Topics in Current Chemistry 373

Thomas Wirth *Editor*

Hypervalent Iodine Chemistry

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373
Topics in Current Chemistry

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Thomas Wirth
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Hypervalent Iodine Chemistry

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Preface

Hypervalent iodine chemistry has received widespread recognition by chemists during the last decade. This book is an update on the current state-of-the-art, including the use of traditional reagents in novel reactions which further highlight the potential of hypervalent iodine reagents as mild, selective and environmentally benign reagents. The development of novel hypervalent iodine reagents with altered reactivities now allow transformations which, only a decade ago, would have been unthinkable. These developments have led to special issues in journals and increased frequencies of conferences dedicated to this subject. They have also attracted young researchers to join the field and further develop the chemistry by means of their creativity and imagination. The compilation of current topics assembled in this book is a testimony to the many scientists who have contributed to the rapid development of hypervalent iodine chemistry in the past decade. The book should serve as a current dictionary and as a source of inspiration for research. I am very grateful to many distinguished colleagues who have contributed with their expert knowledge to make this comprehensive compilation on hypervalent iodine chemistry possible.

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Hypervalent Iodine-Induced Oxidative Couplings (New Metal-Free Coupling Advances and Their Applications in Natural Product Syntheses)

Toshifumi Dohi and Yasuyuki Kita

Abstract Recently, hypervalent iodine reagents have been extensively used in organic synthesis. A variety of reactions available for natural product syntheses have been developed using phenyliodine(III) diacetate (PIDA), phenyliodine(III) bis(trifluoroacetate) (PIFA), and other iodine(III) and (V) reagents. These reactions are expected to have applications in pharmaceutical and agrochemical processes because of their safety, mild reaction conditions, and high yields of pure products. Under such considerations, this chapter focuses on the oxidative coupling reactions of hypervalent iodine reagents found in total syntheses of biologically active natural products and their related compounds.

Keywords Hypervalent iodine reagents • Natural products • Oxidative coupling • Total synthesis

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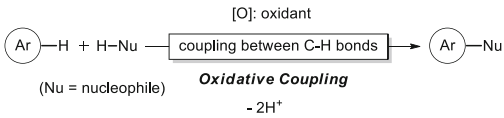
1 Introduction

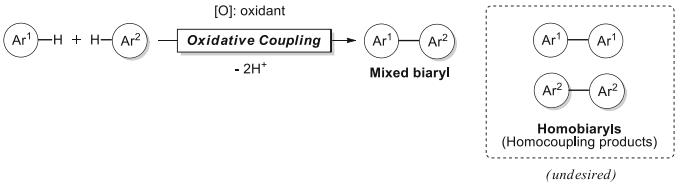
The cross-coupling reactions discovered by Japanese chemists in the twentieth century can provide powerful tools for the construction of complex molecules in organic synthesis. In general, these cross-couplings using organometallic compounds (e.g., [M]=[Zn], Negishi; [B], Suzuki, etc.) with organic halides in the presence of some transition metal catalysts, such as palladium complexes, have been used for the effective formation of new carbon–carbon bonds [1–4]. Although the methods can afford target products in high yields and with good selectivities, these typically require the stoichiometric activated coupling substrates, that is, the metal- and halogen-functionalized organics, and thus produce metallic salts as waste and byproducts from the reactions. The use of these organometallic starting materials is, therefore, not ideal and efficient when considering environmental concerns and practical factors. In addition, the preparation of pre-activated substrates often requires several synthetic operations.

In the concept of green and sustainable chemistry, much effort should be dedicated to the development of more direct cross-coupling reactions. In theory, the oxidative coupling (Scheme 1) is a straightforward route which can reduce the number of synthetic steps by avoiding the preparation of pre-activated substrates. Besides, this strategy involves less waste material generation regarding metal salts. Under such situations, new oxidative coupling methods that directly use the C–H bond of the two substrates instead of organic halides and organometallic compounds have emerged in recent years, enabling the selective formation of cross-coupling products [5–9].

Herein, the authors describe recent advances in hypervalent iodine-induced oxidative coupling reactions as a new strategic choice for metal-free synthesis, and their early applications in natural product synthesis used as the key reactions are summarized. We first briefly outline the fundamental hypervalent iodine-induced reactions and then illustrate the examples of their application to the syntheses of various biologically active compounds, such as natural products.

Scheme 1 Oxidative coupling strategy





Scheme 2 Oxidative biaryl coupling: general situation

2 Recent New Metal-Free Coupling Advances

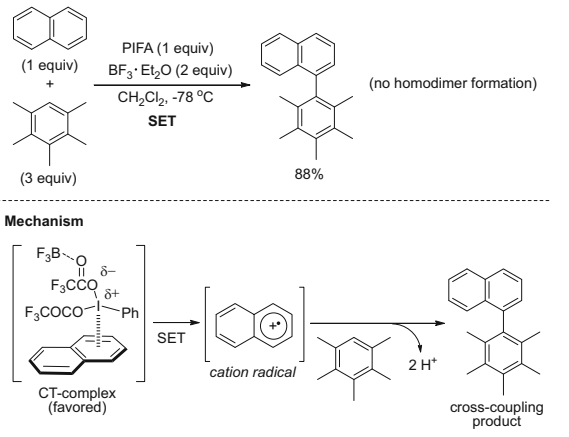
Despite their ideal green chemistry aspect, oxidative couplings employing heavy-metal oxidants have limited synthetic applications regarding chemoselective issues and usually suffer from undesired formation of homo-dimers and uncontrolled over-oxidations. Indeed, studies involving heavy-metal oxidants, electrolytic conditions, and others reported frequent accompanying undesired formation of homodimers and over-oxidations in intermolecular couplings (Scheme 2). Therefore, cross-coupling attempts were rarely reported in the literature during the twentieth century. Early successes include the oxidative cross-coupling of 2-naphthols and naphthyl amines with stoichiometric amounts of copper and iron oxidants ([10–12] and references cited therein), which limited the availability of the substrates to these phenol aromatics showing high sensitivity to induce oxidations.

In 2007, Fagnou and co-workers reported the selective oxidative cross-coupling of indoles or anilines with non-heteroaromatic substrates using palladium salts as catalysts with stoichiometric amounts of copper oxidants [13]. The reaction was performed by the appropriate combination of the catalyst and oxidant, palladium (II) trifluoroacetate (5 mol%) and stoichiometric copper(II) acetate (3 equiv.) at high temperature ($>100°C$). The key to the success of the selective cross-couplings was the selection of the two aromatic substrates having suitable gaps of affinities and reactivities toward the metal catalysts. Thus, excess amounts (30–60 equiv.) of aromatic hydrocarbons were required as coupling partners to react exclusively with indoles over indole homodimerization. Accordingly, the selective cross-couplings between arene molecules with similar characteristics, such as between two aromatic hydrocarbons, are still difficult to achieve by metal-catalyzed oxidative coupling strategies, even after recent advances. Indeed, the reaction of naphthalene with excess mesitylene was not practical in a catalytic system composed of a palladium catalyst with potassium persulfate in the presence of trifluoroacetic acid (TFA) [14, 15], which resulted in low yields of the desired mixed naphthalene-mesitylene biaryl derivative and low turnover numbers (TONs) of the catalyst. In addition, a large amount of an undesired homocoupling product of mesitylene, 2-(3,5-dimethylbenzyl)-1,3,5-trimethylbenzene, was formed. The catalyst combination used by Fagnou's group (palladium(II) trifluoroacetate with copper (II) acetate) even failed and no useful reaction for these aromatic hydrocarbons without heteroatom could be observed. The use of excess metal oxidants, however,

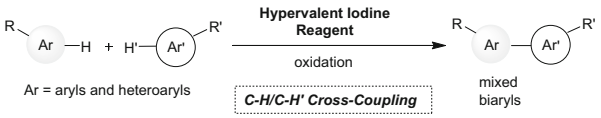
remains a strong contender in the further development of a new oxidative cross-coupling system based on alternative initiators and catalysts.

With the increasing impetus for developing greener synthetic processes, hypervalent iodine reagents have recently received significant attention in organic synthesis as an oxidant by virtue of their low toxicity, controllable reactivity, ready availability, high stability, easy handling, ease of recovery and recyclability, etc. One of the predominant uses of these reagents is replacing the highly toxic heavy-metal oxidizers, i.e., lead(IV)-, mercury(II)-, and thallium(III)-based reagents. Because of their brilliant features, hypervalent iodine reagents are a promising alternative to metal oxidants for developing greener oxidations, the utility of which is already documented in several books and comprehensive reviews ([16] and references cited therein) [17, 18]. Extensive applications as stoichiometric oxidants were found to mediate a wide array of bond-forming reactions and other oxidative transformations, and the synthetic versatility of these reagents has been expanding day by day. For example, oxidation of phenols and related reactions induced by phenyliodine(III) diacetate (PIDA) and phenyliodine(III) bis(trifluoroacetate) (PIFA) have been used for many total syntheses of biologically important natural products and their pivotal intermediates. The pentavalent iodines, Dess–Martin periodinane (DMP) and its precursor, 2-iodoxybenzoic acid (IBX), are widely known as mild and selective oxidants for alcohol functionalities. Based on their unique reactivities, a variety of reactions for constructing complex molecules has been developed, and hypervalent iodine reagents are now extensively accepted for use in natural product syntheses. The reactions using hypervalent iodine reagents can also be utilized for pharmaceutical and agrochemical processes because of their safe and mild reaction conditions.

Regarding the first discovery of the oxidative cross-coupling of aromatic compounds in hypervalent iodine chemistry, we met in 2008 the very exciting success of the oxidative cross-couplings between naphthalenes and alkylbenzenes based on the single-electron-transfer (SET) oxidation strategy [19]. It was a combination of a hypervalent iodine reagent, specifically PIFA, and, for its activation, a Lewis acid, boron trifluoride diethyl etherate. Surprisingly, when the naphthalene and mesitylene, as shown in Scheme 3, were mixed with the activated hypervalent



Scheme 3 First report of metal-free oxidative cross-biaryl-coupling



Scheme 4 Oxidative cross-biaryl-couplings using hypervalent iodine reagent

iodine reagent, the desired cross-coupling was found to occur exclusively, producing the naphthalene-mesitylene biaryl in high yield. Thus, the problematic homocoupling observed in the palladium-catalyzed strategy [14, 15] was apparently suppressed by using the iodine reagent.

Inspired by this elegant success, the authors have pioneered the metal-free oxidative cross-coupling reactions of various electron-rich aromatic compounds (Ar-H) to date using hypervalent iodine reagent (Scheme 4). Indeed, several types of the new oxidative aromatic coupling methods for access to mixed biaryls in high yields with perfect cross-coupling selectivities were realized based on different types of the aromatic ring activation in the mechanisms [20–28]. These research results have been summarized regularly by us since 2011 [29, 30] and others [31–33] as accounts and reviews.

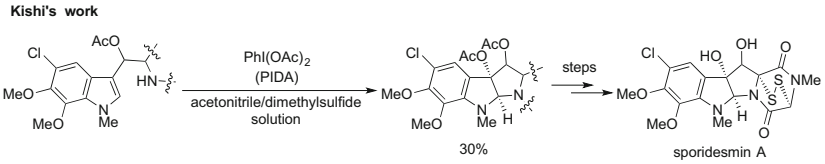
The oxidative coupling strategies with hypervalent iodine reagents were originally used for aromatics in intramolecular reactions without causing issues of homodimer formation, and several applications of total syntheses of natural products are present in the literature. In the following sections, the authors describe the oxidation couplings of aromatic compounds in natural product synthesis together with a brief introduction of their background regarding the establishment of the fundamental reactions.

3 Oxidative Couplings in Natural Product Synthesis

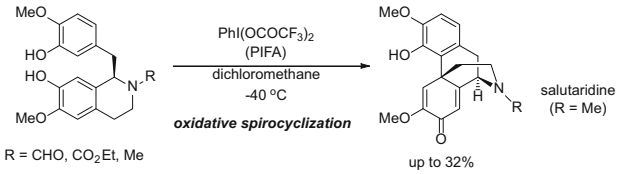
Hypervalent iodine reagents have recently received a great deal of attention in organic synthesis, not only as a mild, safe, and economical alternative to heavy metal reagents, but also because of their variety of unique reactivities applicable to natural product syntheses. Pioneering studies on hypervalent iodine-induced reactions toward total syntheses of several natural products were reported by Kishi and co-workers in the 1970s [34]. Based on the hypervalent iodine-induced oxidative cyclization, a formal stereospecific synthesis of sporidesmin A, a toxic metabolite of *Pithomyces chartarum*, was accomplished, albeit in low yield from the key reaction of the tryptamine derivative at the indole ring (Scheme 5).

Other early applications of hypervalent iodine reagents in natural products are the total syntheses of bioactive alkaloids, by Szantáy's and White's groups in early 1980s, such as salutaridine (Scheme 6), (–)-codeine, and 6a-epipretazettine [35–37]. Although these involved pioneering studies on phenolic coupling reactions, they had not received much attention because of their low yields of the chemical processes (up to 32% yield).

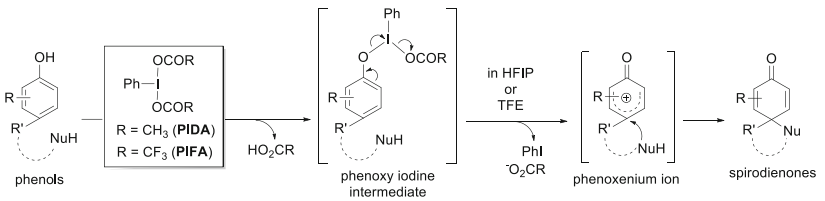
This situation dramatically changed when the efficient phenolic oxidation protocol was developed by Kita and co-workers using a specific hypervalent iodine



Scheme 5 Kishi's early work



Scheme 6 Early report by Szántay

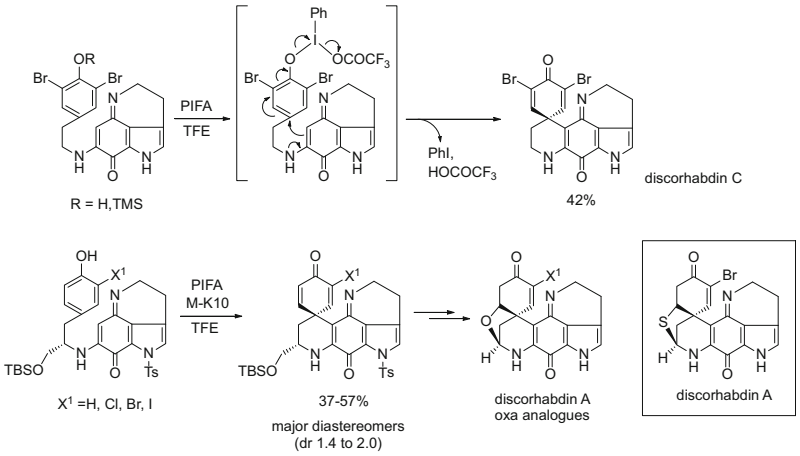


Scheme 7 Hypervalent iodine-induced oxidative dearomatization of phenols leading to spirodienones

reagent, PIFA, in polar solvents [38]. In particular, remarkable improvements of the reaction yields were demonstrated by changing the solvent to polar and weakly nucleophilic solvents, such as 2,2,2-trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) [39–41].

In the 1980s Kita's group introduced these fluoroalcohols to perform the dearomatizing oxidations of phenols using hypervalent iodine reagents for the purpose of synthesizing spirodienones [38]. For the oxidation of phenols using hypervalent iodine reagents (Scheme 7), i.e., PIDA and PIFA, the reactions are typically explained by the two-electron-transfer processes that involve the initial ligand exchange at the iodine(III) centers. PIDA and PIFA react with phenolic oxygens to give the phenoxyiodine(III) intermediates. The excellent leaving ability of the high-valent iodine atoms to produce more stable iodobenzene can smoothly generate the phenoxenium ions in the polar solvents, HFIP and TFE, which are then trapped by various concomitant nucleophiles to complete the dearomatizations.

With these discoveries as a turning point, PIDA and PIFA have started to play particularly important roles in reproducing the biomimetic phenolic oxidation processes under mild conditions, which can be applied to the total synthesis of natural products and their pivotal intermediates having the spirodienone moieties



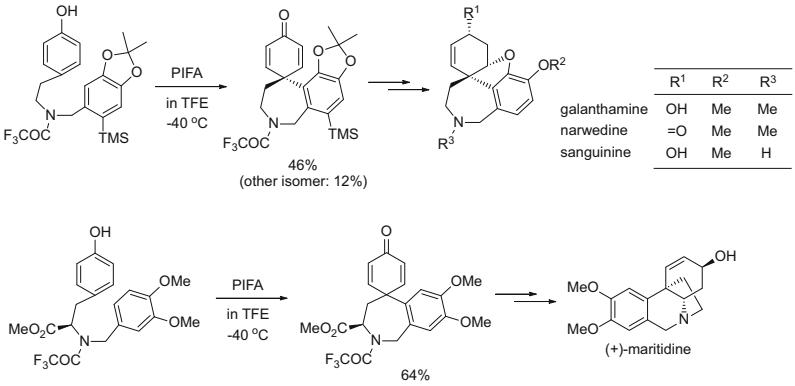
Scheme 8 Total synthesis of discorhabdins by the dearomatizing spirocyclization strategy

[42–47]. After this significant improvement, there are many applications of hypervalent iodine reagents in syntheses of complex molecules.

For example, a variety of natural products bearing spirocyclic systems exist, and many of them are biosynthetically formed by oxidative spiroannulation processes. Hypervalent iodine(III) reagents are thus considered as one of the most effective oxidants for these oxidation processes. Several efficient methods for PIFA-induced spiroannulation reactions of phenols [48, 49] towards the total synthesis of discorhabdin alkaloids [50, 51] and their oxa-analogues have been published [52, 53], which were accomplished via hypervalent iodine oxidation of phenols or *O*-trimethylsilylated phenol derivatives to the azacarbocyclic spirodienones as a key step (Scheme 8).

The similar treatment of the norbelladine derivatives using PIFA proved to be a mild and efficient method for preparing the core structures of *Amaryllidaceae* alkaloids (Scheme 9), such as galanthamine for the treatment of Alzheimer's disease and related alkaloids, i.e., narwedine, norgalanthamine, sanguinine, lycoramine, and maritidine, by dearomatizing carbon–carbon bond formations at the spiro centers [54, 55].

The two most successful areas in oxidative coupling for natural product syntheses include the transformations of aromatic compounds as the key steps. These are classified into (1) phenol oxidative couplings and (2) oxidative functionalizations of other aromatics. The former category is further divided into phenol couplings with or without dearomatizations. In turn, the latter oxidative aromatic substitutions include umpolung strategies regarding aromatic rings or nucleophiles by activations of hypervalent iodine reagents. Category (1) typically includes phenoxyiodine (III) intermediates during the activations of phenol rings during oxidation. In general, the reactivity of hypervalent iodine species depends greatly on the reaction conditions. Indeed, a hypervalent iodine reagent, specifically PIFA, can be extensively utilized as an efficient and selective SET oxidizing agent, enabling formation



Scheme 9 Total synthesis of galanthamine and related alkaloids

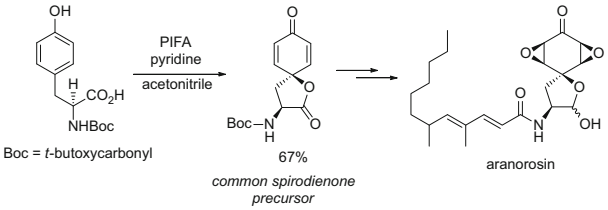
of the charge transfer complex (CT-complex) with aromatic coupling substrates [56, 57], utilized for natural product synthesis in oxidative functionalizations. In category (2), the electrophilic activation of nucleophiles includes the generation of nitrenium ions by the treatment of *N*-methoxyamides with hypervalent iodine reagents, which are captured by intra- and intermolecular aromatic groups for nitrogen bond formation [58, 59]. In the following sections, some aspects of hypervalent iodine-induced oxidative coupling reactions used as the key reactions for the total syntheses of selected natural products are highlighted.

3.1 Phenol Oxidative Couplings

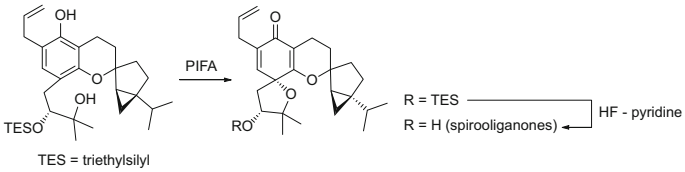
3.1.1 Phenol Dearomatizative Couplings

Utilizing this effective dearomatizing spirocyclization in polar solvent using PIFA or PIDA [38], the total synthesis of the antibiotic aranorosin was accomplished by Rama Rao [60], Wipf [61], and McKillop [62] via the construction of the spirolactone structure as a common intermediate, as shown in Scheme 10.

In addition, Wipf and co-workers achieved the total syntheses of (–)-stenine [63], palmarumycin CP1 [64], and (±)-deoxypreussomerin A [65] by utilizing the hypervalent iodine-induced spirocyclization for substituted phenols carrying nucleophilic side-chains at suitable positions. Similarly, the phenol dearomatization protocols involving intermolecular introductions of oxygen nucleophiles at the *para* and *ortho* positions of the phenol functionality accompanying spirocyclizations were widely applied for many total syntheses of natural products, as reported by Hoshino, Gurjar, Pettus, Katoh, Nicolaou and Chen, Sorensen, Myers, and Ley, respectively, for production of araplysillin-I [66], gymnastatin A [67], epoxysorbicillinol and bisorbicillinol [68], (±)-geodin [69], (+)-haplophytine [70, 71], isotarins E and F [72], cortistatins [73, 74], and (+)-clavolonine [75].



Scheme 10 Diastereoselective spirocyclization for the total synthesis of aranorosin



Scheme 11 Application for spirooliganones total synthesis

A more recent report includes the biomimetic total syntheses of potent antiviral spirooliganones A and B utilizing the phenol oxidative dearomatization/spirocyclization to build the spiro-fused cyclohexadienone/tetrahydrofuran moiety (Scheme 11) [76].

Oxidative dearomatizations with introduction of nitrogen nucleophiles are rather rare in reports. Sorensen and co-workers describe the total synthesis of a powerful immunosuppressant (FR901483) by oxidative aza-spiroannulation with PIDA in HFIP followed by an intramolecular aldol addition (Scheme 12, top) [77]. Similar to Sorensen's procedure, Honda and co-workers completed the formal total synthesis of enantiopure (–)-TAN1251A by dearomatizing spirocyclization reaction of the enantiopure chiral phenol substrate with high stereocontrol at the diastereomeric spiro center [78].

Independently, Ciufolini and co-workers reported the total syntheses of FR901483 and TAN 1251C by utilizing an oxazolidine as a selective nucleophile enabling similar aza-spirocyclizations (Scheme 12, bottom) [79]. The same research group succeeded in several total syntheses by analogous ways using sulfonamide groups instead of the oxazolines for the constructions of nitrogen-containing spiro centers found in the related natural products having the himandrine cores [80–82]. Similar cyclizations leading to spirodienone lactams [83, 84] involving nitrenium ion generation by oxidation of the cation-stabilizing methoxy and phthalimide nitrogen groups were reported by Wardrop [85, 86] in the total syntheses of the muscarinic M_1 receptor antagonist (−)-TAN1251A from *L*-tyrosine and (±)-desmethyl amino FR901483.

Working on the industrial production of galanthamine (see Scheme 9), Node and co-workers improved the yield of this phenolic coupling reaction by employing more suitably protected norbelladine-type derivatives as the intermediates [87]. Later, Shair and co-workers revealed that this synthetic strategy is applicable