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Polyvalent Iodine in Organic Chemistry

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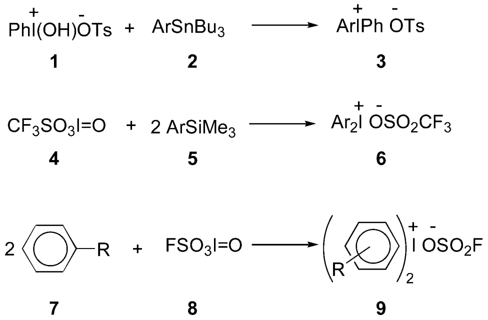
Tricoordinate, I(III), and pentacoordinate, I(V), polyvalent iodine compounds have been known for over a century. In the last twenty years, new polyvalent iodine reagents have been introduced along with synthetic methodologies, based on these and derived reagents, that play an ever increasing role in contemporary organic chemistry. In this Perspective, an overview of these developments is provided with emphasis on the chemistry and uses of aryl-, alkenyl-, and alkynyliodonium salts in preparative and synthetic organic chemistry. It is hoped that this brief overview, along with recent more comprehensive reviews of the field, will stimulate further developments and applications of this useful class of compounds across a broad spectrum of organic chemistry.

Iodine, element 53, was first isolated from the ash of seaweed in 1811 and has an important role in inorganic, organic, and biochemistry. Its name reflects the lustrous, deep purple color of resublimed crystalline iodine and derives from the Greek term for "violet-colored." Iodine is an essential trace element for humans and plays an important role in many biological organisms. Pure KI was used as early as 1819 to treat goiter, an enlargement of the thyroid gland. The thyroid gland produces thyroxine, a hormone essential for metabolism regulation.

Iodine is most commonly found in organoiodine compounds in the monovalent form with an oxidation state of −1. It generally forms relatively weak bonds with carbon, with a bond disassociation energy of about 55 kcal/mol for a typical C−I bond, and plays an important role in organic reactions and synthesis. However, as a consequence of being the largest, least electronegative, and most polarizable of the common halogens, iodine also forms stable, polycoordinate, high-valent compounds, usually as I(III) and I(V) species. In fact, the first polyvalent organic iodine compound, $PhICl_2$, has been known for over a century since first prepared by the German chemist Willgerodt in 1886, just 75 years after the discovery of iodine itself.

In this Perspective, based in part on a George A. Olah Hydrocarbon or Petroleum Chemistry Award address,[1] the focus will be on the increasing uses of polyvalent organoiodine reagents in organic chemistry in the last two decades,[2−26] with emphasis on aryl-, alkenyl-, and alkynyliodonium chemistry[27] along with metal-catalyzed cross coupling as well as some miscellaneous reactions.

SCHEME 1



The increasing importance and significance of multivalent organoiodine compounds may be attributed to factors such as the following: (1) They are readily made from relatively inexpensive commercial precursors such as $PhICl_2$, $PhI(OAc)_2$, and PhI(OH)OTs; they tend to be selective in their reactions and generally can be used under mild reaction conditions (common solvents at or near room temperature). (2) Iodine(III) reagents resemble the reactivity characteristics of Hg(II), Tl(III), and Pb(IV) cognates without the toxic and environmental problems associated with these heavy metal species. (3) The mode of reaction of I(III) compounds, such as ligand exchange, reductive elimination, etc., show similarities with transition-metal species, especially the Ni-triad metals. As a consequence, much of the previous, well-developed chemistry of Hg(II), Tl(III), and Pb(IV) as well as some of the more recent, rich chemistry of the Pt- and Pd-metal systems may be carried out with the less expensive, less toxic, readily available, polyvalent iodine congeners.

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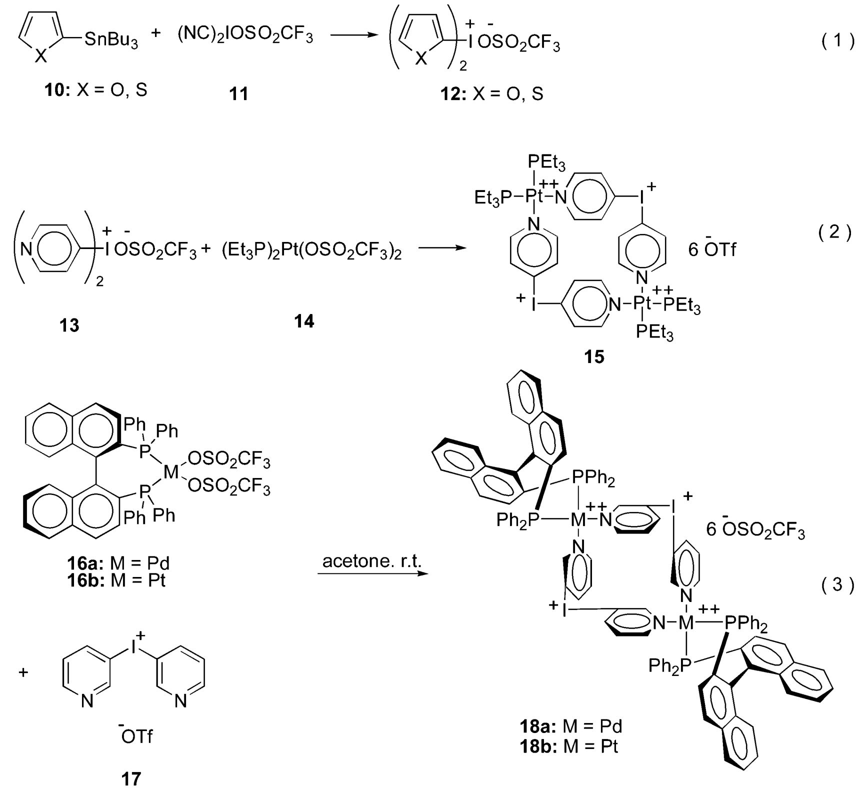
SCHEME 2

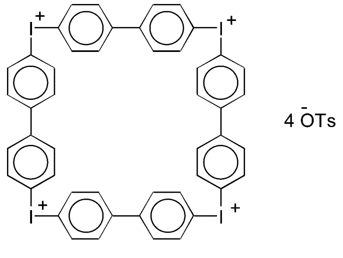


Hence, it is evident that these analogies, albeit clearly limited, open up new vistas and unique opportunities for polyvalent iodine reagents in organic chemistry. Because this Perspective is largely based upon an award address, it will emphasize our own ongoing contributions to the field with but selective recent examples from the work of many others, as summarized in the reviews cited.[2−27]

1. Aryliodonium Salts

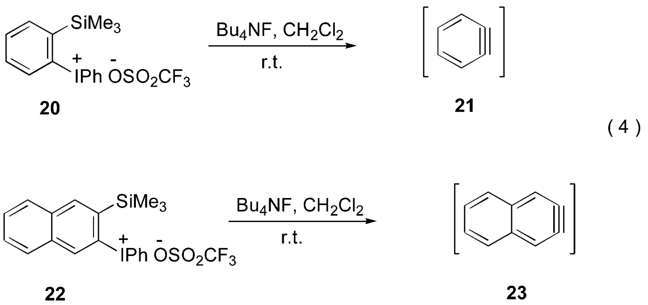
Aryliodonium salts are among the oldest, most common, stable and best investigated polyvalent iodine compounds.[2,19,23,24] Diaryliodonium tosylates[28] **3**, triflates[29] **6**, and fluorosulfonates[30] **9** are readily made from Koser's reagent, **1**, or $CF_3SO_3I{=}O$ and $FSO_3I{=}O$, respectively, as shown in Scheme 1. Aryliodonium salts can be used to directly arylate not only 1,3-dicarbonyl compounds such as Meldurm's acid[31] but also cyclic ketones such as cyclopentanone through cyclooctanone.[32] Diaryliodonium salts readily undergo various efficient metal-catalyzed cross-coupling reactions such as Suzuki-,[33] Stille-,[34] and Heck-type[35] couplings. They are particularly efficient and useful reagents for the Pd/Cu-catalyzed arylation of enynes and electron-deficient alkynes.[36,37] Diaryliodonium salts also undergo alkoxycarbonylations.[38] Bis(heteroaryl)iodonium salts such as **12** have also been prepared in good yields[39,40] as shown in eq 1 of Scheme 2, but their chemistry has not been explored. In contrast, the bispyridyliodonium triflates[40] **13** and **17** have been employed in the self-assembly of hybrid molecular squares[41] **15** (Scheme 2, eq 2) as well as chiral molecular squares[42] **18** (Scheme 2, eq 3).

An interesting aryliodonium species is the macrocyclic[43,44] tetraaryltetraiodonium compound **19** that served as the inspiration in the subsequent self-assembly of a wide range of metallacyclic polygons[45] and polyhedra.[46]



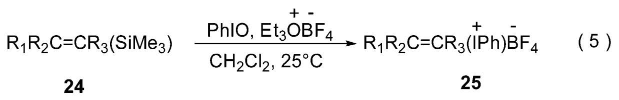
19

Finally, recently Kitamura and co-workers[47,48] have prepared **20** and **22** that serve as premier precursors for the essentially quantitative generation of benzyne, **21**, and 2,3-didehydronaphthalene, **23**, respectively (eq 4).

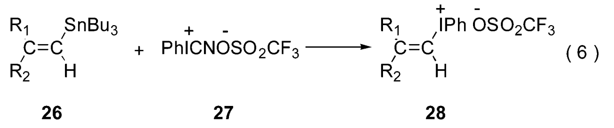


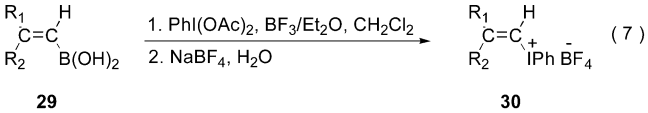
2. Alkenyliodonium Salts

Although a few alkenyliodonium salts have been known for many years, it has only been in the last two decades that these compounds have become readily available and their chemistry developed. Ochiai and coworkers[49] were the first to report a general entry into alkenyliodonium salts **25** via alkenylsilanes **24** as shown in eq 5. A general, simple procedure[50] for the stereospecific synthesis of alkenyliodonium salts, with retention of olefin geometry, involves the use of phenyl(cyano)iodonium triflate **27** as an iodonium-transfer reagent (eq 6). This procedure also works for the preparation of the parent vinyliodonium triflate, $H_2C{=}CHI^+Ph^-OSO_2CF_3$.[51] Similarly, the reaction of vinylboronic acids **29** or esters with $PhI(OAc)_2$ yields alkenyliodonium salts with retention of olefin configuration (eq 7).[52]

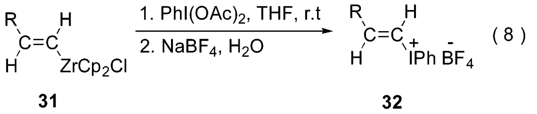


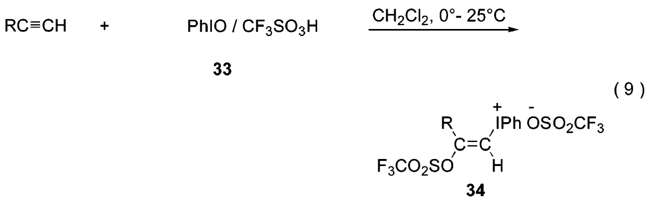
$$\underset{\mathbf{24}}{R_1R_2C{=}CR_3(SiMe_3)} \xrightarrow[CH_2Cl_2,\ 25°C]{PhIO,\ Et_3\overset{+}{O}\overset{-}{B}F_4} \underset{\mathbf{25}}{R_1R_2C{=}CR_3(\overset{+}{I}Ph)\overset{-}{B}F_4} \quad (5)$$



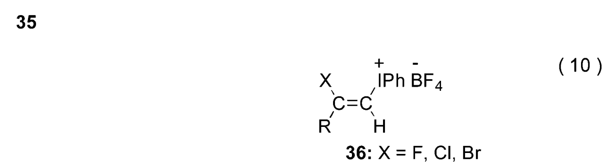


In a similar manner, vinylzirconium derivatives **31** afford alkenyliodonium salts **32** (eq 8)[53] in a stereospecific manner. A variety of functionalized alkenyliodonium salts can be obtained by the addition of hypervalent iodine reagents to alkynes.[54−64] Treatment of terminal alkynes with **33** affords the interesting difunctional E-alkenyliodonium triflate **34** (eq 9).[57−59]





In contrast, (Z)-β-substituted alkenyliodonium salts **36** are obtained by a nucleophilic addition of halides to alkynyliodonium salts **35** (eq 10).[65,66]

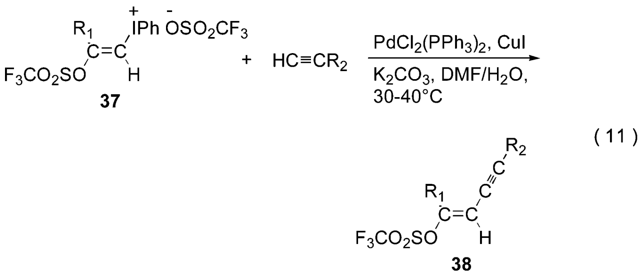


Alkenyl(phenyl)iodonium salts are highly reactive with nucleophiles due to the superior leaving ability of the iodonium moiety. The most reactive commonly employed leaving group is the triflate CF_3SO_3, which is $\sim 10^6$ times more reactive than halides.[67] However, the loss of neutral PhI from an iodonium salt is comparable to the loss of N_2 from a diazonium salt. In fact, recent data[68] establishes that the PhI^+ moiety is a million times better leaving group than a triflate, or about 10^{12} times better as a leaving group than halides. As a consequence, alkenyliodonium salts have been used in solvolysis reactions[3,69−75] to gain new insights into vinyl cation[76,77] chemistry.

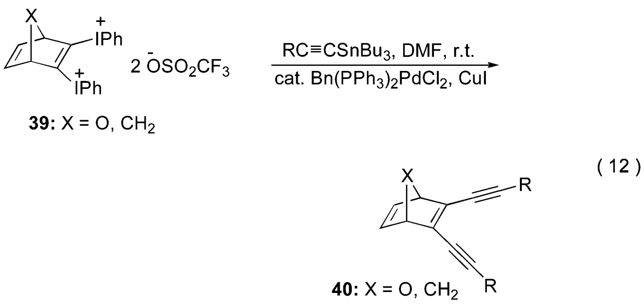
Alkenyliodonium salts undergo reaction with a wide variety of nucleophiles,[78−90] generally with retention of configuration. Ligand coupling and S_N2 addition−elimination like mechanisms have been invoked[7,12] to account for these observations.[91]

Due to the superior leaving ability of the PhI^+ moiety, alkenyliodonium salts are excellent electrophilic partners in a variety of metal-catalyzed cross-coupling reactions. Moriarty and co-workers[92] demonstrated the stereospecific $Pd(OAc)_2$-catalyzed cross coupling of various alkenyliodonium salts with vinyl ketones, $CH_2{=}CHCHO$ and $CH_2{=}CHCO_2CH_3$. We established the stereospecific Stille coupling of alkenyliodonium triflates with alkynylstannanes.[93] Alkenyliodonium salts have been cross-coupled with the aid of transition-metal catalysts with allylic alcohols,[94] organoboron compounds,[95] organostannanes,[96] and Grignard reagents[97] as well as uracyl nucleosides[98] and benzylic organozinc reagents.[99]

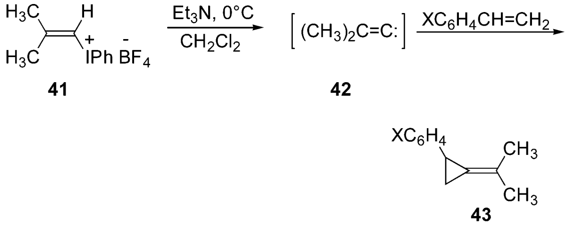
In collaboration with Zefirov, we have shown[100] that iodonium salts preferentially and selectively couple with alkynes in the presence of a triflate in the same molecule, **37**, to give conjugated enynes, **38**, stereospecifically (eq 11).



Similarly, bis-iodonium salts **39** can be cross coupled with alkynylstannanes to give[101] bicyclic enediynes **40** (eq 12). A similar coupling reaction was recently used to make unique dinuclear complexes with a photochromic bridge.[102]



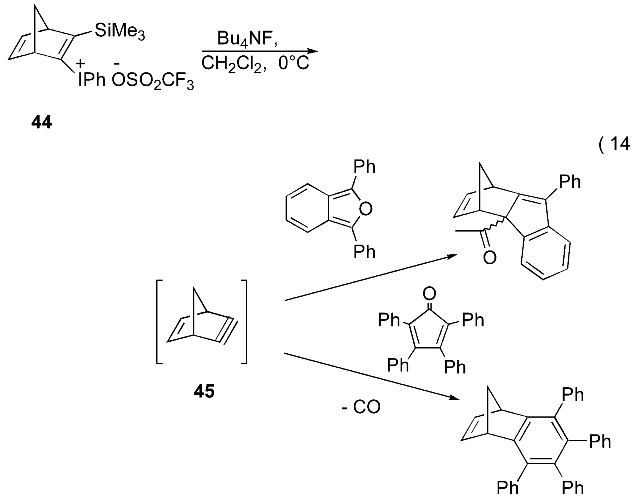
Primary vinyliodonium salts **41** may be used[103] to generate alkylidenecarbenes[104−106] **42** (eq 13). Relative reactivity studies[107] with substituted styrenes (eq 13) and cis/trans olefins established that, analogous[108−111] to the triflate, $(CH_3)_2C{=}CHOSO_2CF_3$-generated alkylidenecarbene, the iodonium derived species is the free carbene, rather than a carbenoid,[104−106] and it is formed and reacts in the singlet state.[107]



41 42 43

(13)

Analogous to the generation of benzyne from **20** (eq 4), Kitamura and co-workers[112] recently generated and trapped the highly strained bicyclic alkyne, **45**, from iodonium salt **44** (eq 14).

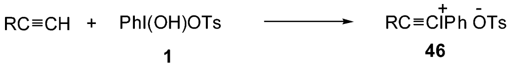


44 45

(14)

3. Alkynyliodonium Salts

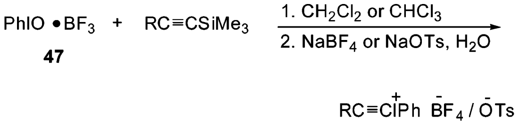
Alkynyliodonium salts are the most recent members of the family of polyvalent organic iodine compounds. Although there were early attempts[27] to prepare such species, the first stable, fully characterized alkynyliodonium salts were tosylates, **46**, prepared by Koser and co-workers[113,114] from terminal alkynes and **1** (eq 15).



$$RC\equiv CH + \underset{\mathbf{1}}{PhI(OH)OTs} \longrightarrow \underset{\mathbf{46}}{RC\equiv C\overset{+}{I}Ph\ \overset{-}{O}Ts} \qquad (15)$$

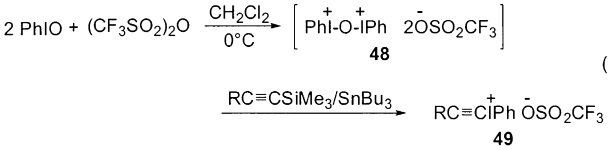
It is now recognized that non-nucleophilic counterions, such as various sulfonates or tetrafluoroborate, are required in order to stabilize alkynyliodonium salts. In the last two decades, a number of general approaches to diverse alkynyliodonium salts have emerged; most involve the reaction of a terminal alkyne or its lithiated, stannylated, or silylated derivative with such λ^3-iodane reagents as PhI(OH)OTs, different Lewis acid complexes of PhIO or $PhI(CN)OSO_2CF_3$. Over the years, improvements in Koser's original synthesis of alkynyliodonium tosylates (eq 15) were developed,[115,116] and these improvements led to the preparation of numerous new alkyliodonium salts, including those with long alkyl chain[117] and chiral[118] alkynyl ligands affording liquid−crystalline systems. Most recently, with minor modifications, this procedure has been adopted for the synthesis of solid support, polymer anchored alkynyliodonium tosylates.[119]

A number of important procedures have been developed for the preparation of alkynyliodonium salts based upon iodosylbenzene, PhIO. Iodosylbenzene is a yellowish, amorphous powder, easily prepared by the hydrolysis of commercial $PhI(OAc)_2$ with aqueous NaOH.[120] Interaction of BF_3 complex **47** of PhIO with alkynylsilanes, followed by treatment with aqueous $NaBF_4$ or NaOTs, affords the respective alkynyliodonium salts (eq 16) in good yields.[121−124]



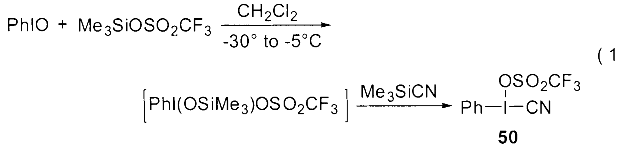
$$\underset{\mathbf{47}}{PhIO\bullet BF_3} + RC\equiv CSiMe_3 \xrightarrow[\text{2. NaBF}_4\text{ or NaOTs, H}_2\text{O}]{\text{1. CH}_2\text{Cl}_2\text{ or CHCl}_3} RC\equiv C\overset{+}{I}Ph\ \overset{-}{B}F_4 / \overset{-}{O}Ts \qquad (16)$$

Interaction of PhIO with triflic anhydride affords Zefirov's reagent **48**, which can be used in situ to react with alkynylsilanes or stannanes to afford the corresponding alkynyliodonium triflates **49** in good yields (eq 17).[125] This procedure was used to also prepare the parent ethynyl(phenyl)iodonium triflate $HC\equiv CI^+Ph^-OSO_2CF_3$ whose X-ray structure was also determined.[126] Variations of these procedures were recently reported, including the use of alkynylboronates as precursors.[127,128] All of the above methods are, however, limited essentially to the formation of only β-alkyl- or β-aryl-substituted alkynyliodonium salts as most functional groups do not tolerate reagents **1**, **47**, **48** and the reaction conditions employed.



$$2\,PhIO + (CF_3SO_2)_2O \xrightarrow[0°C]{CH_2Cl_2} \underset{\mathbf{48}}{\left[Ph\overset{+}{I}\text{-}O\text{-}\overset{+}{I}Ph\ \ 2\overset{-}{O}SO_2CF_3\right]} \xrightarrow{RC\equiv CSiMe_3/SnBu_3} \underset{\mathbf{49}}{RC\equiv C\overset{+}{I}Ph\ \overset{-}{O}SO_2CF_3} \qquad (17)$$

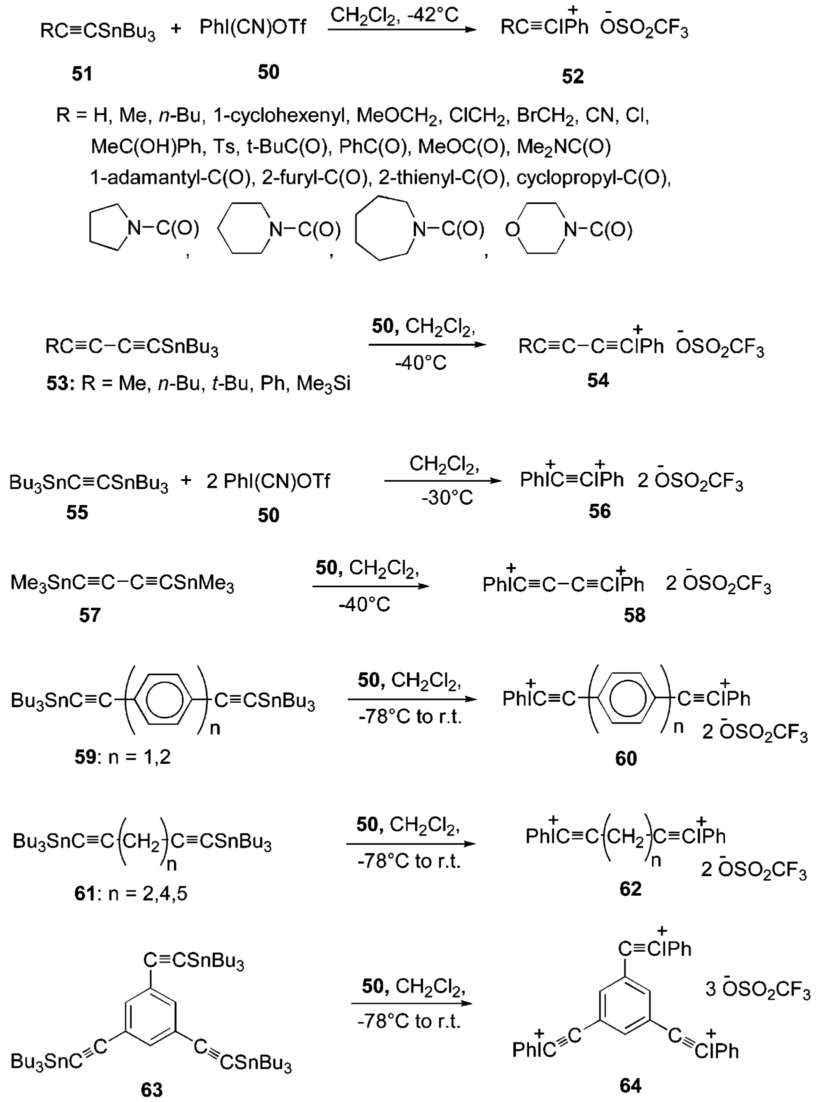
The most general, versatile, and convenient method of preparing a wide range of alkynyliodonium salts involves $PhI(CN)OSO_2CF_3$ **50** as an iodonium transfer reagent. This stable microcrystalline reagent is conveniently prepared from commercial precursors (eq 18).[129,130]



$$PhIO + Me_3SiOSO_2CF_3 \xrightarrow[-30°\text{ to }-5°C]{CH_2Cl_2} \left[PhI(OSiMe_3)OSO_2CF_3\right] \xrightarrow{Me_3SiCN} \underset{\mathbf{50}}{Ph\text{—}\overset{OSO_2CF_3}{\overset{|}{I}}\text{—}CN} \qquad (18)$$

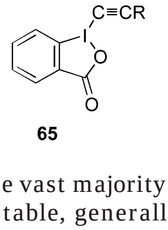
Ligand exchange between a wide range of alkynylstannanes and **50** under mild conditions readily affords a great variety of alkynyliodonium triflates in good yields as summarized in Scheme 3. Diverse β-functionalized alkynylstannanes[131] **51** provide a range of β-functionalized alkynyliodonium triflates **52**.[132,133] Diynylstannanes **53** afford diynyliodonium triflates **54**.[134] Novel bis-iodonium acetylenes **56** and **58** are formed from **55** and **57**, respectively.[135,136] Conjugated, **59**, and unconjugated, **61**, bis-alkynes yield the respective bis(alkynyliodonium)salts **60** and **62**,[137] and the tris-alkynyliodonium species **64** is obtained from **63**.[138]

SCHEME 3

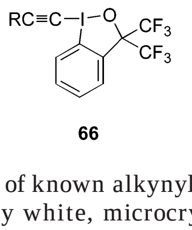


Feldman and co-workers have recently used **50** and this methodology for the high-yield (80−90%) preparation of alkynyliodonium tosylamides[139,140] as well as in the formation of substituted dihydrofurans and cyclopentannelated tetrahydrofurans from the appropriate functionalized alkynyliodonium salts.[141,142]

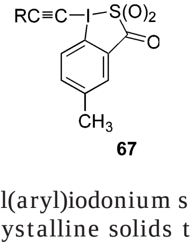
A number of heterocyclic alkynyliodonium species **65**−**67** have also been reported, but their chemistry has not be extensively explored to date.[143−148]



65



66



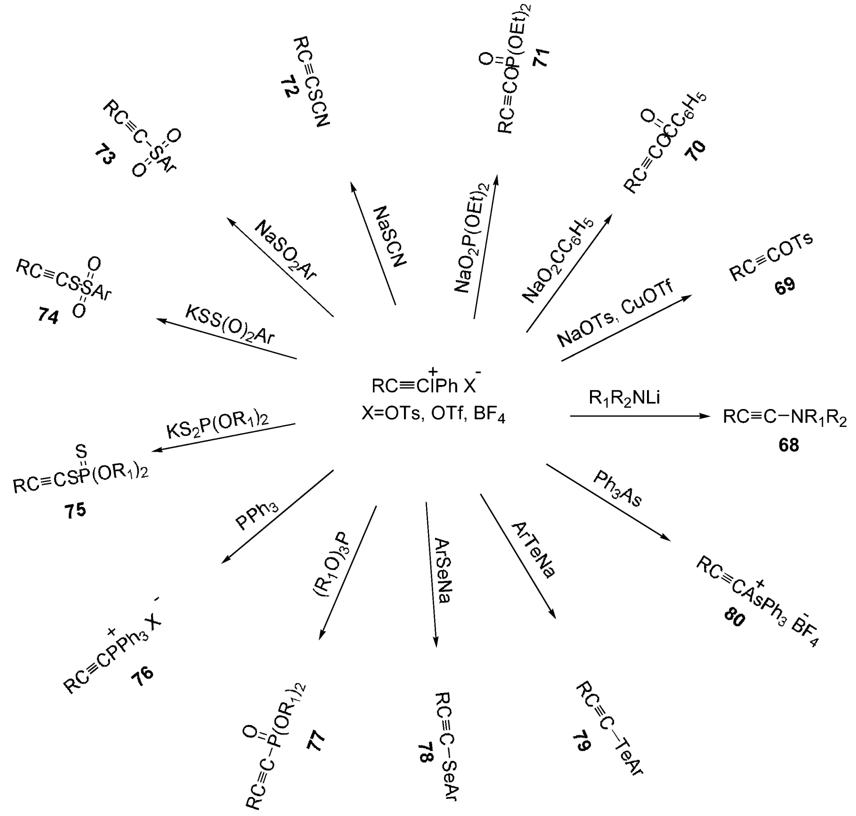
67

The vast majority of known alkynyl(aryl)iodonium salts are stable, generally white, microcrystalline solids that are insoluble in water and nonpolar organic solvents and moderately soluble in acetonitrile and other polar organic solvents.[27] Several have been fully characterized by X-ray, and all are easily characterized by IR and NMR. In the IR spectrum, the triple-bond absorption occurs between 2120 and 2190 cm^{-1}, and in the ^{13}C NMR spectrum the α-acetylenic carbon is generally found between 10 and 40 ppm (upfield from the normal acetylene signal due to the heavy atom effect of the iodine), and the β-carbons generally are found between 110 and 120 ppm (downfield from the normal acetylene signals due to resonance with the PhI^+ moiety). X-ray data confirm the expected pseudotrigonal bipyramidal or T-shaped geometry for these species.[27]

Alkynyliodonium salts are very useful reagents, for they serve as electrophilic acetylene equivalents, a reversal from the usual nucleophilic reactivity of acetylides. Due to the aforementioned superior leaving ability of the PhI^+ moiety, alkynyliodonium salts readily react with a large variety of nucleophiles to afford functionalized alkynes. Likewise, due to the strong inductive electron-withdrawing nature of the PhI^+ group, ($\sigma_I = 1.24$ for PhI^+ vs $\sigma_I = 0.39$ for iodine itself),[149] alkynyliodonium salts readily undergo Michael-type conjugate addition reactions as well as Diels−Alder and 1,3-dipolar cycloadditions.

A wide range of 1,3-dicarbonyl compounds can be directly alkynylated with alkynyliodonium salts.[147,150−153]

SCHEME 4

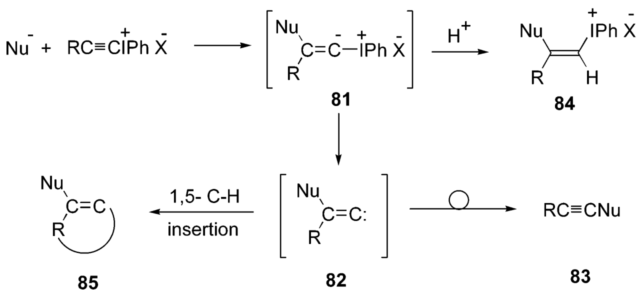


However, simple ketones or aldehydes or their enolates cannot be alkynylated as the enolates, analogous to other hard nucleophiles such as alkoxides, decompose alkynyliodonium salts.

Alkynyliodonium salts, like their aryl and alkenyl analogues, can be efficiently coupled with a range of organometallic species. Interaction with vinylcopper reagents[154] is stereospecific as is the reaction with organozirconium complexes[155−157] with retention of olefin geometry resulting in conjugated enynes. Dialkynyl cuprates lead to conjugated diynes, including unsymmetrical diynes.[158] Alkynylcubane has been made via cross-coupling of iodocubane with an alkynyliodonium triflate.[159] Alkynyliodonium salts undergo alkoxycarbonylation in the presence of CO_2 in methanol or ethanol in the presence of catalytic $Pd(OAc)_2$ and Et_3N to give $RC{\equiv}CCO_2R^1$ in good yields.[160]

Reactions of various alkynyliodonium salts with N, O, S, P, Se, Te, and As nucleophiles are summarized in Scheme 4. Specifically, reaction with lithiumamides affords aminoalkynes[161−163] **68**, including interesting push−pull alkynes.[164] Reaction with tosylate, benzoate, and diethyl phosphate salts provides the hitherto unknown alkynyl tosylates[115,116,165,166] **69**, alkynyl benzoates[167,168] **70**, and alkynyl phosphate[167,169] esters **71**. These alkynyl compounds combine two of the simplest most common functional groups in organic chemistry, namely the triple bond and esters, into a single molecular entity.[170] Moreover, the alkynylbenzoates **70** are potent serine protease inhibitors,[171] whereas the alkynyl phosphates **71** are both serine protease[172] and bacterial phosphotriesterase[173−175] inhibitors.[170]

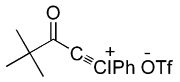
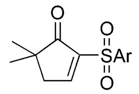
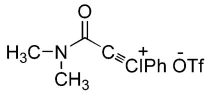
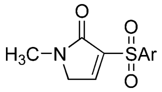
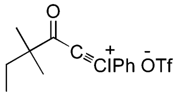
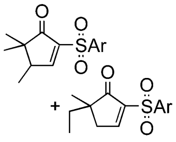
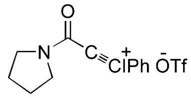
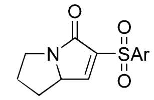
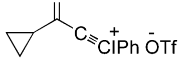
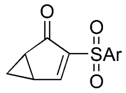
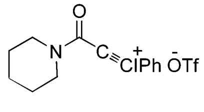
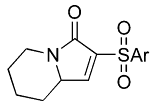
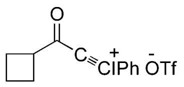
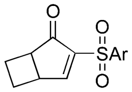
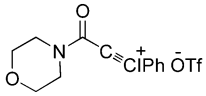
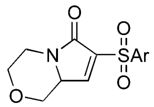
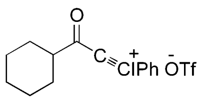
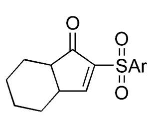
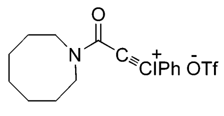
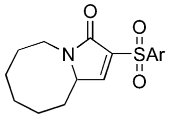
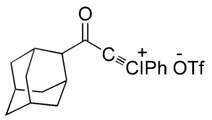
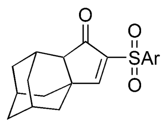
SCHEME 5



Interaction with various sulfur nucleophiles provides ready access to alkynyl thiocyanates[176] **72**, alkynyl sulfones[177,178] **73**, alkynyl thiotosylates[179] **74**, and alkynyl phosphorodithionates[180] **75**. Phosphorus nucleophiles afford alkynylphosphonium salts[137,181] **76** as well as alkynylphosphonates[182] **77**. Acetylenic selenides **78** and tellurides **79** are obtained via reaction with NaSeAr and NaTeAr, respectively.[183] Likewise, Ph_3As gives alkynyl(triphenyl)arsonium salts **80**.[184]

All available evidence indicates that the mechanism[2,23,27] of these reactions involves a conjugate addition of the nucleophile to the electron-deficient β-carbon to form an iodonium ylide **81** (Scheme 5). Loss of iodobenzene forms the alkylidenecarbene **82**, which rearranges via migration of either R or the nucleophile to provide the final product **83**. Among the evidence for this mechanism is that in the presence of acid, ylide **81** can be trapped to give stable alkenyliodonium salts **84**. Moreover, if either the alkyl group or the Nu on the β-carbon

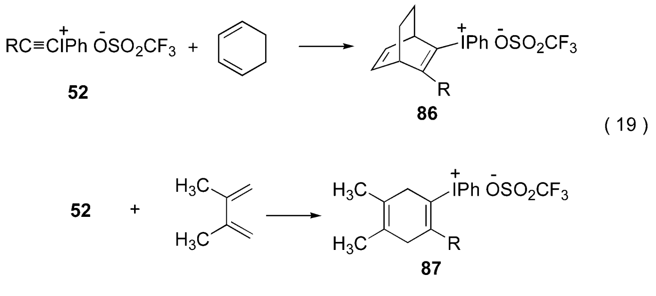
TABLE 1. Substituted Cyclopentenones and γ-Lactams via the Reaction of $NaO_2SC_6H_4CH_3$ with β-Keto and β-Amidoiodonium Triflates

Starting Iodonium Salt	Product	Starting Iodonium Salt	Product
			
			
			
			
			
			

of **82** has a 1,5-C−H bond, the carbene can insert and provide a cyclopentene or five-membered heterocycle **85**.

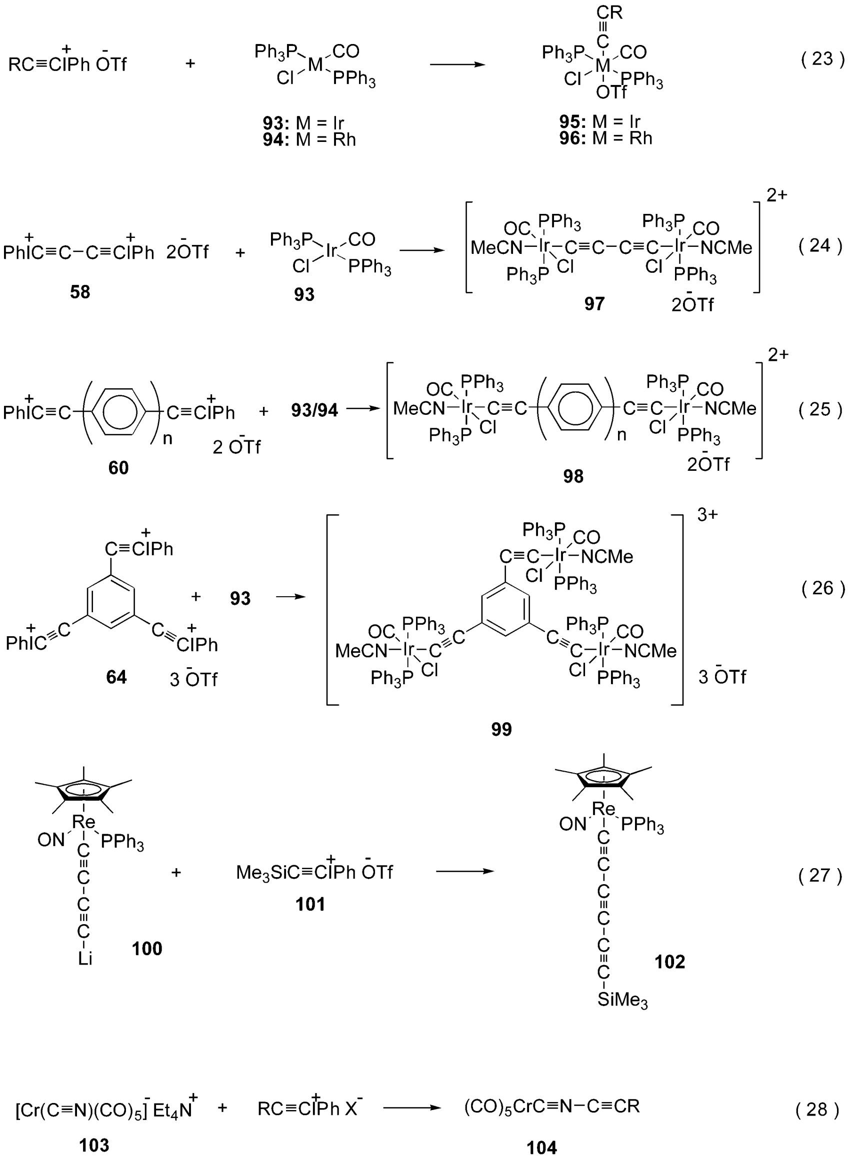
In fact, the formation of carbene **82** from alkynyliodonium salts via ylide **81**, and its subsequent 1,5-C−H insertion, has been exploited in synthesis. By reacting β-keto and β-amidoethynyliodonium triflates with NaO_2-SAr we have shown that cyclopentenones and γ-lactams readily form in moderate to good yields as summarized in Table 1.[185] Feldman and Mareska[186−188] have used this tandem Michael-addition/carbene-insertion procedure to prepare highly substituted dihydropyrrole derivatives via appropriate alkynyliodonium salts. Likewise, polycyclic alkaloids have been prepared using this approach.[140,189] Wipf and Venkatraman[190] have used the tandem Michael addition cyclization approach, via the addition of thioamides to alkynyliodonium salts, as a simple means to various thiazoles. The stereoselective synthesis of 1-acetyl-2-aminomethylcyclopropanes has been reported[191] based upon the addition of tosylallylamine anions and alkynyliodonium salts. Substituted benzofurans[192,193] as well as furopyridine derivatives[194] have been prepared via this methodology, along with 2-mercaptothiazoles.[195]

β-Functionalized alkynyliodonium salts **52** readily undergo Diels−Alder cycloadditions with symmetrical-dienes to afford cyclodducts **86** and **87** in good yields (eq19)[132] Diels−Alder reaction of **52** with unsymmetrically substituted dienes results in a mixture of two regioisomeric cyclohexadienes: low regioselectivity is observed in the case of 2-substituted dienes but better

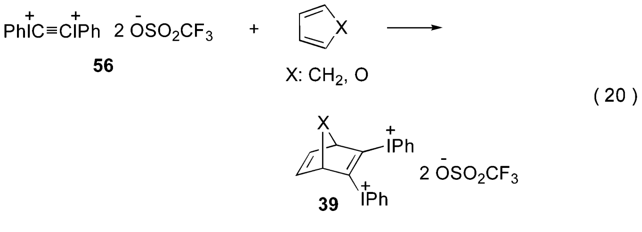


(19)

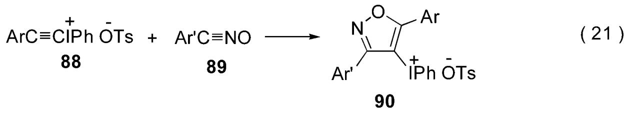
SCHEME 6

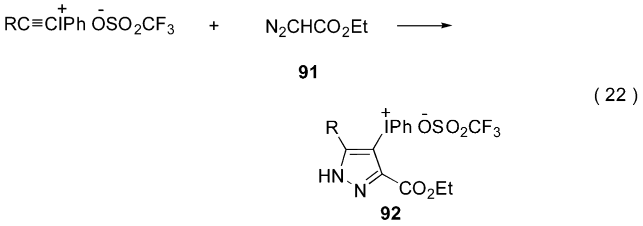


regioselectivity is found with 1-substituted dienes.[196] Likewise, Diels−Alder cycloaddition of **56** with furan or cyclopentadiene affords **39** in good yields (eq 20).[135]

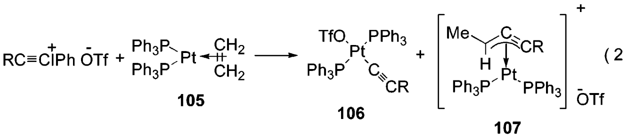


As alkynyliodonium salts are good 1,3-dipolarophiles, various [3 + 2] cycloadditions have also been investigated. Reaction of nitrile oxides **89** gives cycloadducts **90** as sole products in good yields (eq 21).[197] Similar reactions with diazocarbonyl compounds afford pyrazolyliodonium salts and methyl and phenyl azides give triazolyliodonium salts, albeit in low yields,[198] whereas ethyl diazoacetate **91** provides regioisomeric pyrazoles **92** in moderate yields (eq 22).[199]





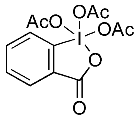
Finally, alkynyliodonium salts readily react with various organometallic nucleophiles to give diverse alkynylmetal complexes (Scheme 6, eqs 23−28). Reaction of alkynyliodonium salts with Vaska's complex **93** or its Rh analogue **94** give the hexacoordinate σ-alkynyl complexes **95** and **96**, respectively.[200] A similar reaction of **58**, **60**, and **64** leads to rigid-rod di- and trimetallic σ-acetylide complexes **97**−**99** (Scheme 6, eqs 24−26).[138,201] These reactions amount to the direct alkynylation of organometallic nucleophiles with alkynyliodonium salts, and the product complexes **95**, **96**, and **97**−**99** are of potential interest in NLO as organic conductors and other materials applications. In contrast, reaction of **101** or **103** with alkynyliodonium salts results in the alkynylation of a ligand, rather than the metal itself, to provide complexes **102**[202] and **104**,[203] respectively (eqs 27 and 28). Reaction of the π-ethylene-Pt(0) complex **105** with alkynyliodonium triflates can lead to either the σ-alkynyl platinum(II) complex **106** or the novel η3-propargyl/allenyl complex **107**, depending both on the nature of R and the exact reaction conditions (eq 29).[204]



(29)

4. Miscellaneous Reagents and Reactions

There are a large number of polyvalent iodine reagents known.[2−27] Several have become of special interest to organic chemists recently. Perhaps the most useful and widely used polyvalent organoiodine compound is the Dess−Martin reagent **108**. This stable, commercially available (Sigma-Aldrich) pentavalent periodinane has emerged as the reagent of choice for the oxidation of primary and secondary alcohols to aldehydes and ketones, respectively. The convenience of use, high chemoselectivity, and mild reaction conditions (neutral pH, room temperature, common solvents) have made this reagent especially useful for the oxidation of substrates containing sensitive functional groups. Due to its functional group tolerance, convenience of use, and unique, selective oxidizing properties, the Dess−Martin reagent is widely employed in complex natural product synthesis. Its synthetic applications have been highlighted in two recent overviews.[205,206]

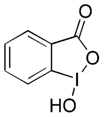


108

The unique oxidizing properties of **108** in key oxidation steps in the total synthesis of several natural products is best illustrated by such recent examples as the synthesis of CP-molecules,[207−214] cyclotheonamide B,[215] (±)-deoxypreussomerin A,[216] racemic brevioxime,[217] erythromycin B,[218] (+)-discodermolide,[219] (+)-cephalostatin 7,[220] (+)-cephalostatin 12,[220] (+)-ritterazine K,[220] 3-*O*-galloyl-(2*R*,3*R*)-epicatechin-4β,8-[3-*O*-galloyl-(2*R*,3*R*)-epicatechin],[221] fredericamycin A,[222] indolizidine alkaloids (−)-205A, (−)-207A, and (−)-235B,[223] 1,19-aza-1,19-desoxyavermectin B,[224] angucytcline antibiotics,[225] tricyclic β-lactam antibiotics,[226] and the platelet aggregation-inhibiting γ-lactam PI-09.[227]

These are but the most recent and significant examples of the many continuing uses of the Dess−Martin periodinane **108** since its discovery and report by Dess and Martin.[228]

Another interesting, related class of hypervalent organoiodine compounds is *o*-iodosyl- **109** and *o*-iodylbenzoic acids **110** and their respective anions **111** and **112**. These and derived molecules are powerful nucleophiles and their phosphorolytic reactivity is of considerable current interest for the degradation and potential decontamination of toxic organophosphorus compounds.[229]



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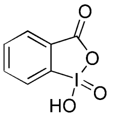

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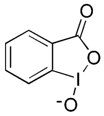

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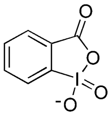
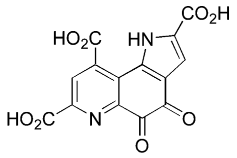


112

There is considerable data in the literature[23,26] on the biological activity of polyvalent iodine compounds. Of particular recent interest is the antimicrobial activity of various iodonium salts. For example, a variety of iodonium salts are potent sequestering agents[230] for PQQ **113**, a pyrroloquinoline quinone and organic cofactor, of importance in diverse redox cycling processes, particularly in dehydrogenases and mitochondrial complex I.



113

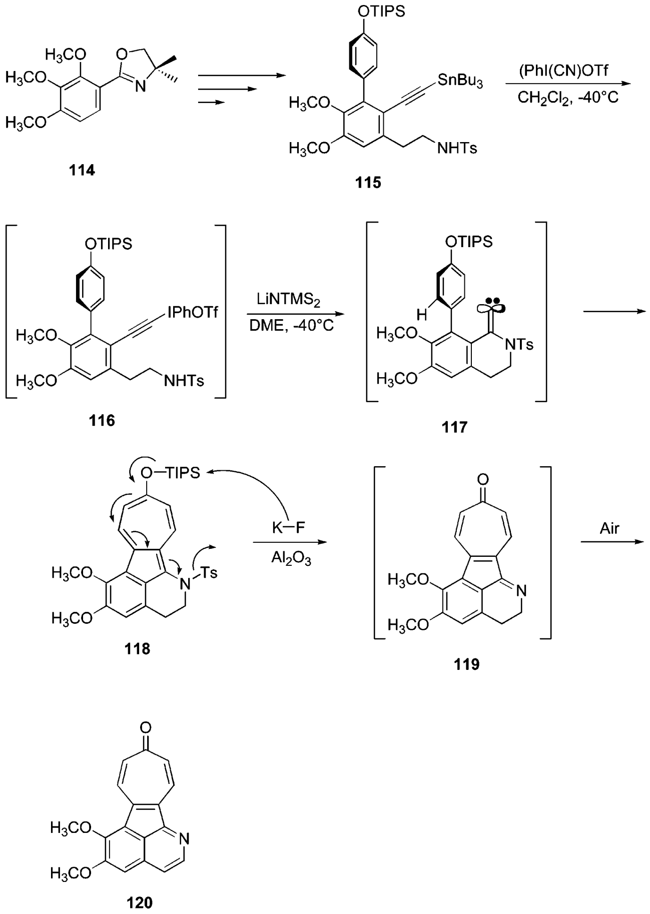
Finally, an elegant, recent example of the use and importance of polyvalent iodine in synthetic organic chemistry is the synthesis of pareitropone **120**, a potent anticancer tropoloisoquinoline alkaloid, by Feldman and Cutarelli,[231] as summarized in Scheme 7. Functionalization of the known oxazoline **114** provided **115**, which was converted to the iodonium salt **116**, that upon treatment with the base $\mathrm{LiN(SiMe_3)_2}$ gave the alkylidenecarbene intermediate **117** via a Michael-type addition to the β-acetylenic carbon and loss of PhI. Addition of the carbene to an aromatic C═C followed by ring expansion afforded **118** that upon treatment with KF on Al_2O_3 and spontaneous air oxidation provided the desired pareitropone product **120** in good overall yield.[231]

5. Summary and Conclusions

It is evident from this Perspective and brief overview that polyvalent organoiodine compounds play an important role in organic chemistry. The last two decades have seen the introduction of new polyvalent iodine reagents and their ever increasing use in synthetic transformations, natural product synthesis, and biochemical processes. Major advances have been made in the uses of various iodonium salts such as their increasing employment in cross coupling reactions. Perhaps the single most useful and widely employed polyvalent organoiodine reagent is the pentavalent Dess−Martin periodinane **108**. Alkynyliodonium salts have become useful, as illustrated by their numerous synthetic applications described herein.

I hope that this Perspective, by highlighting the ready availability and the many beneficial properties and advantages of polyvalent organoiodine species will stimulate their further use in organic chemistry. I anticipate

SCHEME 7



that the next score of years will see an even greater surge of interest and activity in the use of this class of compounds than over the past 20 years, a time that may be considered a renaissance in polyvalent iodine chemistry, since their discovery nearly 120 years ago.

Acknowledgment. I am grateful to the NIH for continued support of our work in this field and to the many able, dedicated co-workers over the years, as cited, who carried out the actual experimental work. I am greatly indebted to Ms. Annie Tykwinski for the design of the cover art accompanying this Perspective and to Professor M. D. Guiry for the use of a photo from www.seaweed.ie.

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