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Review

Recycling and Catalytic Approaches for the Development of a Rare-Metal-Free Synthetic Method Using Hypervalent Iodine Reagent

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Oxidation reactions consist of a number of important transformations in organic synthesis. However, in spite of their utility in both laboratory- and industrial-scale production, oxidations are among the most problematic processes regarding the factors of safety, environmental friendliness, operational simplicity, *etc.* As oxidants, hypervalent iodines, such as phenyliodine(III) diacetate (PIDA) and phenyliodine(III) *bis*(trifluoroacetate) (PIFA), are among promising reagents for developing environmentally benign oxidation reactions due to their low toxicities, mild reactivity, ready availability, high stability, and easy handling. Our research objective is, largely in consideration of economic and environmental viewpoints, to enhance the synthetic values of these reagents as useful alternatives to highly toxic heavy-metal oxidants and even rare transition metals by pioneering their efficient utilization methods and unique reactivities. During this study, we have succeeded in the development of new recyclable reagents 1 and their catalytic utilization, and the design of a new chiral reagent 2 and its application to perform asymmetric oxidations. Accordingly, the recycling and catalytic use of a hypervalent iodine reagent became possible in many representative types of oxidative bond-forming reactions, some of which even include key transformations for natural product synthesis. A summary of these important achievements in hypervalent iodine chemistry are described in this review.

Key words hypervalent iodine; reagent design; recycling; catalyst; asymmetric oxidation; metal-free method

1. Introduction

In modern synthetic research for drug development, providing new medicinal target compounds with safer and more eco-friendly methods that consider the impact on environmental and global resources based on their syntheses are required. In this respect, "oxidation" is one of the most important transformations that frequently occur in many industrial synthetic processes of pharmaceuticals and related compounds as functional group conversions and bond-forming methods.[1—3] On the contrary, the majority of them still have many problems since their improvement lags behind compared with other industrial reactions in terms of safety, efficiency, recycling and waste production, toxicity of reagents, *etc.* In the past, heavy-metal oxidants, such as lead(IV)-, mercury(II)-, thallium(III)-, and cadmium(IV)-based agents, were often used in industrial oxidation processes, but these toxic agents are apparently not the best choice for the synthesis of fine chemicals that require high purity, such as pharmaceuticals. Therefore extensive research on the development of superior oxidation reactions and new oxidizing agents has been conducted to replace the classical methods using highly toxic heavy-metal oxidants. In particular, the development of new reactions is being investigated by employing the transition metals, even in the field of oxidation chemistry, due to their characteristics that are similar to those of the heavy-metal oxidants as well as the discovery of attractive but unknown types of new reactivities. However, in view of sustainable chemistry, these transition metals are the group of "rare-metal" elements that cause concerns over recycling and introduction into the environment despite their great synthetic utility.

Before such a problem was widely recognized in the field of chemistry, we were interested in the synthetic potential of hypervalent iodine reagents as less toxic and safer organooxidant to replace heavy-metal oxidizers in drug development studies. Since the early 1980s, Kita and coworkers have revealed a wide array of reactivities for trivalent iodine reagents, *i.e.*, phenyliodine(III) diacetate (PIDA), phenyliodine(III) *bis*(trifluoroacetate) (PIFA), and iodosobenzene, that are similar to those of heavy-metal oxidants and anodic oxidations and they have achieved the total syntheses of several biologically unique natural products, such as makaluvamine F and discorhabdin alkaloids, galanthamine, and other types of *Amaryllidaceae* alkaloids, utilizing the newly developed reactions.[4—8] In particular, the oxidations of phenols and their derivatives using PIDA and PIFA are useful (Chart 1)[7] and have been utilized for the syntheses of a number of natural products and other complicated organic molecules worldwide, due to their broad generalities and high functional group compatibilities.[8] During this period, the concept of "green chemistry" that stresses the toxicity of reagents, safety and efficiency of processes, *etc.*, became im-

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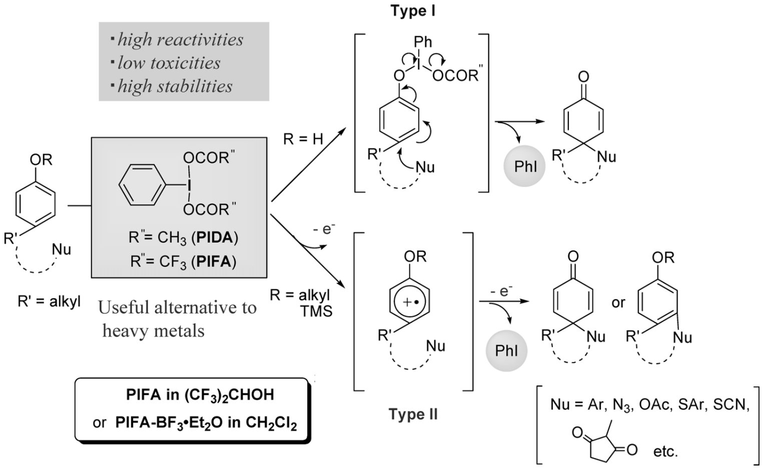

Chart 1. PIDA or PIAF-Mediated Oxidations of Phenols and Phenyl Ethers

portant in organic synthesis at the beginning of the 1990s, and hypervalent iodine reagents are now accepted as universal environmentally friendly organic oxidants.[9,10)]

With this background, the authors have extended their research for the development of versatile synthetic methods utilizing new iodine reagents and related active species, aimed at significantly enhancing the synthetic value of hypervalent iodine reagents. In this project, we first developed the new recyclable reagents **1** that do not show any degradation of the backbones throughout their reuse and recovery processes.[11—17)] By applying the unique regeneration method of the recyclable reagents **1**, we next succeeded in the catalytic use of hypervalent iodine reagents, which led to the effective utilization of the reagents as "organocatalysts."[18—21)] Furthermore, we challenged the asymmetric oxidations as being very difficult with hypervalent iodines and have achieved the highly selective catalytic oxidations of phenols for the first time by designing a new chiral reagent **2′**.[22)] Through such research, the possibility of hypervalent iodines as environmentally friendly alternatives not only to heavy-metal oxidants but also even to rare metals became realistic.

In this short review, the author describes the development of the new recyclable reagents **1** and their successful application for the catalytic use of hypervalent iodine reagents based on our aim of developing versatile synthetic methods using iodine reagents as future replacements for rare-metal methods.

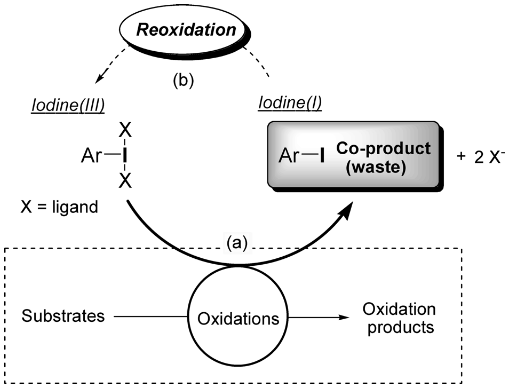

Chart 2. General Reaction Scheme for the Oxidations Using Iodine(III)

2. Development of New Methods for Recycling and Catalytic Use of Hypervalent Iodine Reagents

The high-valent iodine(III) atoms in PIDA and PIFA have a strong tendency to revert to the more stable monovalent state and thus cause the oxidation of substrates with the release of monovalent iodobenzene (Chart 2, a, where Ar=Ph). With the recent demand for the high-purity synthesis of fine chemicals, the removal of stoichiometric amounts of the iodobenzene coproduct is a bottleneck to practical use. Moreover, the use of stoichiometric amounts of relatively expensive organoiodine compounds is another restriction for industrial-scale use. For large-scale production, the development of recyclable types of reagents for which recovery and

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reuse are easy and the development of a new process that can perform the reactions with only catalytic amounts of iodines, are indispensable, similar to the situation of transition metals and organocatalysts.

Therefore a number of approaches for performing practical oxidation reactions that can reuse the reagents and reduce waste are now being actively investigated. Because of the simplicity of the recovery of the reagents by filtration, polystyrene-supported poly(diacetoxyiodo)styrenes (PDAIS), which were originally developed by Okawara,[23] were often used at the time when the author's group started research on the development of a new recyclable iodine reagent. We also studied the development of environmentally benign oxidation reactions using PDAIS and their derivatives, but experienced serious drawbacks with polymer-supported reagents regarding their reactivity and recyclability derived from their low solubilities in organic solvents, steric hindrance of the reactive iodine sites, degradation loss of the resin after repeated use, *etc.*, at the same time. To overcome these drawbacks of conventional polymer-supported reagents, the authors designed unique molecules **1** with admantane or methane cores to which four active iodine(III) sites are effectively attached, as new recyclable reagents (Chart 3).[11,12] All of **1a** and its acid derivatives **1b** and **1c** are stable solids. They are soluble in typical organic solvents (for example, dichloromethane, acetonitrile, methanol, *etc.*) and show almost the same reactivities as the classical PIDA and PIFA in various oxidation reactions.[17] Furthermore, no degradation of the molecules was detected after repeated use as the new reagents **1** have no weak benzylic hydrogens for the oxidations. Regarding recycling, the reagents can precipitate as solids after the reactions by adding methanol or isopropanol and be separated from the products in almost quantitative yields by filtration, as the reduced tetraiodides **1′** coproduced after the reactions are barely soluble in the polar solvents. That is, this protocol applied the unique property of the organoiodine compounds of changing their polarity depending on the valence number of the iodine atoms.

On the other hand, the recovered tetraiodides **1′** should be effectively converted back to the initial trivalent reagents **1** to become superior recyclable reagents. We encountered difficulty in this regeneration step. The general methods for preparing PIDA using peracetic acid[24] and other inorganic oxidants, such as sodium perborate[25] and sodium periodate,[26] were first examined for the tetraiodides **1′** with only low yields of the desired **1a**. After further investigations, we found a new synthetic method of trivalent diacetate using *meta*-chloroperbenzoic acid (*m*CPBA) and succeeded in synthesizing **1a** in nearly quantitative yield using *m*CPBA in a dilute dichloromethane/acetic acid mixed solvent system under homogeneous conditions at room temperature, by which the key regeneration step affecting the effectiveness of the net recycling process shown in Chart 3 was well established. We noted the excellent oxidizing ability of *m*CPBA during the conversion of various iodoarenes to the corresponding trivalent forms and applied the original method with *m*CPBA for the construction of novel organocatalytic processes of iodines by effectively generating active hypervalent iodine species *in situ* during the reactions. That is, we believed that the catalytic use of the reagents would be possible when the series of recycling processes for **1** were performed successively in one flask.

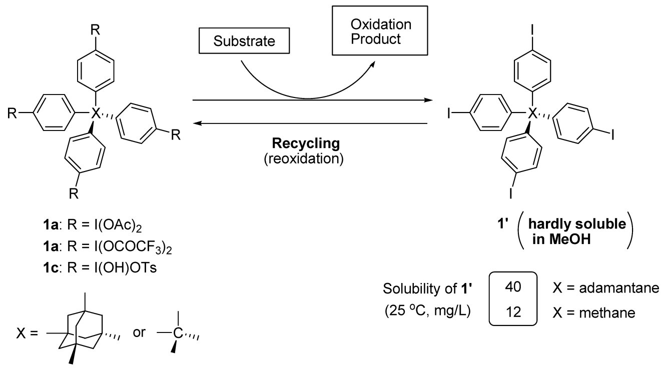
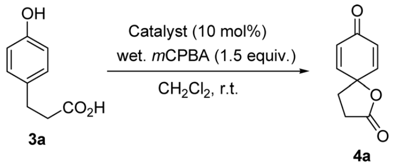


Chart 3. Recycle Diagram for New Hypervalent Iodine(III) Reagents **1**

2.1. Application of the Regeneration Process of the Recyclable Reagents 1: Development of a Catalytic Process Using Hypervalent Iodine Reagents In theory, the iodine reagents can be managed in catalytic amounts during the reactions if the coproduced iodobenzene can be smoothly regenerated to the initial high-valent forms *in situ* under mild conditions by choosing a suitable reoxidant (Chart 2, b).[27] The fluorination reactions that use catalytic amounts of trivalent reagents were reported under electrolytic conditions in 1994,[28] but this did not become a general method because the oxidation potential of iodobenzene is comparatively high and thus many organic compounds potentially cause undesired noncatalyst-participating background reactions under electrolytic conditions required for regeneration of the catalyst. Therefore the reaction, which makes the reagents catalytic, was not reported in the literature until 2005.

We believed that our preparative method with *m*CPBA for the recyclable reagent **1a** would work as effective regenerating conditions allowing iodine(III) to be applied in the catalytic utilization of hypervalent iodines and expand the scope of the concept to other classes of synthetically important bond-forming reactions. Although the oxidation reaction of the phenol **3a**[29] barely progressed with catalytic amounts of PIDA using *m*CPBA as the stoichiometric terminal oxidant, the catalytic phenolic oxidation developed using PIFA instead gave the spirodienone **4a**, although in moderate yield (Table 1, entries 1 and 2). The addition of trifluoroacetic acid to this system was even more effective, and iodobenzene (PhI) could similarly work as the catalyst (entry 3), which supports the assumed catalytic cycle involving both iodine(III) and iodine(I). As a matter of course, the oxidation of phenol **3a** did not proceed without the iodine catalysts. The substituent effect of the aromatic ring of the iodoarene catalyst was observed in this reaction (entries 3—6), and the reaction became markedly slower with the electron-deficient iodoarene (entry 5). This suggests that the generation of the active iodine(III) is probably the rate-determining step. The *para*-substituted 4-iodotoluene (4-Tol-I) maintained the catalytic activity during the reactions over iodobenzene displaying a better catalytic turnover number (TON) among those already examined (entry 6). Based on these considerations, the reaction proceeded in high yield even with 1 mol% of 4-iodotoluene when using trifluoroacetic acid, and the maximum TON of the catalyst reached 71 (entry 7).

Table 1. Survey of the Catalytic Conditions for Spirocyclization of Phenol **3a**



Entry	Catalyst	CF$_3$CO$_2$H	Time (h)	Yield (%)[a]
1	PhI(OAc)$_2$ (PIDA)	—	4	15
2	PhI(OCOCF$_3$)$_2$ (PIFA)	—	3	56
3	PhI	+[b]	2	60
4	4-MeOC$_6$H$_4$-I	+[b]	2	21
5	2,4-FC$_6$H$_3$-I	+[b]	17	60
6[c]	4-Tol-I	+[b]	2	72
7[d]	4-Tol-I	+[e]	2	71

a) Isolated yield. *b*) 1 eq. *c*) Catalyst loading: 5 mol%. *d*) Catalyst: 1 mol%. *e*) 50 eq.

The main active catalytic species for the reactions, 4-Tol-I(OCOCF$_3$)$_2$, was effectively generated from 4-iodotoluene and trifluoroacetic acid *in situ* by the action of *m*CPBA (Chart 4). This PIFA-type active species reacts with the phenolic oxygen of **3a** to produce the electrophilic, highly reactive phenoxenium ion **A** rapidly[7] as the oxidation reactions catalytically occurred in high yields. Finally, the released iodoarene catalyst was reused for the same reactions, thus initiating the second catalytic process.

We performed the catalytic spirocyclization of various types of phenols **3** based on the optimized reaction conditions (Table 2). The catalytic reactions proceeded smoothly in each case using 5 mol% 4-iodotoluene, 1.5 eq of commercial *m*CPBA containing water, and 1 eq of trifluoroacetic acid at room temperature. Interestingly, the yields of the spirocyclized products **4** were comparable to or better than the results using stoichiometric amounts of the previously obtained PIFA.[29] The catalyst system found by the authors thus has a sufficiently broad scope of generality in substrates to become a versatile approach for this type of catalytic oxidation of phenols.[18]

According to our initial plan, the adamantane and methane-based iodoarenes **1′**, which possess high reactivities and durability, are the most suitable as recyclable catalysts, and the catalytic use of **1′** results in a more beneficial method. We carried out the reactions using 5 mol% of iodoarenes **1′** resulting in a yield of product **4** nearly equal to the former cases (Table 2, X=adamantane or methane); moreover, the catalysts could be recovered by the general procedures already shown in Chart 3 and repeatedly reused. Thus, the iodoarene catalysts **1′** are new types of promising “recyclable organocatalysts” meeting the requirement to perform environmentally friendly oxidation reactions.[30]

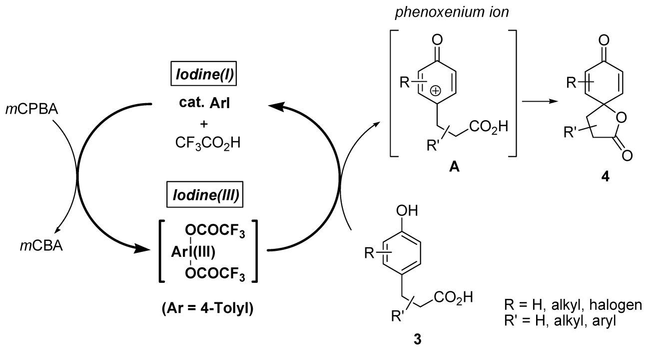
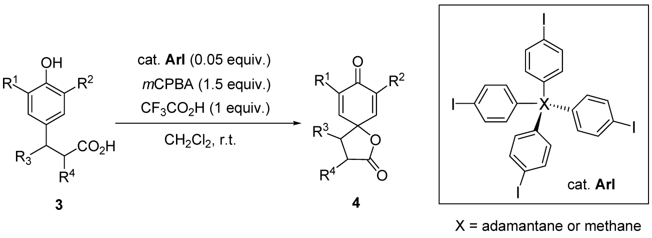


Chart 4. Catalytic Cycle for Spirocyclization of Phenols **3**

*m*CBA, *meta*-chlorobenzoic acid.

Table 2. Reactions Using 4-Iodotoluene or Recyclable Iodoarene **1′** as a Catalyst



R^1	R^2	R^3	R^4	Yield (%)[a]	Yield (%) (X=adamantane)	Yield (%) (X=methane)
H	H	H	H	71	71 (3 h)	67 (8 h)[b]
Br	H	H	H	77	86 (4 h)	70 (6 h)[c]
Me	H	H	H	66	78 (3 h)	76 (12 h)[b]
H	H	Me	H	76	74 (3.5 h)	72 (7.5 h)[b]
H	H	H	Me	73	52 (5 h)	87 (8 h)[c]
Br	Br	Me	H	91	93 (6 h)	92 (8 h)[c]
Me	Br	Me	H	80	85 (2 h)	72 (5 h)[c]

a) Catalyst ArI=4-Tol-I, reaction time=3 h. *b*) Two equivalents of CF$_3$CO$_2$H was used. *c*) Ten equivalents of CF$_3$CO$_2$H was used.

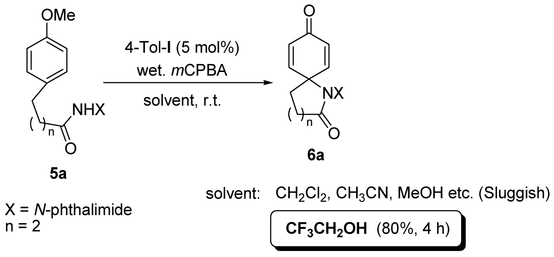


Chart 5. Unique Solvent Effect

2.2. Oxidations of Phenols Using Iodoarenes as Organocatalysts

The oxidations of phenols are extremely important reactions not only for synthetic chemistry, but also for biosynthetic processes, and the quinones, quinols, and cyclohexadienones obtained can be further utilized as the core structures of many biologically active natural products and their pivotal precursors. Apart from the above-mentioned strategy for the direct activation of the phenol aromatic rings, an alternative spirocyclization strategy initiated by the side-chain activation of phenols was also developed in our laboratory for the total synthesis of discorhabdin alkaloids.[31,32] As a similar side-chain activating method, the spirocyclizing reaction of the phenol derivatives by hypervalent iodines, which involves activation of the side-chain nitrogen groups having methoxy or phthalimide functionalities as a key step, has recently been reported[33] and been applied to the total synthesis of biologically unique compounds, such as TAN1251A, FR901483, and (−)-dysebetaine.[34] Next, we planned to extend our method shown in Chart 4 to perform the catalytic carbon–nitrogen bond-forming cyclization of the phenol derivative **5a** (Chart 5).

Accordingly, the optimized catalytic conditions in the carbon–oxygen bond-forming reactions for phenols **3** were first examined with somewhat unsatisfactory yields, even though the complete consumption of the starting **5a** was observed. The addition of the acids and other bases caused side reactions that tended to reduce the product **6a** yield. Thus we performed the reactions without adding trifluoroacetic acid but this resulted in decreased yield and deactivation of the catalysts because the formation of insoluble and unreactive oligomeric iodosoarenes $[\mathrm{ArIO}]_n$ occurred.[35] Therefore we next explored the solvent effect in detail aiming for the development of a new catalytic system, which led to the discovery of a versatile solvent for the generation of active catalytic species of iodines *in situ*, that is, the highly polar but low nucelophilic 2,2,2-trifluoroethanol (TFE),[7,36—39] and significant improvement in the yield of the desired cyclization product **6a**. The fluoroalcohols should be effective additives to expand the utility of the catalytic strategy, and catalytic reactions can develop promptly with their use as a solvent even in the absence of trifluoroacetic acid.

The significant merits of this solvent that we evaluated are that it: 1) promotes the generation of the active hyperavlent iodine(III) species; 2) activates the hypervalent iodine species by acting as an acid; 3) makes the conditions milder with more neutral pH (TFE is a weak acid showing a higher pK_a than that of acetic acid), and notably; 4) enables the use of various reoxidizing agents due to the positive effect of the above (the results are described in Section 2.3). Figure 1 illustrates the regeneration rate of the catalyst, and in this comparison, TFE actually assisted in the smooth generation of the hypervalent iodine(III) species to serve as a replacement for trifluoroacetic acid. The generation of I(III) was confirmed by trapping the active catalytic species with *p*-toluenesulfonic acid (Chart 6). In addition, the recyclable catalysts **1′** were also valid in this system.

The use of TFE is particularly valuable since it performs the reactions of acid-sensitive substrates and suppresses acid-promoted side reactions. The carbon–nitrogen bond-forming spirocyclization of phenols **5** in Chart 7 is a good example in which these advantages were applied to the catalytic syntheses of four- to six-membered spirolactames **6** with various functional groups. The reaction proceeded with high diastereoselectivity and in the acid-labile *N*,*O*-acetal-type product. As such, this new system utilizing the unique property of TFE as a solvent is a useful catalytic condition enabling the extensive use of the substrates for the phenolic oxidations. In the present spirolactam formation, TFE contributed to the generation of the highly reactive iodine(III) catalytic species as well as promoted the formation of the nitrenium ion intermediates leading to the products **6** by taking advantage of its excellent cation-stabilizing ability.[7]

Since the reports of our catalytic strategy[18] and those of other research groups[40,41] in 2005, the representative types of hypervalent iodine-mediated oxidations are now due to the catalytic manner of the organoiodines but mostly limited to the construction of C–O bonds as the bond-forming process. Thus this spirolactam-forming method developed by us is the first and only example to utilize the catalytic strategy for performing effective carbon–nitrogen bond-forming reactions using iodoarenes as organocatalysts to provide the key intermediates of naturally occurring alkaloids.[19]

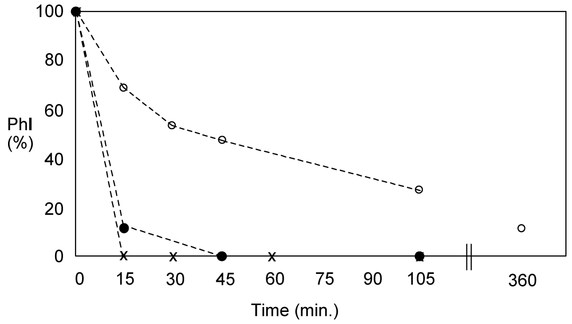


Fig. 1. Comparison of the Reoxidation Rates of Iodobenzene (PhI) in Several Solvents

PhI (0.07 M), wet *m*CPBA (1.5 eq), 25 °C. (○): in CD_2Cl_2, PhI=68% (15 min), 55% (30 min), 44% (45 min), 26% (105 min), 12% (360 min); (●): in CD_2Cl_2 with 1 eq of trifluoroacetic acid, PhI=12% (15 min), 0% (45, 105 min); (×): in CF_3CD_2OD, PhI=1% (15 min), 0% (30, 60, 105 min).

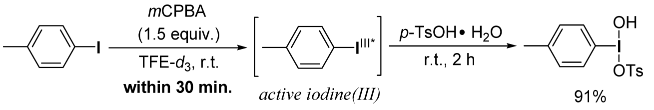


Chart 6. Trapping of the Active Iodine(III) Species in Trifluoroethanol

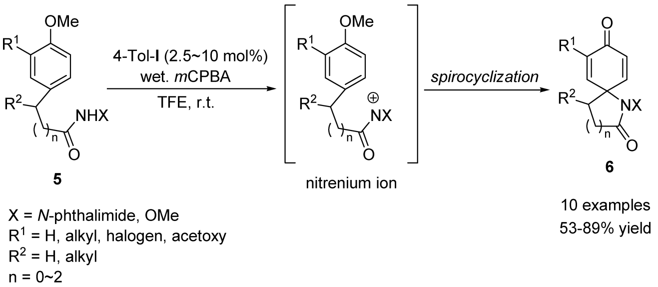


Chart 7. First Catalytic C–N Bond-Forming Reaction Leading to Spirolactams **6**

2.3. Application of the Catalytic Methods to Natural Product Syntheses The catalytic methods have been further improved to become more practical ones using economical and environmentally friendly terminal oxidants, such as peracetic acid and hydrogen peroxide instead of *m*CPBA, and have been used for the large-scale synthesis of useful precursors of some biologically active natural products.[20,21]

We now describe the application to the synthesis of the key intermediates of *Amaryllidaceae* alkaloids. The conversion of phenol **7a** to the maritidine alkaloid precursor **8a** is a good example, and the synthesis of the spirocyclized **8a** could be achieved on a multigram scale (Chart 8). To control the reactions and product selectivity, it is very important to perform the reactions at a temperature below −10 °C, and for this reason, *m*CPBA, which showed the best reoxidizing ability of the catalysts at room temperature, was not suitable as the terminal oxidant. As the generation rate of the active iodine(III) species was remarkably accelerated in TFE (see Fig. 1), various oxidants were examined, and a combination of hydrogen peroxide (the urea adduct, urea$\cdot H_2O_2$, was used in consideration of safety and handling) and trifluoroacetic anhydride (TFAA) provided the optimized reoxidation conditions to give the best results. For solubility reasons of the catalyst toward TFE at low temperature, the use of 4-fluo-

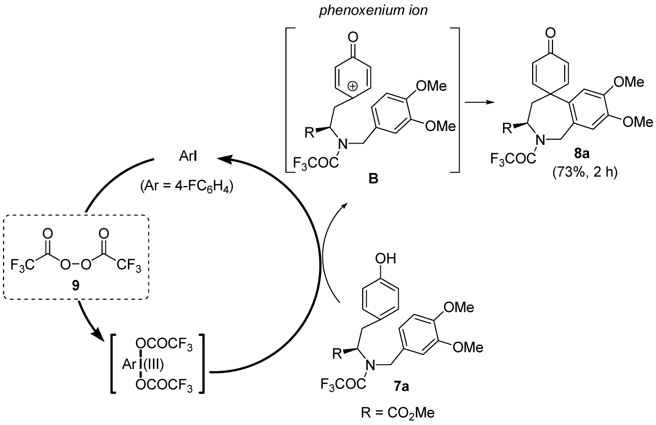


Chart 8. Catalytic Cycle for the Synthesis of a Key Intermediate of (+)-Maritidine

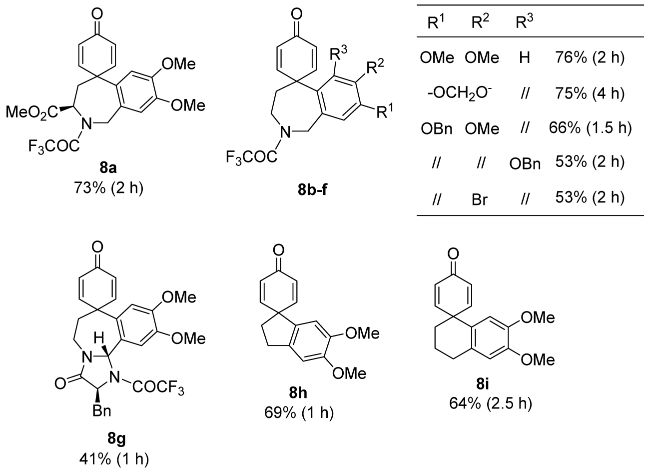


Fig. 2. Spirocyclic Products **8** *via* the Catalytic C–C Bond-Forming Process

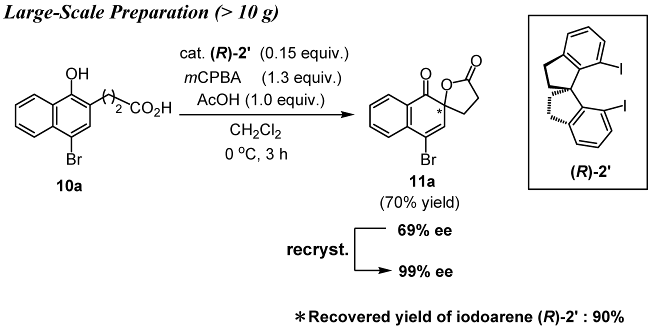


Chart 9. Catalytic Asymmetric Oxidation Using the New Chiral Iodoarene **2′**

roiodobenzene (4-F-C_6H_4-I) as a catalyst was recommended for the catalytic reactions.

The plausible reaction mechanism for the synthesis of a key intermediate of (+)-maritidine is as follows. First, hydrogen peroxide (H_2O_2) attacked TFAA to produce trifluoroacetyl peroxide (TFAP), followed by the further reaction with a second molecule of TFAA, affording the energetically more stable peroxide **9**.[42] This peroxide could act as a real reoxidant for the 4-fluoroiodotoluene catalyst even at low temperature and initiated the catalytic cycle depicted in Chart 8 by generation of the PIFA-like active trivalent iodine, which then reacted with the phenolic oxygen of substrate **7a**. Taking advantage of the cation-stabilizing ability of TFE,[7] the highly reactive phenoxenium ion **B** leading to the spirodienone product **8a** was produced with concomitant reproduction of the initial catalyst iodoarene, thus completing the catalytic cycle. For the selective production of the desired spirocyclized product **8a**, a low reaction temperature was required for inhibiting the side reactions of the highly reactive intermediate **B** that occurred at room temperature. Therefore the reactions should be performed below −10 °C using a combination of hydrogen peroxide and TFAA as the reoxidants, although the major catalytic species is the same as in Chart 4.

In Fig. 2, we applied the method mainly to obtain the key synthetic intermediates of the *Amaryllidaceae* alkaloid families, such as galanthamine and other crinine-type alkaloids, that are useful in the treatment of Alzheimer's disease[43—45] and we achieved their total syntheses.[4—6] At this point, the formation of the desired spirocyclic product **8g** as a major product demonstrated the applicability of the method even in highly functionalized substrates with complex molecular structures. The five and six-membered spirocyclic compounds **8h** and **8i** could also be obtained through the reactions of substrates with pendant alkyl side chains. These results led us to conclude that the new catalytic carbon–carbon bond-forming method has either a versatile or acceptable highly functional group tolerance.[20]

2.4. Catalytic Utilization of the Chiral Reagent 2′ in Asymmetric Oxidation of Phenols With the evolution of an effective preparation method as a turning point, the use of hypervalent iodines as "organocatalysts" is now possible, and the design of new catalysts with unique characteristics and selectivities not shown by the classical stoichiometric reagents is a current trend in this field. In this regard, we have already succeeded in the design of a new chiral reagent and its application in asymmetric oxidations. With the reagent **2′**, the authors have recently accomplished the unprecedented asymmetric oxidative dearomatization of phenols with reagent control.[22] We have also achieved the catalytic version of this oxidation using the chiral iodoarene **2′** as an "organocatalyst" by applying our initial catalytic method with *m*CPBA. For example, the reaction of the functionalized naphthol **10a** with the easily convertible bromo group proceeded using catalytic amounts of iodoarene (*R*)-**2′** with *m*CPBA to give an acceptable result (Chart 9). This is, to the best of our knowledge, the first successful case of the asymmetric oxidation of phenols by an organocatalyst. This reaction has the possibility to become a useful asymmetric transformation in organic synthesis as the products with such spirolactone structures are often seen in the framework of natural products possessing interesting biological activities.[46—48] Although the preparation of the new reagent **2′** requires multistep transformations from a known triflate precursor, the catalytic use of the chiral iodoarene enabled the multigram-scale preparation of the product **11a**. The optically enriched (+)-**11a** (>97% ee) was then obtained on a gram scale after a single recrystallization of the product. Meanwhile, over 90% of the catalyst, iodoarene (*R*)-**2′**, used in the reaction could be recovered after the usual chromatographic separation with silica gel.

Based on the studies described so far, we can reach the first goal of the development of a catalytic utilization method of hypervalent iodine reagents and its application to develop a valuable reagent and catalyst. Under such conditions, the use of a catalytic strategy makes the hypervalent iodine reagents more practical and versatile, and undoubtedly contributes to the progress of hypervalent iodine chemistry in organic synthesis.49)

3. Concluding Remarks

The authors have developed methods for the recycling and catalytic use of hypervalent iodine reagents. By applying these new methods, versatile organocatalytic phenolic oxidations have been achieved for the first time using iodoarenes as catalysts. Many types of oxidative transformation can be performed in a catalytic manner by the development of an effective regeneration method of hypervalent iodine reagents, and based on these advances, these reagents are now widely recognized as a new series of organocatalysts that enable environmentally friendly oxidation reactions. With the further improvement of secondary factors, such as catalyst TON, cost/performance of the method, atom economy of the reoxidant, *etc.*, as well as progress in the design of new iodine catalysts showing unique characteristics in synthesis, the role of the reagents in organic synthesis should expand in the future, which will also simultaneously contribute to the development of a new scientific field of hypervalent iodine chemistry.

In this review, the author mainly focused on recent advances in the use of hypervalent iodines in synthesis based on the design and effective use of reagents, and briefly described the research results of our group. Nevertheless, it is also very important to develop unknown reactivities inherently possessed by hypervalent iodines to enhance the utility of the reagents. We have therefore continuously studied the development of a direct functionalization method of carbon–hydrogen bonds with hypervalent iodine reagents and developed new basic reactions utilizing the unknown active species derived from the iodine(III) reagents during this study.50—58) They are promising as a new environmentally benign synthetic methods for replacing reactions using rare metals. As iodine is one of the few elements in which Japan is self-sufficient, producing about 40% of the total world supply, and most iodine derivatives show lower long-term toxicities compared with metal elements, the establishment of new synthetic methods enabling the practical use of iodines would have a significant benefit for Japan with its poor endowment of natural resources. It is hoped that this review and the methods described herein will contribute to the realization of ideal oxidation processes to provide safe, productive, highly selective reactions using iodines which are suitable for practical applications in organic synthesis.

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