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Organohypervalent Iodine: Development, Applications, and Future Directions†

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The synthetic utility of organohypervalent iodine reagents will be illustrated by their use in the α-hydroxydimethylacetal formation reaction from enolizable ketones, α-hydroxylation, α-tosyloxylation, α-alkoxylation and arylation of ketones, carbon−carbon bond formation, and intramolecular cyclopropanation using iodonium ylides. The uses of these reagents in the Hunsdiecker reaction of carboxylic acids and Hofmann rearrangement of carboxamides is presented. Specific transformation in the cubane series are discussed. The syntheses of a wide range of heterocycle structures are also presented. A unifying pathway for virtually all these diverse reactions is offered; the central features being initial attack at the iodonium center, ligand coupling, with reductive elimination of iodobenzene to yield the product.

Preface

"Iodine exclaimed Holmes to Watson; it must be the work of Professor Moriarty"[1]

I read this line at about the same age when most people first encounter iodine. That is, as a wounded child in the form of "tincture of iodine," used universally for scrapes and bruises. Upon looking up "tincture of iodine" in my dictionary, I learned that it referred to an alcohol solution of iodine. At this instant, three ideas fixed themselves in my young mind: I vowed to become Professor Moriarty. I developed an obsession with iodine, as well as life long aversion to alcohol because of its painful association with the scrapes and abrasions of childhood.

My next significant encounter with iodine ended this obsession. In fact, it was with polyvalent iodine and occurred in 1958 as a first year graduate student in chemistry at Princeton. This was at a time before cumulative exams. A student specializing in organic chemistry was obliged to pass three 4 h comprehensive exams in their minor fields of analytical, physical, and inorganic chemistry as well as an 8 h exam in organic chemistry. All four exams were to be done in one week. The customary preparation for the inorganic exam was to absorb the contents of a 950 page text titled *Inorganic Chemistry* by T. Moeller.[2] Because of the green color of this book, graduate students called it "The Green Death".

In my effort to master this text I suffered a crisis of will. When I arrived at pages 444−447, a section titled interhalogen compounds was introduced. This section presented, in matrix form, all the known combinations of F, Cl, Br, and I, along with physical data on density, melting point, and boiling point. This was too much. Iodine seemed like a many-headed Hydra and the possible combinations with other halogens seemed huge and indeterminate. Since this was an exercise in memorization rather than understanding, I felt my memory was given an unfair and indeterminate task.

Reason and logic bauked; intellectual curiosity vanished. I flung the large green book across my study narrowly missing my startled dog (who coincidentally was named Holmes) and swore never to have anything more to do with iodine, monovalent, or otherwise.

Looking back I believe I was rebelling against the comprehensive exam system at Princeton. Perhaps significantly, interhalogens appeared at page 444 which was the geometric middle of the Moeller text. This episode may challenge the reader's sense of irony, given the fact that I ended up spending a large part of my academic career studying interhalogens, albeit, organic ones.

I passed the inorganic exam, made my peace with Moeller, which is an invaluable reference book standing right next to Cotton and Wilkinson[3] on my book shelf,

† This perspective is not a review of hypervalent iodine chemistry. It is a review of my group's work in this area and, accordingly, is rather narrow in scope. The work of others is brought in contextually as it relates to our research. The classic negative criticism "A better review could be written on everything he left out" legitimately applies here. Much brilliant work by others has not been presented, but this is to be expected in such a rapidly growing field. I apologize for the more egregious omissions, and I trust apologies will be reciprocated in future Perspectives written by future awardees of the ACS Award for Creative Research and Applications of Iodine Chemistry. This perspective addresses ideas, observations, extensions, theory, and verification, in other words, the way in which a field of research moves forward.

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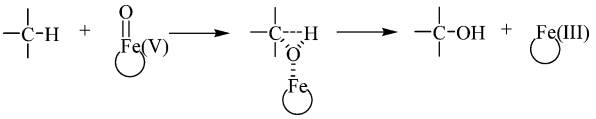

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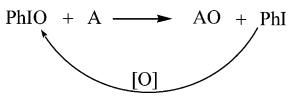

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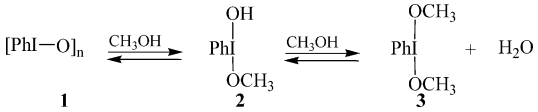

and came to love and partially understand the many headed Hydra of hypervalent iodine compounds. The rest of the story constitutes this Perspective.

A full twenty years later, around 1979, I became interested in the direct insertion of oxygen into unactivated carbon−hydrogen bonds (Scheme 1). Iron monooxygenases carry out this process very efficiently as, for example, with cytochrome P-450.

I envisioned a similar process occurring with iodosylbenzene, PhIO (**1**), being the oxene donor. Uncatalyzed oxygen atom transfer had been observed with pyridinium *N*-oxides[4−6] and 1-pyrroline-1-oxides.[7] The commonality was that the loss or transfer of an oxene yielded a stable molecule, e.g., pyridine, pyrroline, or in the hypothetical case of PhIO (**1**), PhI would be the stable molecule. Scheme 2 shows this pathway.

I further envisioned an oxidative cycle using a column of polymer bond PhIO (polystyrene could be iodinated), and the reaction $PhI + O_3 \rightarrow PhIO + PhIO_2$ had also been reported and represented a way of regenerating the polyiodosylstyrene. In reduction of this idea to practice, the first problem I encountered was the very low solubility of PhIO (**1**) in most organic solvents. However, Hill reported[8] that the polymeric $(PhIO)_n$ (**1**) was soluble in methanol by virtue of the following addition reaction (Scheme 3) to yield (dimethoxyiodo)benzene (**3**).

Using the simple combination of $PhIO/CH_3OH$ + alkene, we observed no reaction under a variety of conditions. Next we changed the substrate from alkene to acetophenone under the belief that the methyl group might be more receptive to oxene insertion; still there was no reaction. Finally, we added base to the mixture with the idea of favoring $PhI(OH)OCH_3$ (**2**) in Scheme 3 as a more reactive oxene donor. Having arrived at these conditions, we of course had totally changed the nature of the reaction as well as the direction of our research. We had discovered the first example of the α-hydroxydimethylacetal formation of enolizable ketone (Scheme 4).[9]

We proposed the mechanism of Scheme 5 which proved valid and testable and served a predictive basis for a multitude of other examples.

The steps that we considered to occur in this reaction are as follows: step a, dissociation of the polymeric iodosylbenzene or hydrolysis of iodobenzene diacetate

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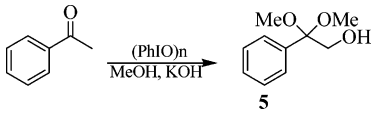

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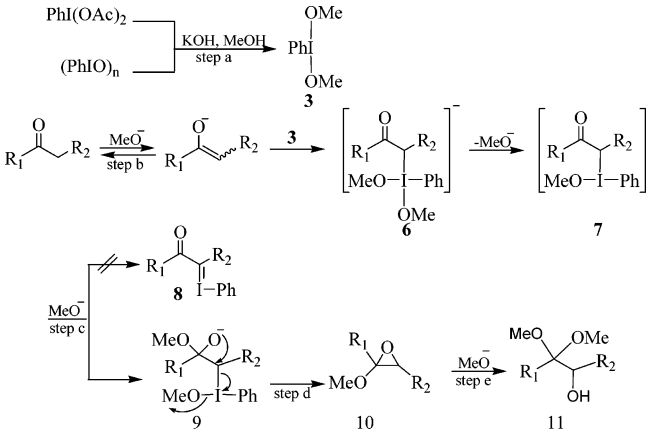
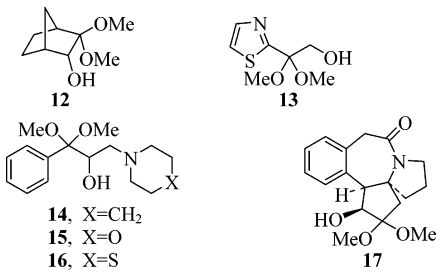


$(PhI(OAc)_2$, IBD) to generate the active reagent (dimethoxyiodo)benzene (**3**); step b, the concomitant formation of the enolate anion and subsequent addition to $PhI(OMe)_2$ (**3**) to yield intermediate **6** which loses methoxide anion to afford intermediate **7**; step c, attack of methoxide anion upon the carbonyl group of intermediate **7** to yield intermediate **9**; and finally intramolecular nucleophilic displacement by alkoxide anion to give the oxirane **10** accompanied by reductive elimination of PhI (step d). The reaction is completed by attack of a second methoxide ion on oxirane **10** to yield product **11** (step e). The procedure worked for a large range of structural types; the following illustrative α-hydroxydimethylacetals (**12**−**17**) were obtained from the precursor ketones.[10−13]



Use of the reaction for the construction of the dihydroxyacetone side chain at the 17β-acetyl position in the pregnane series (Scheme 6) is noteworthy.[14] Other ste-

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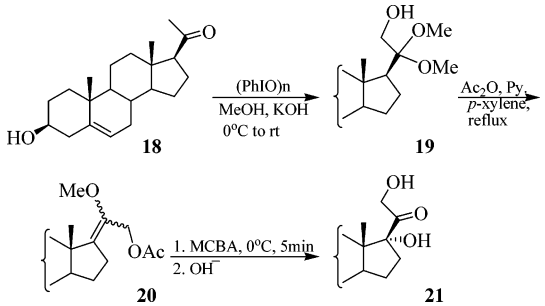

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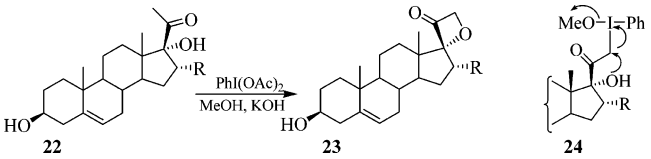

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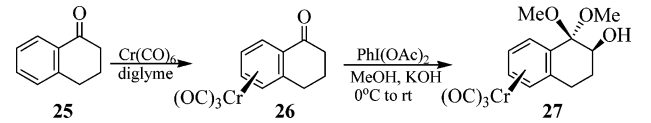

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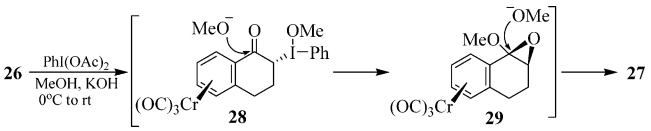

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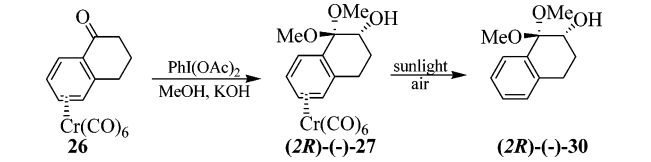


roids containing a keto group at C3 in the A-ring did not give the dimethylacetal product, presumably due to steric constraints in the steroidal ring system, but rather followed a Favorskii type ring contraction.[15,16]

In the case of a 17α-hydroxy steroid the hydroxy group acts as an intramolecular nucleophile to yield the 17-spirooxetan-20-one. It is remarkable that the 3β-hydroxy-Δ5-system is unaffected in Schemes 6 and 7.[17]

This example, **22** → **23**, is one of many in which intramolecular displacement of the iodane intermediate occurs (**24** → **23**).[18,19]

Reaction of the tricarbonyl chromium complex of 1-tetralone (**25**) (Scheme 8) is of interest not only because the $Cr(CO)_3$ group was found to be compatible with I(III) but also because the overall stereochemistry (**26** → **27**) is in agreement with the dictates of the mechanism of Scheme 5.[20,21]

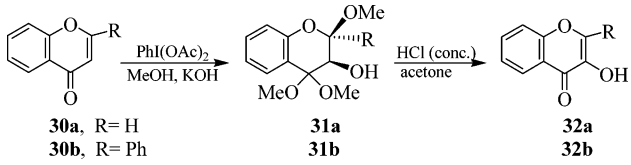
The reaction yielded only product **27** in which the hydroxy group is *syn* with respect to the $Cr(CO)_3$ tripod (Scheme 8). These stereochemical results can be understood in terms of addition of $PhI(OMe)_2$ *anti* to the $Cr(CO)_3$ group due to a steric effect. The relative configuration of the C−I bond in the molecule determines the final stereochemical result as depicted in Scheme 9.

Since **26** can be resolved, application of the reaction in Scheme 8 offers a way of making a pure enantiomer of **30** of known configuration (*R*) after disengagement of the metal ligand from complex (−)-**27** (Scheme 10).

A final example which results in a stereoselective product based upon the mechanism of Scheme 5 is the conversion of chromones **30a** and **30b** to **31a** and **31b,** respectively (Scheme 11).[22,23]

The stereochemistry of intermediates **31a** and **31b** in each case results from initial conjugate addition of

SCHEME 11



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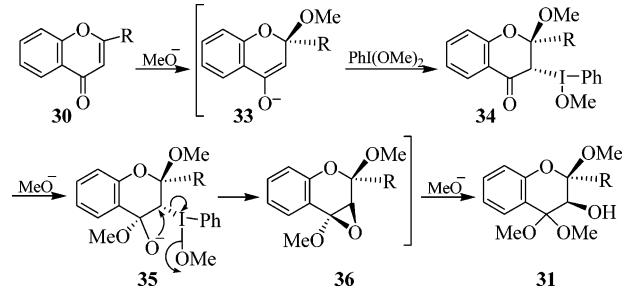


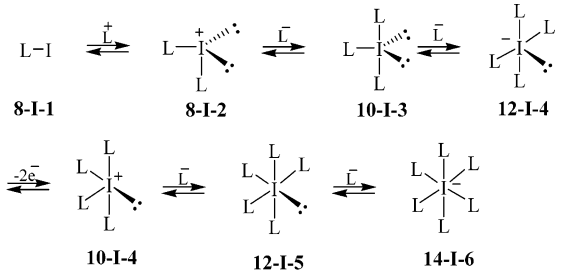
methoxide ion on the chromone **30**. Subsequent attack of thus formed enolate **33** upon $PhI(OMe)_2$ occurs in an *anti* manner to methoxy group because of the steric interaction. Sequential addition of methoxide anion to the carbonyl group of **34** gives **35**, and intramolecular reductive elimination of PhI then occurs with inversion of configuration, **35** → **36**. The reaction is completed by a second addition of methoxide ion to the oxirane ring (Scheme 12).

Our thinking about these hypervalent iodine processes was influenced in a very fundamental way by the work of Jeremy Musher who was a junior fellow at Harvard in 1961 and also a friend. In his seminal *Angewandte Chemie* article[24] he defined hypervalency:

...."We classify as 'hypervalent' molecules and ions all those molecules and ions formed by elements in Groups V−VIII of the periodic table in any of their valences other than their lowest stable valence of 3, 2, 1, and 0, respectively. We refer to these molecules as hypervalent (or HV) since they involve atoms, called donor atoms, which exceed the number of valences allowed them by the traditional theory, and thus utilize more lone-pairs of bonding than provide stability in the Lewis-Langmuir theory". He described the hypervalent bond of iodine as a 3-center-4-electron bond using a valence bond model from Pimentel[25] and Rundle.[26] Later Dykstra, Cahill, and Martin described the hypervalent bond in simple molecular orbital terms.[27]

Contemporaneously with our early work on hypervalent iodine, J. C. Martin at UIUC was actively pursuing research in this area. He referred to organohypervalent iodine compounds as "Organo-nonmetallic systems" because of the similarity the central iodine shared with metals in the sense that ligands could be assembled about the iodine and the fact that ligand exchange was a common process. Our thinking about mechanism was informed by this idea with the additional thought that product formation occurred by ligand coupling via reductive elimination. L_3I is a T-shaped molecule with the linear L−I−L system being a 3-center 4-electron bond. Coupling of the equatorial and axial ligands could be considered the product forming steps from the trigonal

SCHEME 13



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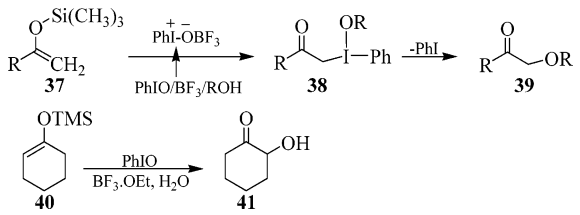
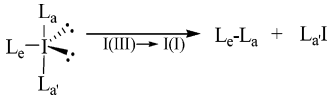


bipyramid which is a fluxional system by virtue of pseudorotation.



Furthermore, Martin introduced a very useful nomenclature called the Martin−Arduengo designation, for the three-dimensional structure of polyvalent iodine compounds (Scheme 13).[28] These structures offered a structural model for mechanistic deductions. The confluence of theory from Musher and Martin and our synthetic examples was most fortuitous for our further progress in the field.

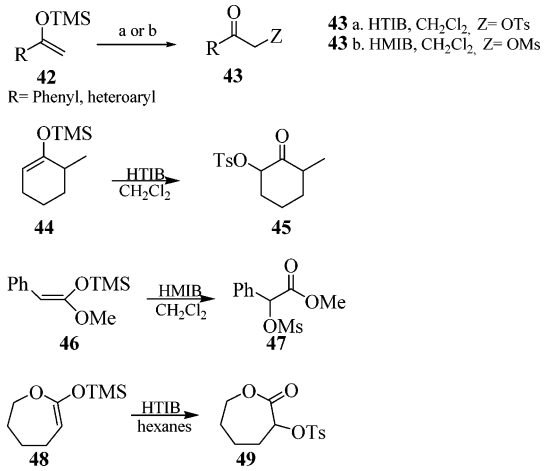
The α-fuctionalization of carbonyl compounds under basic conditions involves 10-I-3 hypervalent intermediates as in Scheme 5. We reasoned that this type of reaction intermediate could also be accessed by the reaction of an anion equivalent and an iodonium ion species.[29,30] The key difference is that we were now dealing with electrophilic addition (Scheme 14).

Koser's reagent, hydroxy(tosyloxy)iodobenzene (PhI(OH)OTs, HTIB), as well as hydroxy(mesyloxy)iodobenzene (PhI(OH)OMs, HMIB) fits into this system because it is the source of same electrophile $PhI^{+}OH$ as is formed under the Lewis acid−PhIO complex used above. Thus α-sulfonyloxylation of enol ether became an extremely useful reaction. The examples in Scheme 15 came from Koser's laboratory.[31]

Although α-functionalizations are more common, both *β*- and Y-functionalizations can be accomplished with certain substrates. Functionalization of the ketones and lactones has been achieved through the agency of substituted cyclopropanols derived from ketones and lactones with the ultimate product being the higher homologous α,*β*-unsaturated compound (Scheme 16).[32]

Further examples of *β*-functionalization studied in detail by Magnus et al. are the formation of *β*-azido ketones from the reaction of the isopropylsilyl enol ethers with $Ph(IO)_n$-trimethylsilyl azide (Scheme 17).[33−35]

SCHEME 15



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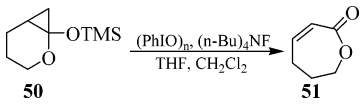

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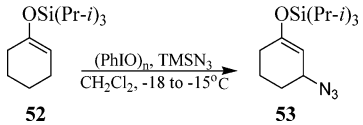

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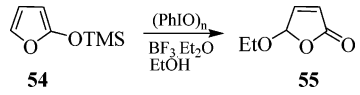

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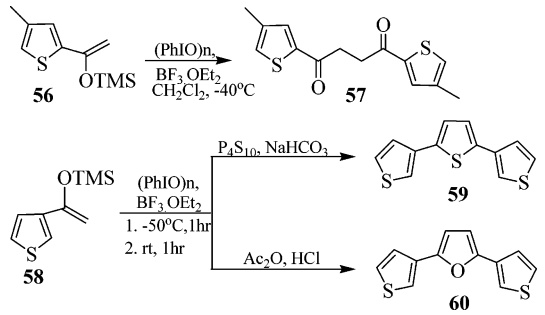


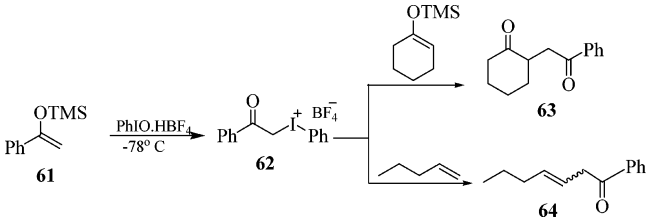
γ-Functionalization occurs when 2-trimethylsilylfuran reacts with iodobenzene and boron trifluoride in the presence of nucleophile (Scheme 18).[36] The products of the reactions are 5-substituted 2-(5*H*)furanones.

Carbon nucleophiles also are effective in the process and this led to a versatile method for carbon−carbon bond formation (Scheme 19).[37]

Other examples of carbon−carbon bond formation have come from very productive Zefirov (Moscow), Zhdankin and Caple (Minnesota) collaborations (Scheme 20)[38,39] as well as from Koser's laboratory as in (**65** → **66**). Other examples yielded **67a**−**f** (Scheme 21).[40]

These reactions may be interpreted in terms of addition of the carbon nucleophile to the positive iodonium center to form the new carbon−carbon bond by ligand coupling with reductive loss of PhI (Scheme 22).

SCHEME 20



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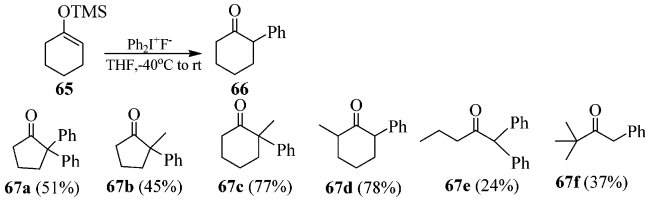

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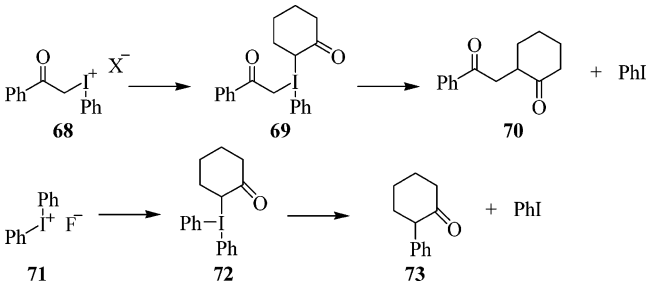

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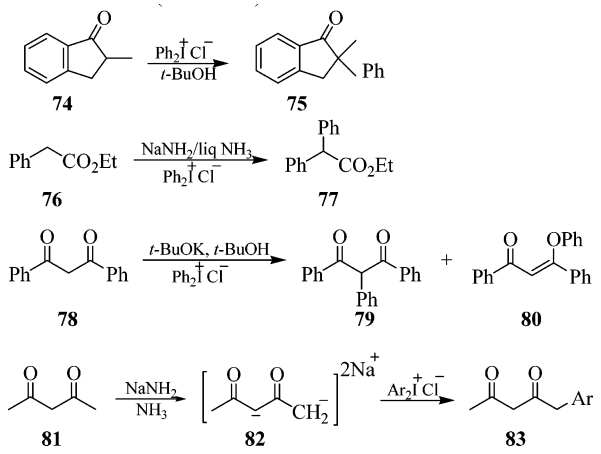
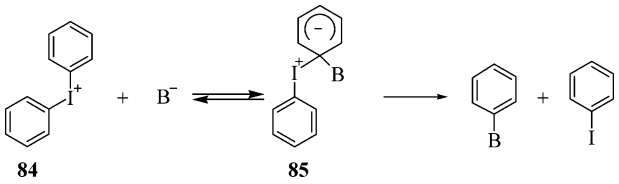


In fact, the latter process is an example of a reaction from the classical period of organohypervalent iodine research which was studied extensively under the area of arylation of carbanions (Scheme 23).[41−44]

The diaryliodonium salts go back to 1894 with their discovery by Hartmann and Meyer.[45] The use of these compounds for arylation has been extensively studied in the context of S_NAr both synthetically and mechanistically. In my opinion an intermediary tricoordinate description (Scheme 25) is better than a Meisenheimer-type intermediate (**84** → **85**) (Scheme 24).[46]

The tricoordinate intermediate accommodates the observation that in the decomposition of $(Ar{-}I^{+}{-}Ph)Cl^{-}$, the chloroaryl resulting from attack of chloride at the most hindered aryl group predominates. The bulkier

SCHEME 24



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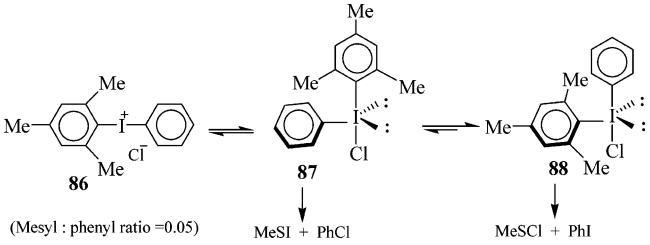

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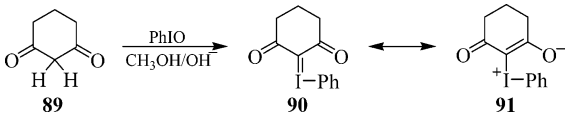

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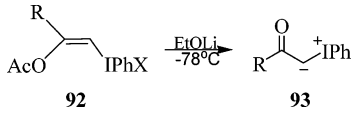


arene group will adopt the less hindered equatorial position. Ligand coupling occurs between the axial Cl and the equatorial mesityl group. I mention this phenomenon because I believe it offers an insight in hypervalent iodine processes in general in cases where attack is at an iodonium center (Scheme 25).[47]

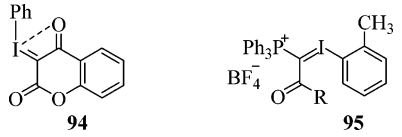
The steric effect of course runs opposite to the inductive effect of the three methyl groups.

The reaction of 1,3-dicarbonyl compounds under the same conditions as those used for the conversion of methyl ketones to α-hydroxydimethyl acetals yields a quite different product, namely, iodonium ylide formation (Scheme 26).[48,49]

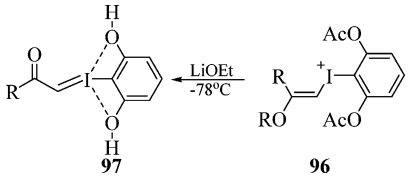
β-Dicarbonyl iodonium ylides are stable well-characterized compounds.[50]

Referring back to Scheme 5, intermediate **7** did not eliminate CH_3OH to yield **8** which could be called a monocarbonyl iodonium ylide. This compound was eventually synthesized by Ochai in 1997 (Scheme 27).[51]

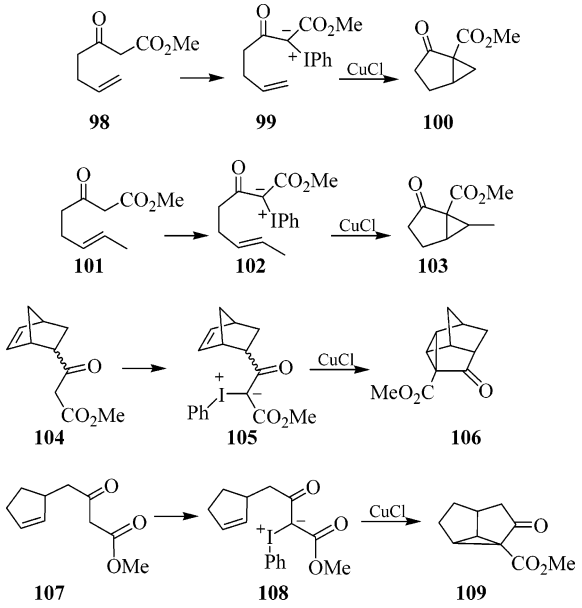
In contrast to **90**, **93** is stable in THF at −78 °C. When R = *n*-octyl, the molecule is stable only up to −30 °C. The traditional explanation for the stability of *β*-dicarbonyl iodonium ylides emphasizes the importance of resonance-delocalized *β*-dicarbonyl anion part. An X-ray structure of **94** reveals the resonance-delocalized negative charge as well as C−I···O secondary bonding.[52]



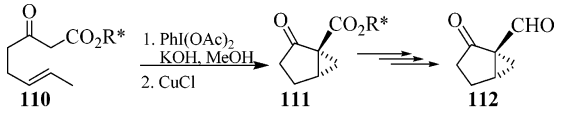
SCHEME 28



SCHEME 29



SCHEME 30



R* = 1-menthyl, 1(*S*)-3(*S*)-exo-hydroxy-2(*S*)-exo-naphthylbornane

I believe the secondary bonding between I and O contributes to the stability of **94** and its absence contributes to the instability of **93**. We synthesized a monocarbonyl iodonium ylide **95** which was stable probably because of the stabilization afforded by secondary bonding provided by the BF_4 counteranion.[53] A structural test of the importance of secondary bonding between I and O in iodonium ylide could be assessed on the basis of theoretical monocarbonyl ylide **97** which certainly could be synthesized (Scheme 28).

A very versatile and synthetically useful reaction of β-iodonium ylide which we pursued was intramolecular cyclopropanation.[54] The following are illustrative (Scheme 29):

An asymmetric synthesis of a vitamin D ring A synthon employed this intramolecular cyclopropanation reaction (Scheme 30).[55]

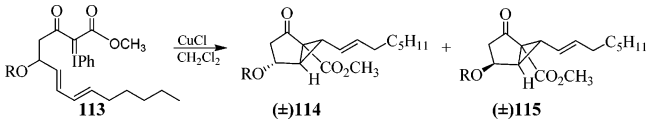
Useful prostaglandin intermediates, (±)-**114** and (±)-**115** were also synthesized (Scheme 31).[56]

Furthermore, a Buchner-type reaction was observed (Scheme 32).[57]

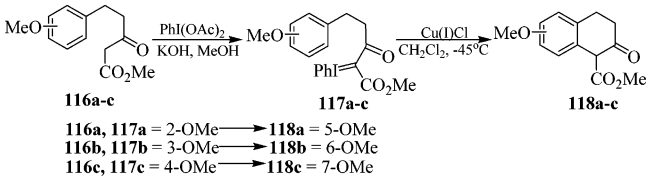
A reaction which I find fascinating within the area of β-dicarbonyl ylides is the iodine to oxygen migration of aryl group under thermal conditions (Scheme 33).[46,58−60]

In virtually all discussions of this rearrangement

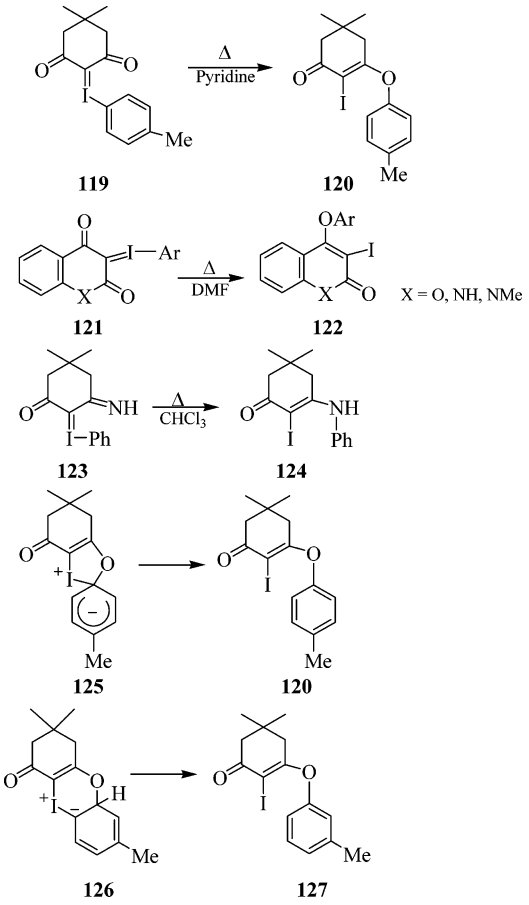
SCHEME 31



SCHEME 32



SCHEME 33



intermediate **125** is drawn. Nozaki et al.[46] found that **119** → **120** and no **127** as would result from **126**. They conclude that, "the rearrangement must proceed through a five-membered intermediate **125** rather than **126**".

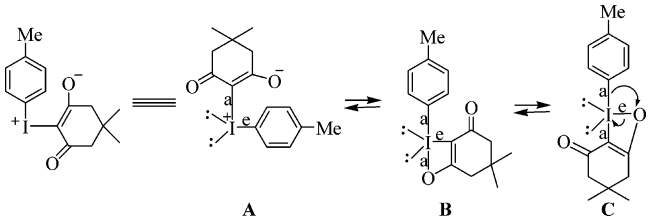
We consider this reaction to proceed by the ligand coupling mechanism suggested for S_NAr mechanism of diaryliodonium salt (Scheme 34).

In pseudorotamers **B** and **C** intramolecular addition of the anionic oxygen atom occurs. In **C** reductive coupling of the axial tolyl group and psuedo equatorial I−O group yields the product of aryl migration.

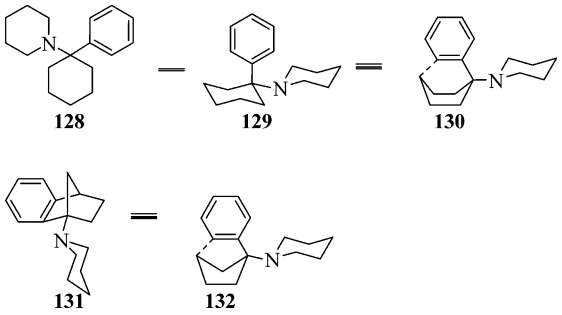
Synthetic Applications of Organohypervalent Iodine

We have used hypervalent iodine reactions in a wide range of cases where synthesis of a desired molecule was

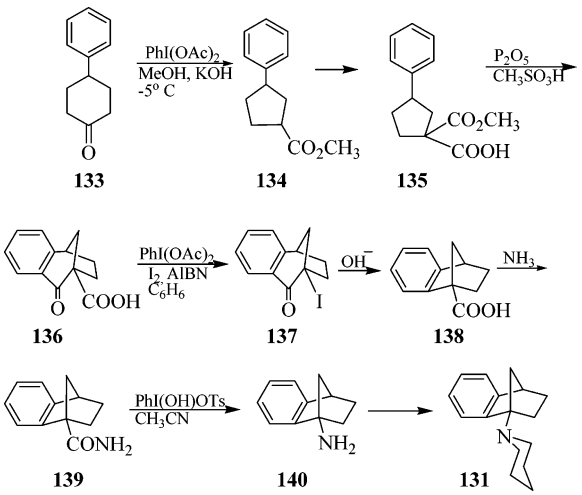
SCHEME 34



SCHEME 35



SCHEME 36

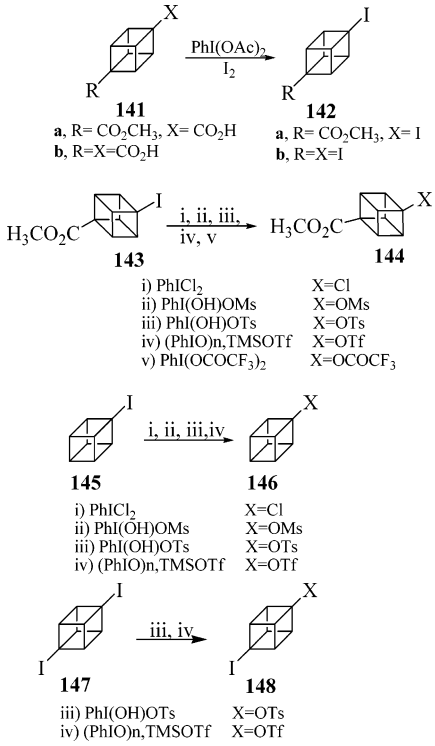


the goal rather than extensions of the scope of the method. For example, in a recent research program we were interested in synthesizing rigid analogues of phencyclidine (PCP) **131** as σ-receptors (Scheme 35).[61]

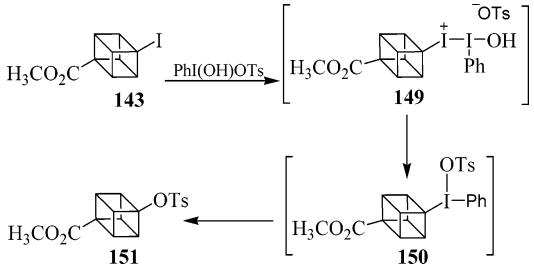
The synthesis **131** of represents a *tour de force* for the use of hypervalent iodine reagents in the synthesis as well as our degree of confidence in these methods (Scheme 36): A hypervalent iodine mediated Favorskii ring contraction (**133** → **134**), a hypervalent iodine Hunsdiecker reaction (**136** → **137**), and hypervalent iodine Hofmann rearrangement (**139** → **140**) were all used in the synthesis. A motto in our research group became *when in doubt, think hypervalent iodine*.

Another area of research within my group in which organohypervalent iodine played an indispensable role was in the functionalization of cubane. Eaton and Cunkle made the important observation that oxidation of iodocubane with *m*-CPBA yields stable I(III) and I(V) molecules which decomposed to yield cubyl-*m*-chlorobenzoate (Scheme 37).[62] These results inspired us to carry out a range of displacement reactions upon cubyl iodides. The

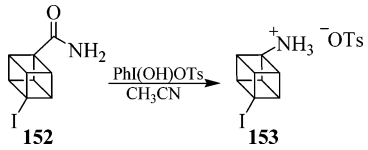
SCHEME 37



SCHEME 38



SCHEME 39



synthesis of cubane by Eaton produces cubane 1,4-dicarboxylic acid (**141b**).[63] Two organohypervalent iodine reactions, namely iodinative decarboxylation and oxidative displacement of iodine, played a key role in a range of synthetic transformations from **141b**.[64−67]

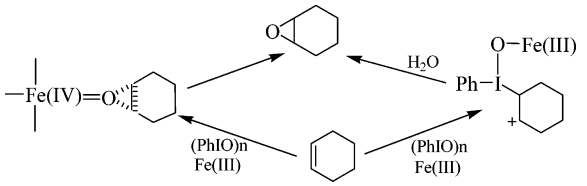
We envision these reactions as occurring via ligand exchange, e.g., in the case of **151** (**143** → **149** → **150** → **151**, Scheme 38).

1-Iodocubane-4-carboxamide (**152**) yields 1-iodo-4-ammoniumcubyl tosylate (**153**) (Scheme 39).[68]

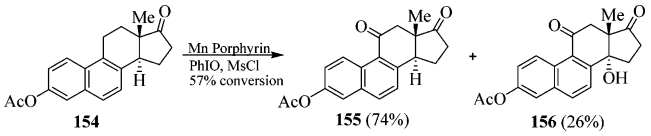
Other Reactions of Organohypervalent Iodine

This perspective has focused on our own work in the field. Other very significant research results have been passed over. For example, probably the best known hypervalent iodine compound is the Dess−Martin re-

SCHEME 40



SCHEME 41



agent.[69] Recently, 2-iodoxylbenzoic acid, IBX, has emerged as an extremely useful oxidant.[70−72] Nicolaou's application to the direct oxidation of saturated alcohols to α,β-unsaturated carbonyl compounds[73] and Corey's oxidation of 1,4-diols to γ-lactones[74] are significant. A stabilized formulation of IBX, namely, SIBX "Safe IBX" has been reported.[75−77]

PhIO as an Oxene Donor

I now come full circle returning to my original idea of oxygen atom transfer from PhIO (Scheme 1). This theme has been pursued widely by many researchers in connection with models for the mechanism of cytochrome P-450, the general objective being that PhIO serves as an surrogate oxene donor in place of molecular dioxygen. My interest in this area was reawakened by the realization that reactions of PhIO require its conversion to the electrophile PhI^+OH or PhI^+OX. We found that $Fe(ClO_4)_3 \cdot 9H_2O$/ PhIO/ MeOH/ H_2O effected epoxidation of *E*- and *Z*-stilbene. We[78] as well as Valentine et al.[79] used as metal component a nonredox $ZnCl_2$ and $Al(OTf)_3$ in epoxidation and both concluded that PhI^+O-M was the key reaction intermediate. Of course the distinction between the two processes, namely, oxene donation and electrophilic addition of PhI^+O-M is fundamental (Scheme 40).

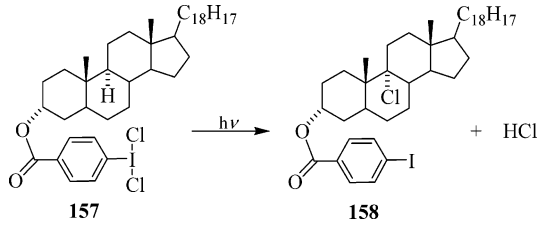
We concluded that model oxygenase system using PhIO involved creation of electrophilic iodonium species and products derived from electrophilic addition of iodine(III) to the alkene. Our results with bleomycin Fe(III)−PhIO were less clear and could not be reconciled with those of Hecht et al.[80] on the oxidation of olefin with Fe(III)·BLM + PhIO. In our work with Zn(II)·BLM a similar distribution of *cis*- and *trans*-stilbene was obtained as those reported by Hecht et al. in the Fe(III)·BLM system.

At about this time, a crystal structure was obtained on Mn(IV)·2PhI(O)Cl complex **2**. This reagent caused high yield (53%) epoxidation of of *E*-stilbene and C−H insertion in cyclohexanone in 7.5% yield.[81]

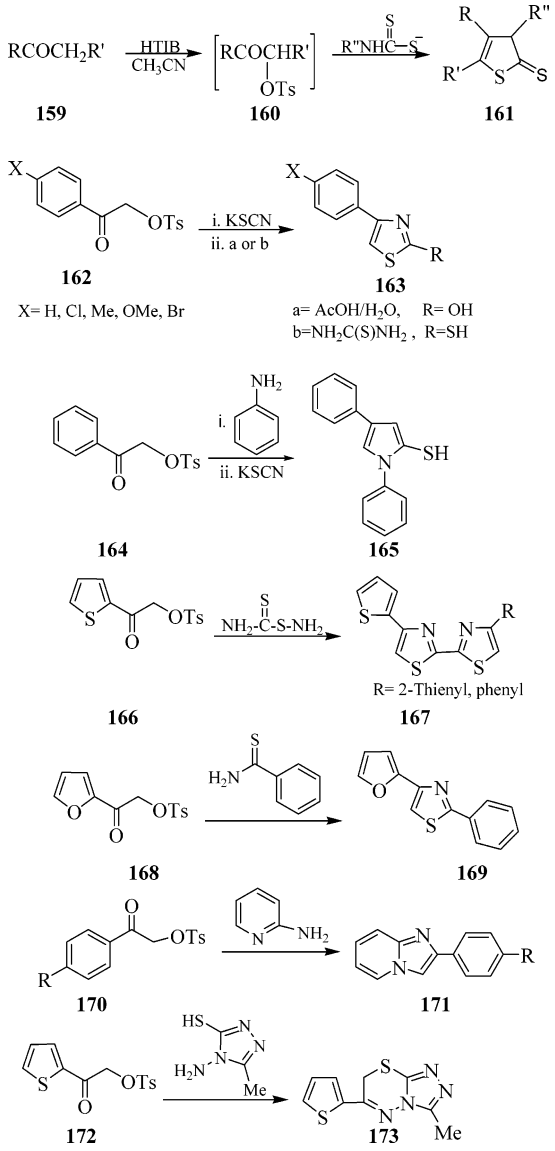
A shift in focus away from oxygenase modeling toward useful synthetic oxidizing reagent based upon PhIO−metal complex has occurred. High chemical yields and high enantioselectivity has been achieved with Schiff base complexes of manganese(III),[82] ruthenium(II),[83] and ruthenium(III).[84]

Iodosylbenzene complexes also catalyze hydroxylation of various hydrocarbons. Breslow et al.[85] have some very interesting steroidal examples (Scheme 41).

SCHEME 42



SCHEME 43

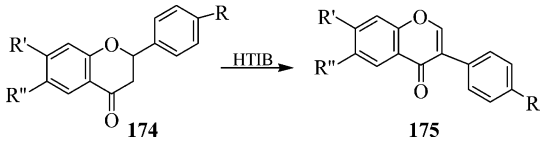


From a chronological viewpoint, it is of interest that 30 years ago Breslow discovered one of the textbook examples of remote functionalization in steroids using hypervalent iodine (Scheme 42).[86]

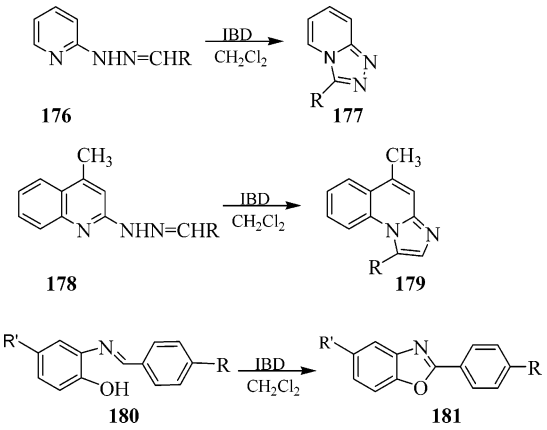
Contribution of Prof. Om Prakash

Professor Prakash has been an equal contributor to our work on organohypervalent iodine, and we have many joint papers and reviews.[87−90] Fortunately, he has been able to spend sabbatical leave from Kurukshetra University in my laboratory, and he has established a school

SCHEME 44



SCHEME 45



of hypervalent iodine in India. I have gained substantially from a flow of postdoctoral workers from his group over the years. Professor Prakash has recently focused on heterocyclic synthesis using hypervalent iodine reagents and achieved impressive results. The following examples indicate the essential utility of these reagents in heterocyclic synthesis. Om together with his colleague Professor Shiv P. Singh developed an extremely versatile synthesis of a wide range of heterocyclic compounds which proceed from the following generalization. A ketone with a methylene group, and most generally a methyl ketone, upon treatment with HTIB yields an intermediary α-tosyloxy ketone. In a one-pot process a nucleophile is added and the corresponding heterocycle is formed (Scheme 43).[91−96]

Several valuable applications to flavonoid-type compounds have been reported from these laboratories. Particularly interesting is a 1,2-aryl shift which constitutes a useful method for synthesis of isoflavones (Scheme 44).[97]

Hypervalent iodine is also valuable in the oxidative cyclization of heteroaryl hydrazones and phenolic Schiff's bases (Scheme 45).[98,99]

Conclusion

The main reaction covered in this Perspective is the α-functionalization of the carbonyl compounds using various hypervalent iodine reagents. These reagents are not only useful for α-hydroxylation of carbonyl compounds but also for a large range of α-sulfonyloxylation, α-phosphorylation, α-phosphoryloxylation, and α-amination reactions. Specific β-functionalization can be carried out and in some cases γ-functionalization is possible. This versatility is not matched by that of any other reagents commonly used for α-hydroxylation of carbonyl compounds such as oxo(diperoxymolybdenum)pyridine−hexamethylphosphoric triamide (MoOPH)[100−102] and the Davis reagent[103,104] (camphorylsulfonyl)oxaziridine). Other methods include addition of molecular oxygen (O_2) to a lithium enolate with subsequent reduction of the thus-formed α-hydroxyperoxy group by either by triethyl phosphite[105,106] or zinc in acetic acid,[107] oxidation of silyl enol ethers with dioxygen,[108] MCBA,[109−115] osmium tetraoxide−*N*-methylmorpholine *N*-oxide,[116] chromyl chloride,[117] lead teraacetate,[118] direct oxidations with *N*-sulfonyloxaziridines,[104,119] benzeneseleninic anhydride,[120] dimethyl dioxirane,[121,122] or thallium(III) nitrate.[123] Use of organohypervalent iodine reagents avoids toxic lead(IV), chromium and thallium(III) reagents; moreover, the iodine(III) reagents are operationally more convenient to work with as compared to these methods.

Organohypervalent iodine reagents, which are quite stable at room temperature and less toxic, can provide superior and safer alternatives to these toxic reagents. The iodine(III) based methods are more effective than others because of its ease, simplicity, generality and efficiency. Another important aspect of this approach is the ability to proceed directly to next step without isolation of the α-oxidized ketone. One-pot syntheses of a wide variety of heterocyclic compounds are available as a result of this approach. α-Tosyloxyketones, used in such one-pot heterocyclic syntheses, are readily accessible through HTIB-mediated oxidations. They are synthetically equivalent to α-haloketones[124] but are more stable and are not lachrymatory. Finally, iodobenzene produced as side product can be recycled to regenerate the iodine(III) reagents.

Future of Organohypervalent Iodine

I strongly expect that organohypervalent iodine will play an increased synthetic role in selective hydroxyl group oxidation. This is because PhIO and $PhIO_2$ can be converted into many modified oxidizing reagents of varying selectivity. Co-oxidants, polymer bond variants and chirally modified forms will also play a big role. Certain processes lend themselves well to industrial scale-up. For example, the hypervalent iodine mediated Hoffmann rearrangement[125] is an extremely efficient scalable process.

Because of the hypervalent iodine's propensity for secondary bonding not only will novel structures emerge in future, but forthcoming information about structure will also play a key role in mechanistic investigations. The contemporary description of mechanistic pathways in this area is generally vague, speculative, and totally unsupported by serious physical organic research. Likewise, theoretical calculations have not added much, but this definitely should change.

Acknowledgment. We thank Sociedad Química y Minera de Chile S.A. (SQM), the donors of the award for Creative Research and Application of Iodine Chemistry. I thank many graduate students and postdoctoral workers who have carried out this chemistry. My first grant on hypervalent iodine was from PRF in 1982 and subsequent funding from NSF is also gratefully acknowledged. Support from ONR was invaluable. I also thank Harpreet Kaur and Rajesh Naithani for the assistance in putting together this Perspective.

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