents in synthetic chemistry in general, and α -oxygenation in particular has become increasingly widespread in recent years. These environmentally benign reagents are now prevalent in areas traditionally dominated by metal-based reagents.

3 Halogenation

Standard reagents for halogenation reactions are often aggressive, unstable, toxic and corrosive. The introduction of hypervalent iodine reagents has enabled mild reaction conditions, selective reactions and nontoxic waste. Recent progress includes the use of recyclable reagents, which further reduce the environmental impact. The following section describes halogenations of saturated carbonyl compounds, whereas halogenations of unsaturated carbonyl compounds are discussed in section 8.4.

3.1 Fluorination

4-(Difluoroiodo)toluene (TollF₂) is an efficient α -fluorination reagent for several types of carbonyl compounds. Hara and co-workers have shown that this reagent fluorinates various β -dicarbonyl compounds in the presence of HF-amine complex.^[79] The reagent can also be formed electrochemically in Et₃N·5HF.^[80] The same group recently reported a modified procedure, which gives monofluorinated products without added HF-amine (Scheme 36). This reaction is slower, but proceeds under neutral conditions to yield α -fluorinated β -ketoesters, β -ketoamides and diketones.^[81]

Scheme 36 Monofluorination under neutral conditions.

Direct fluorination of simple ketones cannot be performed with hypervalent iodine reagents, but α -fluoroketones can be obtained by fluorination of the corresponding silyl enol ether.^[82]

Motherwell and co-workers have developed an α -fluorination of α -phenylthio esters^[83] and amides^[84]. The reaction proceeds in good yields via a fluoro-Pummerer mechanism (Scheme 37). Addition of more reagent leads to α,α -difluorinated product (2 equiv) and oxidation to the corresponding sulfoxide (3 equiv).

Scheme 37 Fluoro-Pummerer reaction.

In a similar fashion, α -seleno esters and amides can be fluorinated in moderate yields.^[85]

3.2 Chlorination

Similar to the fluorinations discussed above, α -chlorination of carbonyl compounds can be performed using 4-(dichloriodo)arenes. Ketones and β -diketones were selectively monochlorinated in high yield with PhICl₂ under photochemical conditions in benzene.^[86]

α -Chlorinated phosphonium salts can be prepared by reaction of phosphonium ylides with PhICl₂. Subsequent hydrolysis delivered the α -chlorinated ketones (Scheme 38).^[87]

Scheme 38 Chlorination of phosphonium ylides.

Togni and co-workers developed a catalytic asymmetric α -chlorination of β -ketoesters using 4-(dichloriodo)toluene and titanium complex **14**, which

delivered the products in good yields and enantioselectivities (Scheme 39).^[88]

Scheme 39 Asymmetric α -chlorination (1-Nph = naphthalen-1-yl).

Fluorous aryl- and alkyl iodine(III) chlorides have recently been used as chlorinating agents, with the added benefit of easy recovery and reuse of the resulting iodine(I) compound. Monochlorination was selectively obtained with dibenzoylmethane, whereas reaction with acetophenone resulted in a mixture of mono- and dichlorination.^[89]

In 2009, Ibrahim and co-workers reported a rapid PIDA-mediated chlorination of 1,3-dicarbonyl compounds using substoichiometric amounts of TiCl_4 as the chloride source (Scheme 40).^[90] Diketones, β -ketoesters, β -ketoamides and β -ketophosphonates could be employed in good to excellent yields.

Scheme 40 Chlorination of dicarbonyl compounds with PIDA.

Treatment of the carbonyl compound with TiCl_4 results in a Ti-enolate complex with concomitant release of a chloride ion, which is oxidized *in situ* by PIDA to an electrophilic chloronium ion equivalent, resulting in a net umpolung of the halide reactivity (Scheme 41).^[90]

Scheme 41 Umpolung strategy for chlorination.

For a sequential chlorination procedure, see the following section.

3.3 Bromination and Iodination

Bromination of 1,3-dicarbonyl compounds can be performed by treatment with PIDA in a reaction analogous to that described in the chlorination section

(*vide supra*). Using TiBr_4 , the reaction is extremely fast and gives excellent yields for diketones, β -ketoesters, β -ketoamides and β -ketophosphonates (Scheme 42).^[90]

Scheme 42 Bromination of dicarbonyl compounds with PIDA.

Lee *et al.* showed that ketones can be α -iodinated by sequential treatment with [hydroxy-(*p*-nitrobenzenesulfonyloxy)iido]benzene (HNIB), forming an α -sulfonyloxy intermediate (see Section 2.1) followed by potassium iodide or samarium(II) iodide (Scheme 43).^[91] Replacement of HNIB with HTIB resulted in reduced yields. The two iodination methods gave similar results in all cases but cyclic ketones, which were more efficiently iodinated with SmI_2 .

Scheme 43 Sequential iodination of ketones.

The same group later developed a general α -halogenation protocol with HTIB followed by magnesium halides under solvent-free microwave irradiation conditions (Scheme 44).^[92] This method halogenated ketones, β -ketoesters and malonates in short reaction times and high yields.

Scheme 44 Sequential halogenation of ketones.

4 Trifluoromethylation

The trifluoromethyl group is often present in synthetic drugs and agrochemicals, as it can favorably alter uptake, metabolism and mode of action. Synthetic strategies to incorporate the CF_3 group include nucleophilic, electrophilic and radical methods.^[93]

Togni's group recently developed electrophilic, hypervalent iodine-based trifluoromethylation reagents **15** and **16**, the latter has become known as "Togni's reagent" (Figure 4).^[94]

Figure 4 Togni's trifluoromethylation reagents.

Compound **16** was reacted with β -ketoesters under basic phase transfer catalysis (PTC) conditions to deliver α -trifluoromethyl substituted products (Scheme 45). Cyclic β -ketoesters were good substrates in this transformation, whereas the less reactive, acyclic substrates gave no product.

Scheme 45 Trifluoromethylation of β -ketoesters (NMR yields).

α -Nitro esters could be trifluoromethylated in the presence of a catalytic amount of CuCl, thereby providing a route to the corresponding α -trifluoromethyl- α -amino acids (Scheme 46).^[95]

Scheme 46 Trifluoromethylation and reduction to α -amino acid (NMR yields).

Furthermore, reagents **15** and **16** have been used in trifluoromethylation of silyl enol ethers and silyl ketene acetals at elevated temperature, delivering the corresponding α -trifluoromethylated carbonyl compounds.^[95b]

MacMillan and co-workers have applied Togni's reagent in an enantioselective α -trifluoromethylation of aldehydes via organocatalytic enamine formation (Scheme 47).^[96] The transformation is both high-yielding and highly enantioselective using catalytic Fe^{II} or Cu^I salts together with imidazolidinone catalyst **17**.

Scheme 47 Enantioselective, organocatalyzed trifluoromethylation.

There are few reports on other types of perfluoroalkylations of carbonyl compounds. Umemoto and co-workers have developed (perfluoroalkyl)phenyliodonium triflates as perfluoroalkylation reagents of various nucleophiles. The yields obtained in reactions with enolates were, however, moderate due to formation of both O -R_f and C -R_f products.^[97]

5 Arylation

α -Arylated carbonyl compounds are commonly occurring subunits in biologically active molecules and are therefore of high interest to the pharmaceutical industry.^[98] The introduction of aryl moieties to the α -position of carbonyl compounds, particularly in an asymmetric fashion, is an ongoing challenge in organic synthesis.^[98] Conventional procedures often use stoichiometric amounts of toxic reagents and harsh reaction conditions. There are several metal-catalyzed methods to accomplish α -arylation using aryl halides, but these routes suffer from high temperatures, long reaction times and drawbacks associated with the use of heavy metals in industry.^[2, 99]

Diaryliodonium salts and other hypervalent iodine reagents provide a means by which α -arylation can be achieved without the need for toxic or expensive transition metal reagents.

5.1 Arylation with Diaryliodonium Salts

5.1.1. General α -Arylation Strategies

Beringer and co-workers reported the first α -arylation of carbonyl compounds using diaryliodonium salts already in 1960.^[100] Phenylation of a cyclic 1,3-dione with diphenyliodonium chloride was achieved in 22% yield, together with 23% of the bis-phenylated product (Scheme 48). The reaction was also conducted using (2-nitrophenyl)phenyliodonium bromide, which resulted in chemoselective transfer of only the 2-nitrophenyl group, *i.e.* the most electron deficient arene.

Scheme 48 The first reported α -arylation of a diketone using a diaryliodonium salt.

Beringer *et al.* subsequently investigated the α -arylation of other carbonyl compounds, and reported moderate-yielding arylations of 1,3-indandiones,^[101]

malonates,^[102] esters and β -ketoesters,^[103] and 1-indanones.^[104] *tert*-Butanol was used as the solvent and sodium or potassium *tert*-butoxide as base throughout these investigations. Similar conditions were later employed in the arylation of Meldrum's acid.^[105]

The arylation of diones was further investigated by Hampton and co-workers, who performed the phenylation of 2,4-pentanedione using sodamide in liquid ammonia.^[106] It was possible to conduct this reaction on a multigram scale, furnishing the product in up to 64% yield.^[107]

In the arylation of ketones, Ryan and Stang used LDA to generate the lithium enolate of cyclohexanone.^[108] Treatment of the enolate with diphenyliodonium triflate was found to yield less than 5% of the desired product, improving to 50% on addition of 1 equivalent of copper(I) cyanide (Scheme 49). A mixture containing a 1:1:2 ratio of product, cyclohexanone and iodobenzene was obtained. It was also noted that five-membered cyclic ketones furnished diarylated products whereas larger rings were only mono-arylated.

Scheme 49 Copper-mediated arylation of cyclohexanone.

Using a similar strategy, Gao and Portoghesi were able to arylate a highly substituted ketone using diphenyliodonium iodide and LiHMDS as the base. Under these conditions, the reaction diastereoselectively delivered the monophenylated product in 71% yield, without scrambling the α -stereocenter already present in the starting material (Scheme 50).^[109] The reaction was used as a key step in the synthesis of a series of 7-arylmorphinans to be tested for opioid agonist and antagonist activity.^[110]

Scheme 50 Diastereoselective phenylation of morphinan-6-ones.

In 1999, a highly efficient arylation of malonates was reported by Oh *et al.* (Scheme 51).^[111] In this extensive study, the preference for transfer of the electron deficient aryl moiety of an unsymmetrical diaryliodonium salt was reaffirmed. It was also shown that addition of a palladium catalyst does not improve

the reaction outcome, and that an aryl iodide cannot be used instead of the diaryliodonium salt.

Scheme 51 Chemoselectivity in aryl group transfer.

As an alternative strategy to direct arylation of ketones, silyl enol ethers react with diaryliodonium fluorides to deliver α -arylated ketones. The use of salts with fluoride anions to activate the silyl enol ethers means that no base is needed, thereby avoiding problems with diarylation and scrambling of stereocenters.

In 1991, Chen and Koser demonstrated the arylation of silyl enol ethers using diphenyliodonium fluoride. Either α -phenyl or α,α -diphenyl ketones were produced in 20-88% yield; cyclic substrates were in general more suitable than acyclic substrates.^[112]

Rawal and co-workers were able to arylate TMS-enol ethers using (2-nitrophenyl)phenyliodonium fluoride (Scheme 52). As previously reported, only the electron deficient 2-nitrophenyl group was transferred.^[113] This methodology was applied in the total synthesis of tabersonine, an *Aspidosperma* alkaloid.^[114]

Scheme 52 Chemoselective arylation of TMS-enol ethers.

5.1.2 Asymmetric α -Arylation Strategies

A general asymmetric α -arylation of carbonyl compounds remains elusive. Metal-catalyzed strategies have been presented only for a very limited substrate class, and asymmetric reactions using diaryliodonium salts are conspicuous by their almost complete absence. To date, only two asymmetric α -arylations of this type have been reported.

In 1999, Ochiai *et al.* utilized chiral diaryliodonium salts based on a binaphthyl core in the arylation of β -ketoesters.^[115] Use of the standard *tert*-butoxide/*tert*-butanol system enabled the arylation to proceed with up to 53% *ee* (Scheme 53). Although the enantiomeric purity of the products is moderate, this paper remains the only example of an asymmetric α -arylation where

the diaryliodonium salt is the source of asymmetric induction.

Scheme 53 Asymmetric arylation using chiral iodonium salts.

The second example employs a chiral base to desymmetrize 4-substituted cyclohexanones prior to arylation. This strategy was successfully used by Aggarwal and Olofsson in a short and elegant total synthesis of (–)-epibatidine. (Scheme 54).^[116]

Scheme 54 Asymmetric arylation using Simpkins' base.

Olofsson and co-workers have recently reported two attempts towards asymmetric arylation. The first approach involved the use of a diaryliodonium salt bearing a chiral anion. Camphorsulfonate was used as the chiral anion to direct the electrophile to one face of the enolates of cyclic β -ketoesters, but the products were racemic under all tested conditions (Scheme 55).^[117]

Scheme 55 Attempted asymmetric arylation with a chiral anion.

Next, the same substrates were reacted with achiral diaryliodonium salts under chiral phase transfer catalysis (PTC*) conditions. The chosen PTC* cation should block one face of the enolates, as demonstrated in asymmetric S_NAr reactions of the same substrates.^[118] However, the obtained products were racemic (Scheme 56).^[117]

Scheme 56 Attempted asymmetric arylation with a chiral PTC.

5.1.3 Mechanistic Studies of α -Arylation

In the 1960s, Beringer proposed a radical mechanism for the arylation of carbonyl compounds using diaryliodonium salts,^[101, 119] which was subsequently supported by a number of publications from other research groups.^[106, 112] Although this type of mechanism indeed could be operative under certain conditions, later studies have provided evidence for a non-radical mechanism, as detailed below.

Oh *et al.* proposed that an addition-elimination mechanism operates in the arylation of malonates, as no radical byproducts could be detected (Scheme 57).^[111]

Scheme 57 Proposed mechanism for the arylation of malonates.

In 2003, Ochiai performed a detailed mechanistic study on α -phenylation of β -ketoesters with diaryliodonium salts. The results of intramolecular aryl radical trapping experiments further disputed radical intermediates; instead a tandem ligand exchange-ligand coupling mechanism was proposed (Scheme 58). Polarized transition states were suggested to account for the preferred coupling of enolates with the more electron-deficient phenyl group in unsymmetric salts.^[120]

Scheme 58 Ochiai's mechanistic study.

Prompted by the unsuccessful attempts towards asymmetric arylation using chiral anions or chiral PTC (*vide supra*), Norrby and Olofsson undertook a mechanistic study using quantum mechanical calculations. The energy difference between neutral Ar_2IX and the cationic Ar_2I^+ were too small to allow a distinct starting point in the reaction with the enolate (Scheme 59). Two intermediates, with oxygen or carbon bonded to iodine, were identified as isoenergetic. These form the product through different reductive elimination mechanisms; [2,3] rearrangement or [1,2] rearrangement, respectively, where the first pathway is the favored one.^[117]

The most important finding was that the isomerization barrier between the C-I and O-I intermediate was low enough (16 $\text{kJ}\cdot\text{mol}^{-1}$) to give a fast equilibration. Thus, any asymmetric induction obtained in the formation of a C-I intermediate will be lost by equilibration with the O-I intermediate. This is in good agreement with the lack of selectivity observed in the experimental work (*vide supra*).^[117]

Scheme 59 Proposed mechanism based on calculations.

5.2 Arylation with other Reagents

Kita *et al.* have thoroughly investigated the reactions of phenol ethers with PIFA and various nucleophiles. When *para*-substituted phenol ethers are used in polar, poorly nucleophilic protic solvents such as TFE or HFIP, nucleophilic substitution *ortho* to the ether substituent takes place in moderate yields. In this fashion, β -diketones and β -ketoesters could be employed as nucleophiles to deliver α -arylated products (Scheme 60).^[121]

Scheme 60 Kita's arylation with PIFA.

The mechanism is believed to involve formation of cationic radicals via single electron transfer (SET) from an initially formed charge transfer complex, followed by nucleophilic attack (Scheme 61).^[121]

Scheme 61 Mechanism for arylation with PIFA.

This transformation was subsequently employed in the synthesis of benzannulated and spirobenzannulated compounds. The use of phenol ethers bearing a cyclic 1,3-dicarbonyl moiety as the *para*-substituent resulted in intramolecular cyclization onto the *meta* position (Scheme 62).^[122]

Meta-substituted phenol ethers could also be employed in this transformation; cyclization occurred regioselectively in the *para*-position due to steric hindrance. Substrates containing acyclic dicarbonyls gave no arylation in either case.^[122]

Scheme 62 Intramolecular α -arylation with PIFA.

Another intramolecular α -arylation was achieved by a Pummerer-type reaction of α -acyl sulfides with PIFA, forming various heterocyclic structures (Scheme 63).^[123]

Scheme 63 PIFA-mediated Pummerer-type reaction.

A sequential aminopalladation/C-H activation reaction of alkynyl amides **18** was recently reported. When treated with palladium acetate and PIDA, the alkyne was difunctionalized to produce α -arylated amides **19** in good yields (Scheme 64).^[124]

Scheme 64 Aminopalladation/C-H activation reaction.

6 Alkynylation and Alkenylation

Reactions of certain enolates with alkynyl(aryl)iodonium salts^[8, 125] and alkenyl(aryl)-iodonium salts^[126] lead to α -alkynylated and α -alkenylated products, respectively. Reports on these transformations are scarce compared to α -arylations (*vide supra*), and the chemoselectivity versus α -arylation can pose a problem. The reactions of these iodonium salts proceed via other mechanisms than reactions with diaryliodonium salts, and different reaction pathways are followed, depending on the structure of the salt, the nucleophile and the reaction conditions employed.^[8, 125-126]

Beringer demonstrated the α -alkynylation and α -alkenylation of phenyl-1,3-indanone using iodonium salts (Scheme 65).^[127] The reactions were performed under the same conditions as his α -arylations (see

Section 5.1.1), *i.e.* using sodium *tert*-butoxide in refluxing *tert*-butanol.

Scheme 65 Alkynylation and alkenylation with iodonium salts.

In 1986, Ochiai reported an efficient cyclopentene annulation using alkynyliodonium salts (Scheme 66).^[128] The reaction proceeds via a tandem Michael-carbene insertion to form the annulated product in good yield.

Scheme 66 Cyclopentene annulation.

Kitamura *et al.* later continued this theme using alkynyliodonium salts containing an *o*-carboxyphenyl moiety to facilitate recovery of the iodoarene.^[129] Upon reaction with phenyl-1,3-indanone, alkynylation or alkenylation was obtained, depending on the alkynyl substituent in the iodonium salt.

α -Ethynylation of a range of 1,3-dicarbonyl compounds can be achieved in good yields using ethynyl(phenyl)iodonium tetrafluoroborate.^[130]

Bachi and Stang investigated the alkynylation of an iminomalonate using variously substituted alkynyliodonium salts (Scheme 67). The products were obtained in moderate to good yield, and are useful precursors to α -alkynyl- α -amino carboxylic acid derivatives.^[131] The same group also reported the reaction of 2-oxoazetidin-1-ylmalonates with TMS-protected alkynyliodonium salts, delivering products with a terminal alkynyl group.^[132]

Scheme 67 Alkynylation of an iminomalonate.

Ochiai reported a chemoselective α -alkenylation of 1,3-dicarbonyl compounds with alkenyl(aryl)-

iodonium tetrafluoroborates (Scheme 68).^[133] Competing α -arylation could be avoided by using a *p*-methoxyphenyl moiety. In this detailed study, the use of an aryl radical trap inhibited radical-induced decomposition of the alkenyl(aryl)iodonium salts, thereby improving the yields. The reaction works for cyclic β -ketoesters, 1,3-diketones and 1,3-diester.

Scheme 68 Alkenylation using a radical trap.

In 2010, Waser and co-workers developed a very reactive ethynylation reagent **20**, formed *in situ* from benziodoxolone **21** (Scheme 69a).^[134] This reagent ethynylated cyclic and acyclic β -ketoesters, 1,3-diester, cyano- and nitro esters in high yields. One enantioselective example was presented, where a chiral PTC was employed to give moderate asymmetric induction (Scheme 69b).^[134]

Scheme 69 Ethynylation of 1,3-dicarbonyl compounds.

7 Homocoupling

The oxidative coupling of two carbonyl compounds to form 1,4-dicarbonyl compounds is of interest as the target compounds are versatile intermediates in the synthesis of natural products. This transformation can be performed using a range of oxidants, including hypervalent iodine reagents.^[135]

Early investigations by Moriarty *et al.* showed that aryl methyl ketones, when converted to the corresponding TMS enol ethers, could be homocoupled using iodosobenzene and $\text{BF}_3 \cdot \text{OEt}_2$. The butane-1,4-dione products were formed in moderate yields.^[56, 136]

The groups of Caple and Zefirov later developed iodosobenzene tetrafluoroborate and iodosobenzene hexafluorophosphate as stable and superior reagents

for the homocoupling of TMS enol ethers (Scheme 70).^[137] These reagents were also efficient in the coupling of aliphatic substrates.

Scheme 70 Oxidative homocoupling of silyl enol ethers.

The same groups reported the use of $\text{PhIO} \cdot \text{HBF}_4$; with this reagent a stepwise approach enabling heterocouplings between two different TMS enol ethers was possible.^[138]

Direct homocoupling of carbonyl compounds, rather than the corresponding silyl enol ether, was reported by Moriarty in 1988.^[70] β -Diketones and β -ketoesters were treated with iodosobenzene and boron trifluoride etherate to give homocoupled products (Scheme 71).

Scheme 71 Homocoupling of 1,3-dicarbonyl compounds.

Chen and co-workers employed substituted derivatives of Meldrum's acid with PIDA, potassium carbonate and a phase transfer catalyst to give homocoupled products in moderate yield (Scheme 72).^[139]

Scheme 72 Homocoupling of Meldrum's acid.

More recently, the homocoupling of enolates derived from oxazolidinones and imidazolidinones has been reported.^[140] When chiral substrates were employed, moderate to good diastereoselectivities were observed in the coupling (Scheme 73).^[140b] A radical mechanism was postulated.

Scheme 73 Homocoupling of chiral substrates.

8 Functionalization of α,β -Unsaturated Carbonyl Compounds

Hypervalent iodine compounds are generally used as electrophilic reagents in reactions with nucleophiles. Oxidation of the alkene moiety in α,β -unsaturated carbonyl compounds requires a nucleophilic reagent, and most of the reactions presented below utilize another reagent for this purpose, followed by oxidation of the resulting intermediate with the hypervalent iodine reagent. In certain cases, however, the hypervalent iodine compound is used without aid from other reagents.^[141]

8.1 Epoxidation

In 2000, Ochiai *et al.* developed the first hypervalent iodine compound that could epoxidize enones (Scheme 74). The reagent, tetrabutylammonium oxido- λ^3 -iodane, contains an oxyanion that can attack the electron-deficient olefin, followed by ring-closure to form the epoxide and expel the iodoarene.^[142]

Scheme 74 Epoxidation of enones.

The epoxidation of a range of cyclic, highly electron-deficient enones was demonstrated using iodosylbenzene.^[143] While limited in scope, this method gives high yields under mild reaction conditions.

A chemo- and stereoselective epoxidation of an advanced intermediate in the synthesis of epoxysorbicillinol was realized in excellent yield using PIFA (Scheme 75).^[144]

Scheme 75 Epoxidation with PIFA.

A one-pot conversion of enones to the corresponding α,β -epoxyketones was recently developed using sequential addition of IBX- I_2 and 10% NaOH. The reaction proceeds via iodohydroxylation (see Section 8.4) followed by base-induced ring-closure (Scheme 76).^[145]

Scheme 76 Epoxidation with IBX.

Lee and MacMillan have reported an enantioselective, organocatalytic epoxidation of α,β -unsaturated aldehydes.^[146] An imidazolidinone catalyst was employed to form an enamine intermediate with the aldehyde (*cf* Section 4), which was subsequently epoxidized by iodosobenzene. To circumvent unwanted oxidation of the catalyst, an “internal syringe pump” strategy was devised using [(nosylimino)iodo]benzene, which slowly released PhIO under the reaction conditions. The protocol was applied to a range of α,β -unsaturated aldehydes, giving the corresponding epoxides in good yields and high enantiomeric excess. (Scheme 77).^[146]

Scheme 77 MacMillan's enantioselective epoxidation.

8.2 Aziridination

In 1991, Evans *et al.* reported the first aziridination of α,β -unsaturated carbonyl compounds with a hypervalent iodine reagent.^[147] The reaction was catalyzed with copper salts and used (*N*-(*p*-tolylsulfonyl)imino)phenyliodinane (PhI=NTs) as the nitrene precursor, providing *N*-tosylaziridines in moderate yields. An improved procedure was later presented, where α,β -unsaturated esters were aziridinated in good yields (Scheme 78).^[148] Unsaturated ketones were less reactive, and provided only trace amounts of product.

Scheme 78 Aziridination of α,β -unsaturated esters.

An enantioselective version of this reaction was developed, where bis(oxazoline)-copper complexes were employed as catalysts to give aziridinated products in good yields and high enantiomeric excess (Scheme 79).^[149]

Scheme 79 Evans' enantioselective aziridination.

Jacobsen and co-workers reported a similar catalytic system, employing bifunctional Schiff bases derived from *trans*-1,2-diaminocyclohexane.^[150] Other groups have also developed ligands useful for asymmetric aziridination of α,β -unsaturated esters under similar conditions.^[151]

A one-pot enantioselective aziridination of α,β -unsaturated esters was accomplished by using sulfonamide/PIDA as the nitrene source with copper catalysis, although the yields were not comparable with reactions using PhINTs.^[152]

Yudin and co-workers developed a metal-free aziridination of chalcones by combination of PIDA and *N*-aminophthalimide, resulting in good yields of aziridines under mild conditions (Scheme 80).^[153]

Scheme 80 PIDA-mediated aziridination, Phth= phthalimide.

Asymmetric aziridination of chalcones was developed by Xu *et al.* in 2004.^[154] The use of more rigid bis(oxazoline)-copper complexes in dichloromethane delivered aziridines in moderate to good yields and high enantioselectivity (Scheme 81).^[155]

Scheme 81 Asymmetric aziridination of chalcones.

8.3 Aminohalogenation

Wang and co-workers have reported several aminohalogenations of enones using PIDA. Aminochlorination was performed under solvent-free conditions using Chloramine-T and PIDA, giving α -amino- β -chloroketones with high diastereoselectivities and complete regioselectivities. Chalcones were the best substrates, but esters and

amides also underwent this transformation (Scheme 82).^[156] The reaction could also be achieved without PIDA under phase transfer conditions.^[157]

Scheme 82 Aminochlorination of enones.

Likewise, aminobromination of enones was achieved under solvent-free conditions using tosylamine, NBS and a catalytic amount of PIDA. Also in this case, high stereoselectivities and good yields were observed.^[158] The reaction could also be performed in water at elevated temperature.^[159]

8.4 Other Functionalizations

In 1984, Rebrovic and Koser reported a *vic*-ditosyloxylation of alkenes using HTIB. One example of ditosyloxylation of an enone was presented; chalcone delivered the disubstituted product in 57% yield.^[160] This methodology was recently applied to several aromatic enones in good yield (Scheme 83).^[161]

Scheme 83 Ditosyloxylation of chalcones.

Iodohydroxylation of α,β -unsaturated carbonyl compounds can be performed using the IBX-I₂ redox couple in DMSO. Enones, α,β -unsaturated esters and amides are tolerated in this reaction. The active reagent is hypoiodous acid (IOH), which adds to the olefin with high *anti* stereoselectivity (Scheme 84).^[145] A one-pot conversion to the corresponding epoxide was also developed (see Section 8.1).

Scheme 84 IBX-mediated Iodohydroxylation.

Chalcones can undergo oxidative rearrangement in the presence of HTIB.^[162] The reaction can also be performed using PIFA,^[163] or PIDA in the presence of TsOH (Scheme 85).^[164] This transformation has been employed as key step in the synthesis of isoflavone natural products.^[165] Under certain conditions, the aryl moiety attached to the carbonyl group (Ar¹) migrates instead.^[166]

Scheme 85 Oxidative rearrangement of chalcones.

α,β -Unsaturated aldehydes and ketones can be chlorinated or brominated in the α -position in good yields using PIDA and the HCl or HBr salt of pyridine.^[167] Uracil bases and protected nucleosides can be chlorinated in excellent yield using PhICl_2 .^[168] Dihydropyridones can be iodinated using NIS and a catalytic amount of HTIB (Scheme 86).^[169]

Scheme 86 Iodination of dihydropyridones.

Oxidative spirocyclization of phenols is an important PIFA-mediated transformation.^[12] Using this methodology, intramolecular oxidation of *O*-silylated phenols bearing various types of aminoquinones at the para position gave azacarbo-cyclic spiro dienones in good yields (Scheme 87).^[170] This reaction was applied in the total synthesis of discorhabdin C.

Scheme 87 Synthesis of azacarbo-cyclic spiro dienones.

A certain type of iodonium ylides, called iodonium bis(sulfonyl)methylides, react with enones in a [3+2] cycloaddition catalyzed by rhodium(II) acetate, delivering arylindanes in moderate yields (Scheme 88).^[171]

Scheme 88 Cycloaddition of enones with iodonium ylides.

9 Miscellaneous

Moriarty reported α -azidation of 1,3-dicarbonyl compounds in 1988.^[70] β -diketones and β -ketoesters were treated with iodosobenzene and trimethylsilylazide to give azidosubstituted products (Scheme 89).

Scheme 89 Azidation of 1,3-dicarbonyl compounds.

α -Azidation of ketones can be performed by sequential treatment with [hydroxy-(*p*-nitrobenzenesulfonyloxy)iodo]benzene (HNIB), forming an α -sulfonyloxy intermediate (see Section 2.1 and 3.3) followed by sodium azide (Scheme 90).^[172] Replacement of HNIB with HTIB resulted in reduced yields. This transformation is analogous to the iodination shown in Scheme 43.

Scheme 90 Azidation of ketones.

A similar approach using sequential addition of HTIB and sodium sulfinate to ketones delivered the corresponding β -keto sulfones in moderate to good yields.^[173]

Prakash and Moriarty reported that the combination of (dichloroiodo)benzene and lead(II) thiocyanate effects thiocyanation of β -ketoesters and 1,3-diketones (Scheme 91).^[174] [Bis(thiocyanato)iodo]benzene is believed to be the active reagent in this process. Ketones and esters are not reactive under these conditions, but the α -thiocyanated products can be obtained from the corresponding silyl enol ethers.^[174]

An improved method for thiocyanation of 2-aryllindan-1,3-diones was later found, where (dichloroiodo)benzene was combined with potassium thiocyanate.^[175]

Scheme 91 Thiocyanation of dicarbonyl compounds.

A PIDA-mediated oxidative addition of cyclic and acyclic 1,3-dicarbonyl compounds to olefins provides an efficient synthesis of 2,3-dihydrofuran derivatives (Scheme 92).^[141]

Scheme 92 Synthesis of 2,3-dihydrofuran derivatives.

Metal-catalyzed aziridination of silyl enol ethers and silyl ketene acetals with $\text{PhI}=\text{NTs}$ provides α -tosylamido carbonyl compounds.^[148] The details of this transformation falls outside the scope of this review.

Very recently, Ishihara and co-workers presented an enantioselective oxidative cycloetherification. The reaction was stoichiometric in hydrogen peroxide, and employed chiral quaternary ammonium iodide catalyst **22** as source of asymmetric induction (Scheme 93).^[10c] A wide range of cyclized products were obtained in excellent yields and enantioselectivities. The active oxidant was proposed to be hypoiodite (IO^-) or iodite (IO_2^-), formed by hydrogen peroxide-oxidation of the iodide.

Scheme 93 Ishihara's enantioselective cycloetherification.

10 Summary

This review has summarized the use of hypervalent iodine reagents in α -functionalization of carbonyl compounds, delivering a diverse set of products under mild reaction conditions. With the development of catalytic and asymmetric hypervalent iodine-mediated α -functionalization reactions over the past decade, hypervalent iodine compounds show great potential as environmentally benign and selective reagents in many, yet undiscovered transformations to come.

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Biographical sketches

Eleanor A. Merritt, born in the UK in 1982, obtained her MChem degree from Cardiff University in 2004. She then began postgraduate studies in the research group of Dr. Mark C. Bagley at Cardiff University, where she worked on the synthesis of thiopeptide antibiotics. Since obtaining her PhD in 2008, she has commenced postdoctoral research at Stockholm University under the direction of Assoc. Prof. Berit Olofsson where she is working on the development of environmentally benign methodology within hypervalent iodine chemistry.

Berit Olofsson was born in 1972 in Sundsvall, Sweden. She got her M Sc in 1998 from Lund University, and finished her PhD in asymmetric synthesis at KTH, Stockholm (with P. Somfai) in 2002. She then moved to Bristol University, UK for a post doc in the field of methodology and natural product synthesis with V. K. Aggarwal. Returning to Sweden, she became assistant supervisor at Stockholm University in the group of J.-E. Bäckvall. In 2006 she was appointed to Assistant Professor, and was recently appointed to a permanent position as Associate Professor. Her research interests include the synthesis and application of hypervalent iodine compounds in asymmetric synthesis.

Graphical abstract

maximum dimensions 12 x 4 cm

Short title α -Functionalization of Carbonyl Compounds