# HYPERVALENT IODINE IN CARBON-CARBON BOND-FORMING REACTIONS

Reported by Peter J. Yao                                                    October 17, 2005

## INTRODUCTION

Hypervalent iodine compounds have been known since the late $19^{th}$ century, and their use in organic synthesis as mild oxidizing agents, particularly IBX and its derivatives such as Dess-Martin periodinane, has become widespread. In recent years there has been an intensified interest in the use of hypervalent iodine, and several reviews have appeared from prominent members in the field, covering all aspects of its chemistry.[1a-c] An emerging area of research is the use of hypervalent iodine compounds for carbon-carbon bond formation. This review covers the basic structure and reactivity of hypervalent iodine compounds and recent developments in their application to carbon-carbon bond-forming reactions.

## HYPERVALENT BONDING

*Hypervalent* compounds are those which contain a main group element with more than an octet of electrons in its valence shell.[2] These molecules were first described as hypervalent by Musher who laid out the foundations of their chemistry in a 1969 paper[3] though their characteristic bonding had earlier been described by Pimentel in a 1951 report on bonding in trihalide anions[4] and by Rundle in a report on the pentaiodide anion[5] in the same year. The fundamental feature of these compounds is the highly polarized three-center-four-electron (3c-4e) bond, in which the central atom bears a positive charge and two monovalent ligands share the corresponding negative charge. This type of bonding serves to distinguish hypervalent compounds from transition metal complexes in which *d*-orbital hybridization is invoked to account for bonding beyond the stable octet.

The concept of hypervalent bonding described by Musher was later supported by theoretical studies from Kutzelnigg[6] in 1984 and Reed[7] in 1990. These studies showed that σ-bonding in higher main group elements (those beyond period 2) is significantly ionic and that *d*-orbitals are not directly involved in bonding. A simplified model of the hypervalent apical bond in $IF_3$ is shown in Figure 1.[2] A 5*p* orbital of iodine overlaps with a 2*p* orbital of each fluorine to give a bonding orbital (ψ), a nonbonding orbital (ψ$_n$), and an antibonding orbital (ψ*). The apical bond is longer and weaker than the equatorial bonds (1.983 Å and 1.872 Å, respectively),[8] and in the HOMO, the electron density is localized on the fluorine atoms. Because of the polarized nature of the 3c-4e bond, ligands with higher

electronegativity tend to occupy the apical positions in hypervalent compounds.

      Hypervalent compounds are commonly named according to *N*-X-*L* nomenclature[9] (Martin-Arduengo designation), where *N* describes the number of electrons formally assigned to the central atom, X is its symbol from the periodic table, and *L* describes the number of ligands bonded to it. Thus, $PF_5$ is a 10-P-5 compound, and its



**Figure 1.** Hypervalent bond of $IF_3$.

trigonal bipyramidal structure is typical of 10-X-5 and 10-X-4 species, with an apical 3c-4e bond and three equatorial covalent bonds (or two bonds and a lone pair). Compounds with 12-X-5 or 12-X-6 designations such as persulfuranes (12-S-6) typically have square bipyramidal or octahedral structures, with two or three orthogonal 3c-4e bonds. In ten-electron species isomerization of axial and equatorial positions is rapid due to facile Berry pseudorotation as well as turnstile rotation, while such isomerization is slower in twelve-electron species (Bailar and Ray-Dutt twists).[2]
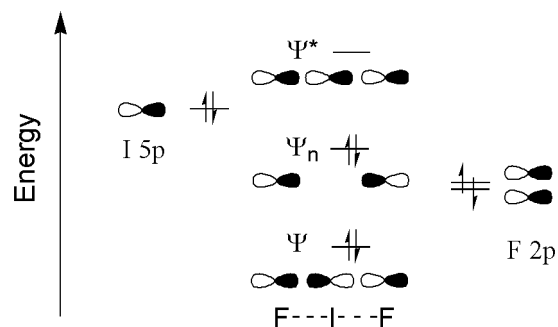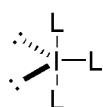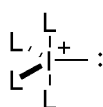
## HYPERVALENT IODINE

### Structure

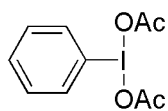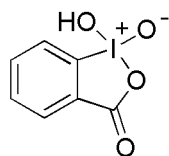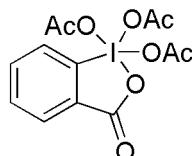      Iodine forms many compounds in which it exists at a positive oxidation state, typically +3 or +5 (as well as +7 in some purely inorganic species). The most common structures of organic hypervalent iodine compounds are 10-I-3, 10-I-4 and 12-I-5, examples of which are shown in Figure 2. In IUPAC nomenclature, 10-I-3 compounds are referred to as $\lambda^3$-iodanes, while IBX and the Dess-Martin reagent are referred to as $\lambda^5$-iodanes.[10] The



**Figure 2.** Examples of hypervalent iodine compounds.

majority of hypervalent iodine reagents used for the formation of carbon-carbon bonds are $\lambda^3$-iodanes, with either aryl, alkenyl or alkynyl carbon ligands.

      In the literature, $\lambda^3$-iodanes with two carbon ligands and a heteroatom ligand are often referred to as iodonium salts; for example chloro(diphenyl)-$\lambda^3$-iodane **1** is called diphenyliodonium chloride,

implying that its actual structure is tetrahedral as in **2** and that it is an 8-I-2 species with no hypervalent bond (Figure 3).[10]  However the crystal structure of this compound[11] shows a Ph-I-Ph bond angle of 92.6° and a Cl-I-Ph angle of 179.3°, much closer to the expected linear T-shape in the 10-I-3 species than the bent shape in the 8-I-2 species.  Following literature precedent, however, these compounds are referred to herein as iodonium salts, although their bonding is better described by the hypervalent model.
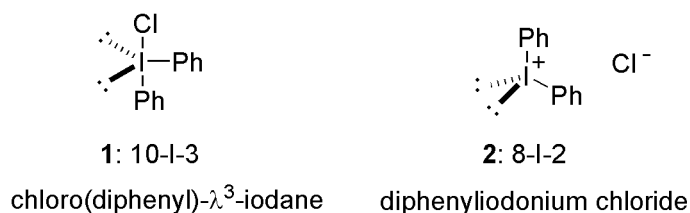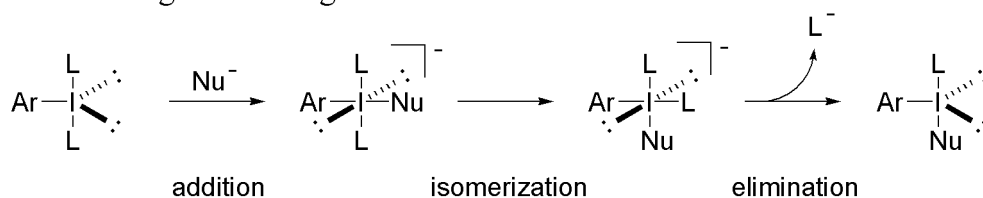
**1**: 10-I-3
chloro(diphenyl)-$\lambda^3$-iodane

**2**: 8-I-2
diphenyliodonium chloride

**Figure 3.** Possible structures of $Ph_2ICl$

**Reactivity**

Hypervalent iodine compounds participate in three main types of reactions: *ligand exchange*, *reductive elimination*, and *ligand coupling*.  Ligand exchange of $\lambda^3$-iodanes is believed to occur by an associative pathway, in which a nucleophile first adds to the electrophilic iodine center, followed by isomerization and elimination, as shown in Scheme 1.[10]  Examples of 12-I-4 species formed upon the initial addition of a nucleophile to a 10-I-3 iodane have been isolated and characterized.  For example, benzyltrimethylammonium tetrachloroiodate has been isolated as a crystalline solid from the reaction of benzytrimethylammonium chloride and iodine trichloride.[12]  The proposed isomerization and elimination steps to date have not been studied in depth.

**Scheme 1.** Ligand exchange.

addition    isomerization    elimination

Aryl-$\lambda^3$-iodanes are sometimes referred to as *hypernucleofuges*, owing to their high dissociation rates when compared to leaving groups such as triflate (as measured by pseudo-first-order rate constants of solvolysis).  For example, the leaving group ability of $Ph(BF_3)I$ is roughly six orders of magnitude greater than that of OTf.[10]  In the dissociation process of aryl-$\lambda^3$-iodanes, the iodane is eliminated from the substrate with concomitant reduction to univalent iodine, as

**Scheme 2.** Reductive elimination.

$\alpha$-elimination
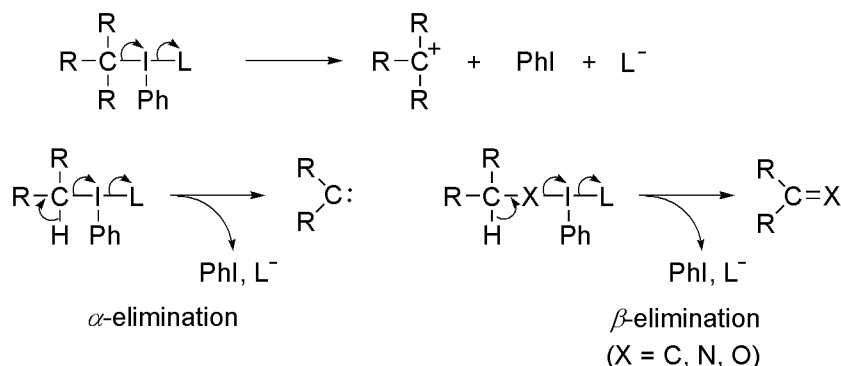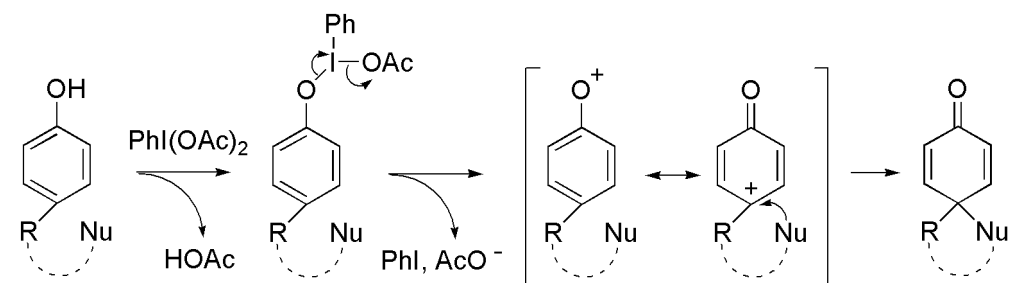
$\beta$-elimination
(X = C, N, O)

shown in Scheme 2; this process is called *reductive elimination*. Reductive elimination can yield carbocations, carbenes (*α*-elimination) or an unsaturated bond (*β*-elimination). The use of this term is slightly different from that in organometallic chemistry, where *reductive elimination* implies reduction of the metal and concomitant bond formation between two ligands on the metal center. For hypervalent compounds this process is referred to as *ligand coupling*. The mechanism of ligand coupling in hypervalent iodine compounds currently is not well understood. Apical-equatorial coupling has been proposed to account for the *ortho*-effect, where bulky *ortho*-substituted arenes occupying equatorial sites couple to apical halides preferentially over an unsubstituted phenyl ligand.[13] This may require a non-concerted process, as apical-equatorial coupling is symmetry-forbidden.[14]

## CARBON-CARBON BOND FORMING REACTIONS

### Oxidative Cyclization

Oxidative cyclization of phenols and phenol ethers with hypervalent iodine is a well-developed method for forming polycyclic systems, particularly those with spirocyclic centers. Intramolecular cyclization of *para*-substituted phenols is believed to proceed *via* phenoxenium ions, as shown in Scheme 3.[15] The cation is generated *via* ligand exchange

**Scheme 3.** Spirocyclization *via* phenoxenium cation.

followed by reductive *β*-elimination, but without concomitant loss of proton as in Scheme 2. The phenoxenium intermediate is postulated based on studies of the intermolecular case. Solvolysis of *ortho*-alkoxy substituted phenols in methanol occurs preferentially at the alkoxy-bearing carbon, thus giving a stereogenic center in the *ortho*-position. Oxidation with a chiral $\lambda^3$-iodane gave only racemic product, which is consistent with an achiral phenoxenium intermediate.[16]

Intramolecular oxidative cyclization of phenols with $\lambda^3$-iodanes has been applied by Kita in total synthesis. Spirocyclization of phenol **3** with [bis(trifluoroacetoxy)]iodobenzene in 2,2,2-trifluoroethanol (a polar non-nucleophilic solvent) gave the spirodienone **4** in 64% yield (Scheme 4).[17] Here, the electron-rich aryl ring tethered to the phenol acts as the nucleophile. Spirodienone **4** is an intermediate for the total synthesis of (+)-maritidine, so this constitutes a formal synthesis of the natural product. A series of galanthamine-type Amaryllidaceae alkaloids was synthesized by Kita and coworkers in a similar way.[18] Intermolecular trapping of the phenoxenium intermediates has also been accomplished

**Scheme 4.** Formal synthesis of (+)-Maritidine.



**3**          **4 (64%)**          (+)-Maritidine
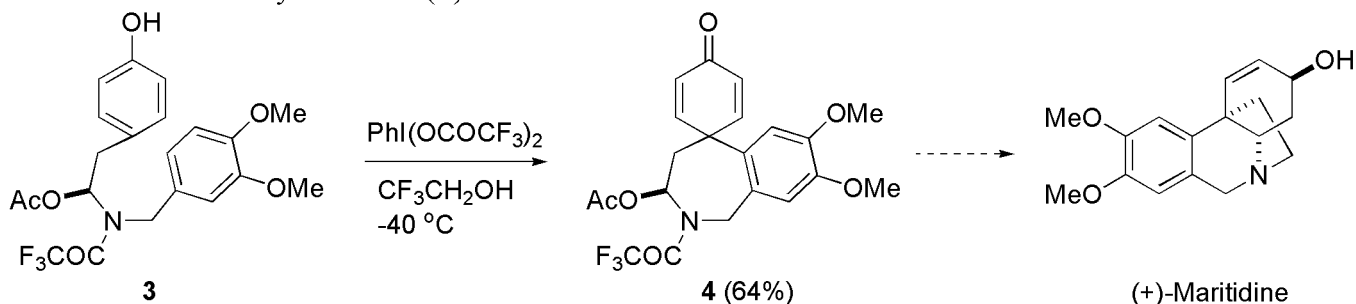
with silyl enol ethers and allyl silanes as the carbon nucleophiles, though this has not yet been applied to any total syntheses.[19]

Kita and coworkers have also developed the oxidative cyclization of phenol ethers, which are believed to proceed *via* cation radicals.[20] This has been applied to the synthesis of (+)-glaucine by oxidative cyclization of the 1,2-diarylethylamine derivative **5**, as shown in Scheme 5.[21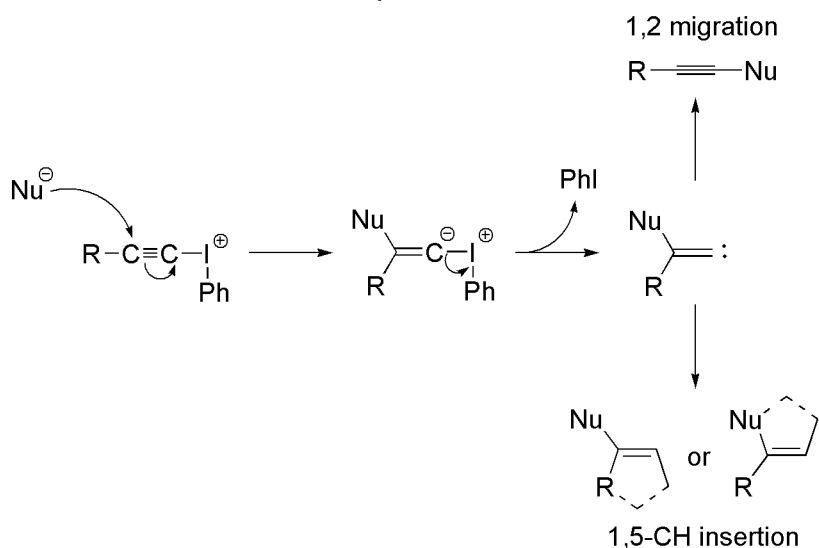] Similar conditions have been applied for the syntheses of phenanthro-fused isoxazoles,[22a] pyrimidines[22a] and thiazoles.[22b] Oxidative cyclizations of phenol ethers with tethered $\beta$-dicarbonyl nucleophiles rather than electron-rich aryl rings have also been developed.[23]

**Scheme 5.** Synthesis of (+)-Glaucine *via* oxidative cyclization



**5**          (+)-glaucine, 75%
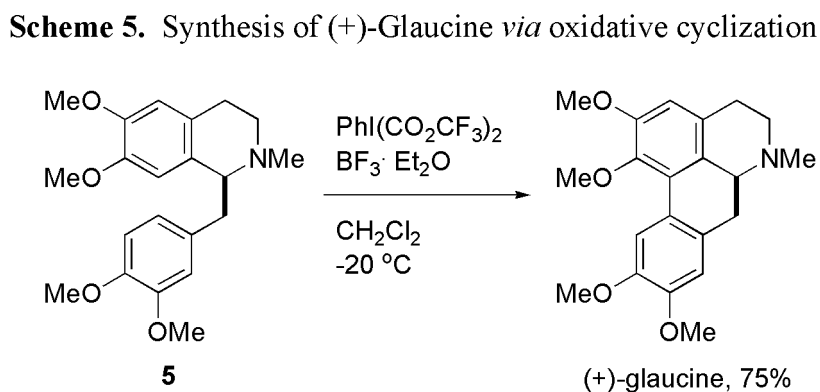
**Generation of Alkylidene Carbenes**

Alkynyl(phenyl)iodonium salts react with nucleophiles in a Michael-type addition to give iodonium ylides, which can undergo reductive $\alpha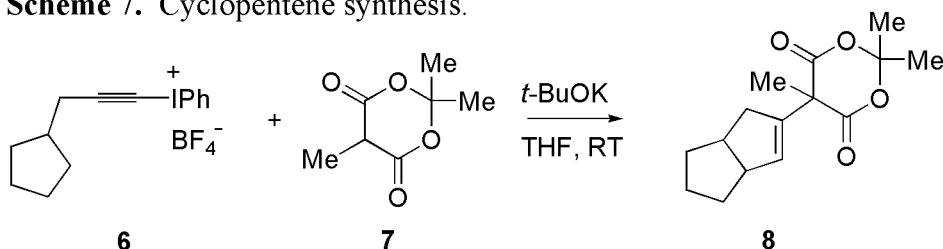$-elimination to give alkylidene carbenes. These carbenes rearrange to give either substituted alkynes or products of 1,5-carbene insertion. The latter process has been exploited to synthesize five-membered rings. The mechanism for this tandem sequence is illustrated in Scheme 6.[15] A wide variety of rings can be synthesized by this method, a few of which are highlighted here.

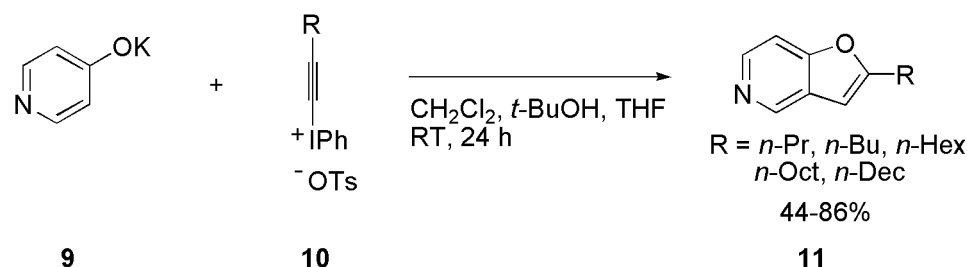**Scheme 6.** Generation of alkylidene carbenes.

Cyclopentenes such as **6** are synthesized from alkynyl(phenyl)iodonium salts most commonly by reaction with carbon nucleophiles such as *β*-dicarbonyl enolates, an example of which is shown in Scheme 7.[24] Oxygen heterocycles such as furopyridine **11** can be derived from oxygen nucleophiles such as the 4-hydroxy pyridine potassium salt **9**, as shown in Scheme 8.[25] In a similar manner, polycyclic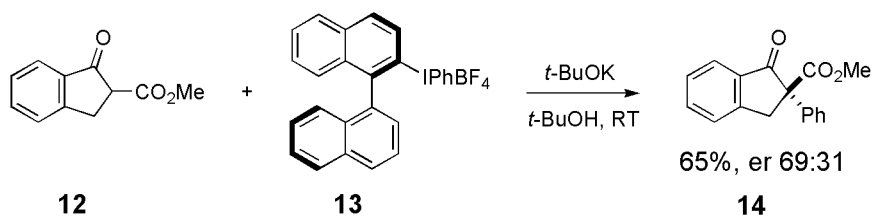 alkaloid skeletons have been obtained by the intramolecular reaction of tethered nitrogen nucleophiles with alkynyliodonium salts.[26]

**Scheme 7.** Cyclopentene synthesis.



**Scheme 8.** Furopyridine synthesis.



## Ligand Coupling

Carbon nucleophiles such as malonate derivatives[27] can be arylated with diaryliodonium salts by the ligand coupling mechanism. Asymmetric coupling between the enolate of cyclic *β*-ketoester **12** and the chiral iodonium salt **13** has been achieved with modest enantioselectivity (Scheme 9).[28] Silyl enol ethers can also be used as the carbon nucleophiles; these have been applied to the synthesis
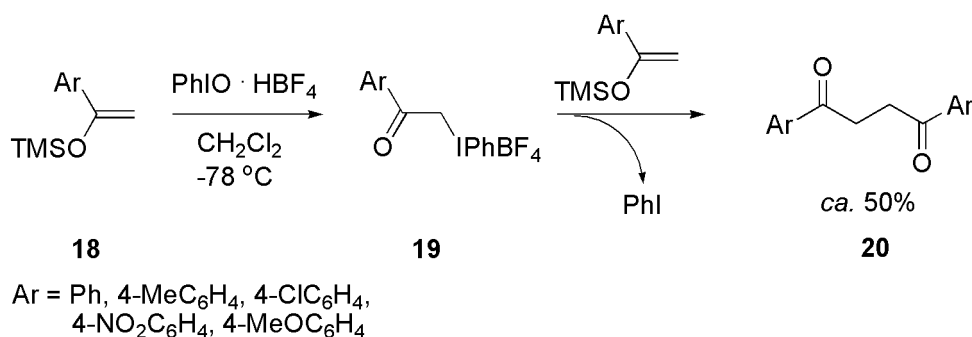
**Scheme 9.** Asymmetric ligand coupling.



of substituted indoles *via o*-nitro arylation of a silyl enol ether followed by reduction with TiCl$_3$ (Scheme 10).[29] An interesting feature of this synthesis is the use of the *ortho*-effect to preferentially transfer the *o*-nitrophenyl substituent to the silyl enol ether. Indoles can be obtained by this method in moderate overall yields; the main advantage is the improved selectivity compared to the standard Fischer indole synthesis, in which enamine formation often affords a mixture of regioisomers.[28]

**Scheme 10.** Indole synthesis *via* arylation of silyl enol ether.
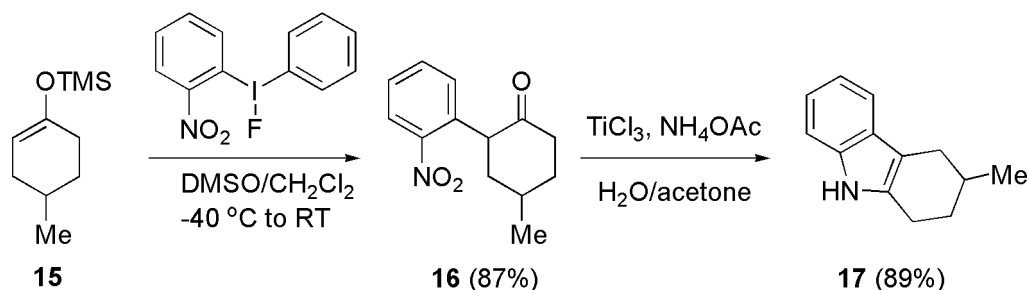


Hypervalent iodine provides a method for coupling two nucleophiles together by sequential ligand exchange reactions followed by ligand coupling. This concept has been applied to the coupling of silyl enol ethers to give 1,4-diones (Scheme 11). This type of coupling is conceptually interesting but unfortunately does not generally give good yields and has not been further developed.[30]

**Scheme 11.** Ligand coupling of silyl enol ethers.



**CONCLUSION**

Hypervalent iodine compounds can be used in a variety of carbon-carbon bond forming reactions. Some of the less-developed methods not included here include cyclopropanation with iodonium ylides and generation of benzynes and their cycloaddition reactions.[15] A common theme in many of these methods is the generation of high energy transient species such as the phenoxenium cation and free carbenes. Oxidative cyclization is by far the most developed of these approaches and has been applied to the total syntheses of some relatively simple natural products. The tandem nucleophilic addition-carbene insertion reaction has also been used to create moderately complex polycyclic structures and shows promise as a route for accessing natural products. In contrast ligand coupling, which has a close analogue in transition metal mediated bond-forming reactions, has received little attention, possibly owing to ambiguity in the fundamental mechanism. Understanding of the basic processes in ligand exchange and ligand coupling is still limited, and fundamental studies will be necessary before the potential for carbon-carbon bond formation with hypervalent iodane can be fully realized.

# REFERENCES

1.  a. Wirth, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3656-3665.
    b. Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893-2903.
    c. Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523-2584.
2.  Akiba, K. In *Chemistry of Hypervalent Compounds*; Akiba, K., Ed.; VCH Publishers: New York, 1999; Chapter 1, pp. 1-8.
3.  Musher, J. I. *Angew. Chem. Int. Ed.* **1969**, 8, 54-68.
4.  Pimentel, G. C. *J. Chem. Phys.* **1951**, *19*, 446-448.
5.  Hach, R. J.; Rundle, R. E. *J. Am. Chem. Soc.* **1951**, *73*, 4321-4324.
6.  Kutzelnigg, W. *Angew. Chem. Int. Ed.* **1984**, *23*, 272-295.
7.  Reed, A. E.; von Rague Schleyer, P. *J. Am. Chem. Soc.* **1990**, *112*, 1434-1445.
8.  Hoyer, S; Seppelt, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 1448-1449.
9.  Perkins, C. W.; Martin, J. C.; Arduengo, A. J.; Lau, W.; Alegria, A.; Kochi, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 7753-7759.
10. Ochiai, M. In *Hypervalent Iodine Chemistry*; Wirth, T., Ed.; Spring-Verlag: New York, 2003; Chapter 2, pp. 5-68.
11. Alcock, N. W.; Countryman, R. M. *J. Chem. Soc., Dalton Trans.* **1977**, 217-219.
12. Kajigaeshi, S.; Kakinami, T.; Moriwaki, M.; Tanaka, T.; Fujisaki, S. *Tetrahedron Lett.* **1988**, *29*, 5783-5786.
13. Lancer, K. M.; Wiegand, G. H. *J. Org. Chem.* **1976**, *41*, 3360-3364.
14. Yamamoto, Y.; Akiba, K. In *Chemistry of Hypervalent Compounds*; Akiba, K., Ed.; VCH Publishers: New York, 1999; Chapter 9, pp. 279-294.
15. Zhdankin, V.V. In *Hypervalent Iodine Chemistry*; Wirth, T., Ed.; Spring-Verlag: New York, 2003; Chapter 4, pp. 99-136.
16. Kurti, L.; Herczegh, P.; Visy, J.; Simonyi, M.; Antus, S.; Pelter, A. *J. Chem. Soc., Perkin Trans. 1*, **1999**, 379-380.
17. Kita, Y.; Takada, T.; Gyoten, M.; Tohma, H.; Zenk, M. H.; Eichorn, J. *J. Org. Chem.* **1996**, *61*, 5857-5864.
18. Kita, Y.; Arisawa, M.; Gyoten, M.; Nakajima, M.; Hamada, R.; Tohma, H.; Takada, T. *J. Org. Chem.* **1998**, *63*, 6625-6663.
19. Quiedeau, S.; Looney, M. A.; Pouysegu, L. *Org. Lett.* **1999**, *1*, 1651-1654.
20. Takada, T.; Arisawa, M.; Gyoten, M.; Hamada, R.; Tohma, H.; Kita, Y. *J. Org. Chem.* **1998**, *63*, 7698-7706.
21. Anakabe, E.; Carrillo, L; Badia, D.; Vicario, J. L.; Villegas, M. *Synthesis* **2004**, 1093-1101.
22. a. Olivera, R.; SanMartin, R.; Pascual, S.; Herrero, M.; Dominguez, E. *Tetrahedron Lett.* **1999**, *40*, 3479-3480.
    b. Moreno, L.; Tellitu, I.; SanMartin, R.; Carrillo, B.; Dominguez, E. *Tetrahedron Lett.* **1999**, *40*, 5067-5070.
23. Arisawa, M.; Rameh, N. G.; Nakajima, M.; Tohma, H.; Kita,Y. *J. Org. Chem.* **2001**, *66*, 59-65.
24. Ochiai, M.; Kunishima, M.; Nagao, Y.; Fuji, K.; Shiro, M.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 8281-8283.
25. Kitamura, T.; Tsuda, K.; Fujiwara, Y. *Tetrahedron Lett.* **1998**, *39*, 5375-5376.
26. Schildknegt, K.; Bohnstedt, A. C.; Feldman, K. S.; Sambandam, A. *J. Am. Chem. Soc.* **1995**, *117*, 7544-7545.
27. Oh, C. H.; Kim, J. S.; Jung, H. H. *J. Org. Chem.* **1999**, *64*, 1338-1340.
28. Ochiai, M.; Kitagawa, Y.; Takayama, N.; Takaoka, Y.; Shiro, M. *J. Am. Chem. Soc.* **1999**, *121*, 9233-9234.
29. Iwama, T.; Birman, V. B.; Kozmin, S. A.; Rawal, V. H. *Org. Lett.* **1999**, *1*, 673-676.
30. Zhdankin, V. V.; Tykwinski, R.; Mullikin, M.; Berglund, B.; Caple, R.; Zefirov, N. S.; Kozmin, A. S. *J. Org. Chem.* **1989**, *54*, 2605-2608.