Hypervalent Iodine Induced Metal–Free C–H Cross Couplings to Biaryls

Yasuyuki Kita, * Toshifumi Dohi, and Koji Morimoto

College of Pharmaceutical Sciences, Ritsumeikan University
1-1-1 Nojihigashi, Kusatsu 525-0058, Japan

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Abstract: Hypervalent iodine reagents, such as phenylidene diacetate (PIDA) and phenylidene bis(trifluoroacetate) (PIFA), are promising alternatives to metal–based oxidants for developing environmentally benign oxidation reactions, due to their low toxicities, mild reactivities, ready availability, high stabilities, and easy handling. During the study on the hypervalent iodine chemistry, we first determined in the 1990’s the single–electron–transfer (SET) oxidation ability of the hypervalent iodine(III) reagent toward electron–rich aromatic rings, such as the phenyl ether compounds, affording the corresponding aromatic cation radicals. This discovery led us to develop a series of metal–free carbon–hydrogen (C–H) bond functionalizations of aromatic compounds using the hypervalent iodine oxidants. We have extended the strategy to the carbon–carbon bond formation of biaryls based on the double aromatic C–H bond couplings, which can now provide a novel technology to the synthetic area of metal–free cross couplings for producing mixed biaryls from two molecules of unfunctionalized aromatic compounds. These achievements found by us during the development of hypervalent iodine–induced metal–free C–H cross couplings are now summarized in detail.

1. Introduction

The cross couplings can provide powerful tools for the construction of complex molecules in organic synthesis, and thus the development of a novel coupling method has been intensively studied by synthetic chemists. In general, the cross couplings using organometallic compounds (e.g., [M]=[Zn]; Negishi, [Bi]; Suzuki–Miyaura, [Sn]; Stille, etc.) with organic halides in the presence of transition metal catalysts, such as palladium complexes, have been conducted as useful methods for the formation of new carbon–carbon bonds (Scheme 1, eq. 1).1 These well–known coupling methods can afford target products in high yields and with good selectivities. However, these methods typically require stoichiometric amounts of the activated coupling substrates, that is, the metal and halogen–functionalized organics, and produce metallic salts as wastes and byproducts. Furthermore, the preparation of the pre–activated substrates often requires several synthetic operations, which is not ideal and efficient based on economic and environmental concerns. Inspired by the concept of green and sustainable chemistry, much effort has been dedicated to the development of direct cross coupling reactions.

Over the past decades, the carbon–hydrogen (C–H) bond functionalization strategies using organic halides or organometallic compounds as one of the coupling partners have been utilized for developing C–H cross couplings (eq. 2).2 ACTually, these direct C–H cross couplings are useful for creating carbon–carbon bonds without use of pre–activated substrates that are required in the traditional methods.

In theory, the most direct approach for constructing the carbon–carbon bond is oxidative coupling using two C–H bonds in each coupling molecule (eq. 3).3 The advantages of this strategy include a lower cost and less waste in contrast to the methods in eqs. 1 and 2, as the pre–activation steps of the two coupling substrates are not necessary. Despite their ideality regarding green chemistry, the oxidative coupling method would usually suffer from the formation of undesired homo-coupling and over-oxidation products. Arguably, the most important and remaining challenge in this area is the development of an effective oxidative cross coupling method to control the production of the desired products. Recently, K. Fagnou et al. reported the palladium–catalyzed oxidative cross coupling of heteroaromatic compounds such as indoles and pyrroles.4 This novel method can directly afford the mixed heteroaromatic biaryl motifs, which are the important structures for accessing natural products, such as alkaloids, as well as the ones found in the numerous biologically active parts of pharmaceutical and agrochemical molecules.5 However, even in this methodology, use of a transition metal catalyst and excess amounts of the coupling compounds remains indispensable. Therefore, further advances should be possible to enhance the oxidative cross coupling strategy being more efficient by developing a new metal–free and less waste method.

In this account, we would like to describe a summary of our achievements on the metal–free oxidative couplings of two different aromatic C–H bonds in electron–rich arenes for

![Scheme 1. Strategy for C–C bond–forming cross coupling.](image-url)
producing biaryls based on new strategies and concepts using hypervalent iodine reagents, along with a brief introduction of their excellent single-electron-transfer (SET) ability toward aromatic and heteroaromatic rings.


In modern synthetic research, new technology providing safer and more eco-friendly methods for the conversions of molecules that can positively impact the environmental and global resources are strongly desired. Such a situation has prompted many chemists to develop new reactions and reagents meeting the concept of green chemistry. In the oxidation area, hypervalent iodine compounds (iodanes) have rapidly emerged in recent decades as the attractive reagents for developing environmentally benign oxidations. Due to their reactivities similar to those of such toxic heavy metal–based oxidants that include lead, mercury, and thallium elements, in combination with the inherent low toxicities, high safety, ready availability, and easy handling, the iodine reagents are now widely recognized as promising alternatives to the heavy metal oxidants. Accordingly, a variety of useful oxidation reactions using hypervalent iodine reagents have already been developed, replacing the classical methods that use the highly toxic oxidizers. A number of previous reviews dealt with the unique properties and versatile utilities of the hypervalent iodine reagents in organic synthesis.

In the 1980’s, the authors perceived the synthetic potential of hypervalent iodine reagents as less toxic and safer organo–oxygen compounds that are favorable in drug development studies, and started to investigate their chemistry. Over the past quarter century, we have revealed a wide array of reactivities of trivalent iodine reagents, especially for phenylidodioaceta (PIDA, PhI(OAc)₃), phenyliodine bis(trifluoroacetate) (PIFA, PhI(OCOF₃)₂), [hydroxy]tosyloxyiodo]benzene (HTIB, PhI(OH)OTs), and iodosobenzene (PhIO), and have achieved the total syntheses of several biologically active naturally–occurring compounds. In particular, the oxidations of phenols and related compounds using PIDA and PIFA developed in our laboratory are extremely useful when considering their broad generalities and high functional group compatibilities. We noted in this investigation that the use of polar and weakly nucleophilic fluorocarboxyl solvents such as hexafluoroisopropanol (HFIP, (CF₃)²CHOH) and 2,2,2-trifluoroethanol (TFE, CF₃CH₂OH), had a significant positive effect on the yield of the oxidation products. The PIDA and PIFA–induced oxidations of phenols initially react with the iodine center of the reagents and then the formed phenyliodine intermediates are attacked by the nucleophiles to give various quinone–type products. These useful transformations have since been widely applied to many total syntheses of biologically important natural products and their pivotal intermediates.

Similar to this phenolic oxidation, the reactivity of hypervalent iodine reagents is typically explained as ionic processes in most cases. Thus, the reactions of oxygen–protected phenol ethers have been limited and would typically form diaryliodonium salts rather than the oxidation product. On the other hand, the hypervalent iodid(III) reagents can work as selective and efficient single-electron-transfer (SET) oxidizing agents for electron–rich aromatic compounds, when treated under specific reaction conditions.

Regarding this, we first determined the SET oxidation ability of the hypervalent iodine reagents toward phenyl ethers to afford the corresponding aromatic cation radicals at the beginning of the 1990’s. The UV and ESR studies of the cation–stabilizing solvents, HFIP and TFE, could support the generation of the aromatic cation radical species of the para–substituted phenyl ethers. Interestingly, the umpoling of the electron–rich aromatic rings occurred without the use of any metal oxidant. Thus, the treatment of the para–substituted phenyl ethers with PIFA in the presence of appropriate nucleophiles led to unusual oxidative aromatic substitutions as a result of the effective trapping of the formed cation radicals by the nucleophiles (Scheme 2). Based on this strategy, various nucleophiles, such as azide, acetate, thiophenolate, thiocyanate, and β–dicarbonyl compounds, could be selectively introduced at the ortho position of the phenyl ethers. This discovery has surely encouraged the recent elucidation of the hypervalent iodine reagents as selective and efficient SET–oxidizing agents that enable a variety of oxidative C–H functionalizations of aromatic rings in electron–rich arenes.

The related types of nucleophilic substitutions could also be carried out by activating PIFA with Lewis acids in standard solvents such as dichloromethane and acetonitrile. Typical examples include the classically–known boron trifluoride (BF₃·Et₂O) and trimethylsilyl triflate (TMSOTf) as well as the soft solid acids, such as heteropoly acids (HPAs) and other series of solid clay catalysts. This modified strategy has significant advantages in controlling the reactivity of the hypervalent iodine reagents and the reaction courses, which can offer a wide array of optional reactivities to the reagents. The hypervalent iodines became versatile SET oxidizing agents that are compatible with more extensive applications. Elaboration of the SET processes to the biarylation synthesis directly from unfunctionalized aromatic compounds based on the reaction mechanism (Scheme 3) is now possible using the combination of hypervalent iodine reagents and Lewis acids. Thus, the generation of an aromatic cation radical would occur by the SET oxidation through a charge-transfer (C–T) complex of the iodine atom and electron–rich aromatic compounds. Subsequent in situ trapping of this cation radical by other existing aromatic molecules followed by a further one–electron oxida-
tion and deprotonation as the final events would form the aryl-aryl bond to produce the corresponding biaryls.

Similar SET strategies were proposed for the oxidative biaryl couplings using metal oxidants as well as for anodic oxidations, but these methods apparently have drawbacks regarding the stoichiometric use of the metal oxidants which resulted in low product yields, thus being considered not a best choice for the synthesis of fine chemicals that require a high purity.\textsuperscript{16} With these aspects in mind, the authors have developed the hypervalent iodine-induced metal-free C–H couplings for access to a variety of electron-rich biaryls.\textsuperscript{17–20} In the next section, we discuss our metal-free biaryl coupling methodologies based the excellent SET oxidizing ability of the hypervalent iodine reagents.

3. Oxidative Intramolecular C–H Cross Couplings to Biaryls

The intramolecular oxidative biaryl couplings of phenyl ether derivatives could smoothly proceed using the strategy of PIFA activation by BF\textsubscript{3}·Et\textsubscript{2}O or HPAs.\textsuperscript{17–19} The effect of these Lewis acid activations is remarkable as represented by the coupling results of 1,3-diypropene 1a by PIFA with or without BF\textsubscript{3}·Et\textsubscript{2}O (Scheme 4). In the absence of BF\textsubscript{3}·Et\textsubscript{2}O, the reaction of 1a in HFIP gave an intramolecular coupling biaryl 2a in 63\% yield at 0°C. In the reactions in other solvents, TFE, acetonitrile, and dichloromethane, could proceed at the lower temperature of −40°C, giving the biaryl 2a in up to a moderate yield (25–65\%). In turn, the treatment of BF\textsubscript{3}·Et\textsubscript{2}O under the same conditions dramatically improved the yield of 2a. Thus, the biaryl coupling smoothly proceeded at a lower temperature (−40°C) in good yields, and 91\% of the pure coupling product was obtained when using dichloromethane.

![Image](https://example.com/image.png)

**Scheme 4.** Effect of BF\textsubscript{3}·Et\textsubscript{2}O in the intramolecular biaryl coupling.\textsuperscript{17–19}

<table>
<thead>
<tr>
<th>solvent</th>
<th>temp (°C)</th>
<th>isolated yield of the biaryl (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFIP</td>
<td>0</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>containing BF\textsubscript{3}·Et\textsubscript{2}O</td>
</tr>
<tr>
<td>TFE</td>
<td>−40</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH\textsubscript{2}CN</td>
<td>−40</td>
<td>46</td>
</tr>
<tr>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>−40</td>
<td>25</td>
</tr>
</tbody>
</table>

*Reactions were performed for 3 hours at the stated temperatures.

This is because BF\textsubscript{3}·Et\textsubscript{2}O could enhance the SET oxidizing ability of the iodine atom toward an aromatic compound by coordination to the trifluoroacetoxy group of PIFA, and thus assist in the smooth generation of aromatic cation radical species. Therefore, the SET oxidation was slower in the absence of BF\textsubscript{3}·Et\textsubscript{2}O, which caused a slow coupling of substrate 1a and undesirable over-oxidation of the formed biaryl, that is, an oxidation-sensitive electron-rich aromatic compound, decreasing the yield of the biaryl 2a due to the kinetic reason.

The versatility of the reaction was proved by the extensive series of pro-biaryl substrates (Scheme 5). Other 1,3-diarylpropanes, N-benzyl-N-phenethylamine derivatives, and N,N-dibenzylamine derivatives were similarly converted into the cyclized biaryls in good yields under the optimized conditions. The intramolecular couplings selectively occurred at each para ring position of the methoxy groups. The combination of PIFA and HPAs or montmorillonite K10 (M–K10) clay could be also used for the intramolecular couplings.\textsuperscript{19}

![Image](https://example.com/image.png)

**Scheme 5.** Intramolecular biaryl couplings using hypervalent iodine reagent.\textsuperscript{15}

<table>
<thead>
<tr>
<th>entry</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>R\textsuperscript{3}</th>
<th>R\textsuperscript{4}</th>
<th>R\textsuperscript{5}</th>
<th>yield of biaryl (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>OMe</td>
<td>H</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>−OCH\textsubscript{3}H</td>
<td>−OCH\textsubscript{3}H</td>
<td>H</td>
<td>OMe</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
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<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>OAc</td>
<td>75</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>entry</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>R\textsuperscript{3}</th>
<th>R\textsuperscript{4}</th>
<th>R\textsuperscript{5}</th>
<th>n</th>
<th>yield of heterocyclic biaryl (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>H</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>2</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>2</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>2</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>−OCH\textsubscript{3}H</td>
<td>−OCH\textsubscript{3}H</td>
<td>H</td>
<td>OMe</td>
<td>94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>1</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>1</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>OTBS</td>
<td>1</td>
<td>64</td>
</tr>
<tr>
<td>8</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>OAc</td>
<td>H</td>
<td>1</td>
<td>60</td>
</tr>
</tbody>
</table>

Particularly, our developed biaryl synthetic method utilizing the oxygen, sulfur, and silicon-tethered templates could provide a practical two-step route for the non-cyclic mixed biaryls 5. These methods were extended to the non-cyclic mixed biaryl synthesis, by performing the intramolecular oxidative biaryl coupling process and successive removal of the heterocyclic templates (Scheme 6). Thus, each substrate 3 similarly afforded the cyclized coupling products 4 in excellent yields by the SET process with the activated PIFA. The dibenzoheterocyclic structures in the cyclic 4 were then cleaved by the treatment of TBAF/THF, Raney Ni, or DDQ to give the ortho–substituted symmetrical and unsymmetrical biaryls 5 possessing formyl, methyl, and hydroxy group functionalities. These structures are essentially useful for constructing the highly oxygenated mixed biaryl structures as these are ubiquitous as the potent central building block of not only a large number of bioactive natural products, such as polyketides, terpenes, lignanes, coumarins, flavonoids, tannins, and many alkaloids, but also the ligand of metal catalysts for asymmetric synthesis.
The oxidative biaryl coupling strategy was also successful in an intermolecular fashion. The intermolecular couplings of phenyl ethers and alkylarenes were achieved using the already described standard reagent combinations and conditions (Scheme 7). Thus, the intermolecular coupling could smoothly proceed using a variety of phenyl ethers and alkylarenes to give the corresponding biaryl dimers in excellent yields by the treatment with PIFA/BF$_3$-Et$_2$O in CH$_2$Cl$_2$ at low temperature. Similarly, binaphthyl compounds were obtained in good yields under these reaction conditions. The yields of the biaryls were theoretically and experimentally best when using 0.50–0.55 equiv. of PIFA, otherwise the use of excess amounts of the oxidant induced over-oxidations of the products that would lead to the formation of oligomers and/or quinone derivatives as the byproducts. We have also extended the method for phenyl ethers and alkylarenes to work even in a series of heteroaromatic compounds, such as thiophenes, pyrroles, and indoles, by optimizing the suitable Lewis acid additive and reaction conditions.

The intermolecular coupling was further applied to the synthesis of the optically pure atrop biaryls (Scheme 8). Utilizing $\alpha\rightarrow\beta$-glucose frameworks as inexpensive chiral templates, the biaryls were generally obtained with high diastereoselectivities. Removal of the sugar template in the biaryls by LiAlH$_4$ as shown for the conversions in Scheme 6 produced the optically pure biphenyls (typically, >99% e.e.), which are considered as a potent precursor leading to ellagitannins.

In general, the oxidative coupling strategy is convenient for directly obtaining homo-biaryls from the electron-rich aromatic compounds, but its extension to intermolecular cross coupling is believed to be unsuccessful because the undesired homocoupling dimer formation should apparently compete (Scheme 9). Indeed, typical heavy metal oxidants (i.e., V(V), Mn(III), Mo(V), Fe(III), Ti(III), and Pb(IV)-based oxidants),$^{27a}$ nitric acid based oxidants, and anodic oxidations were previously tested for several types of intermolecular cross couplings but all failed in regard to the selective access to mixed biaryl compounds.$^{27j,k}$ There still remain limited applications due to the chemoselective issue in the oxidative cross coupling area. Aiming at resolving this specific problem, many synthetic efforts have been devoted to realize the attractive direct route to mixed biaryl compounds.

Recently, one of the solutions was suggested by Stuart and Fagnou,$^4$ Canesi's group,$^{28}$ and others$^{29}$ regarding the selective cross couplings of indoles, anilines, naphthols and other heteroaromatic compounds, respectively. These strategies have been realized by utilizing the reactive and coordinative nitrogen and oxygen functionalities to catalysts and oxidants. Despite few

### Scheme 6. Tether strategy for approach to non-cyclic mixed biaryl.$^{11}$

### Scheme 7. Intermolecular biaryl coupling of phenyl ethers and alkylarenes.$^{20}$

<table>
<thead>
<tr>
<th>entry</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>$R^3$</th>
<th>$X$</th>
<th>$Y$</th>
<th>yield of the first step (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>O</td>
<td>0</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>-OCH$_3$</td>
<td>H</td>
<td>O</td>
<td>0</td>
<td>S/Br$_2$</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>OMe</td>
<td>OMe</td>
<td>CH$_3$</td>
<td>O</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>4</td>
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<td>OMe</td>
<td>CH$_3$</td>
<td>O</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>5</td>
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<td>OMe</td>
<td>CH$_3$</td>
<td>O</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>OMe</td>
<td>OMe</td>
<td>CH$_3$</td>
<td>O</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

4. Oxidative Intermolecular Cross Couplings

The oxidative biaryl coupling strategy was also successful in an intermolecular fashion. The intermolecular couplings of phenyl ethers and alkylarenes were achieved using the already described standard reagent combinations and conditions (Scheme 7). Thus, the intermolecular coupling could smoothly proceed using a variety of phenyl ethers and alkylarenes to give the corresponding biaryl dimers in excellent yields by the treatment with PIFA/BF$_3$-Et$_2$O in CH$_2$Cl$_2$ at low temperature. Similarly, binaphthyl compounds were obtained in good yields under these reaction conditions. The yields of the biaryls were theoretically and experimentally best when using 0.50–0.55 equiv. of PIFA, otherwise the use of excess amounts of the oxidant induced over-oxidations of the products that would lead to the formation of oligomers and/or quinone derivatives as the byproducts. We have also extended the method for phenyl ethers and alkylarenes to work even in a series of heteroaromatic compounds, such as thiophenes, pyrroles, and indoles, by optimizing the suitable Lewis acid additive and reaction conditions.

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### Scheme 7. Intermolecular biaryl coupling of phenyl ethers and alkylarenes.$^{20}$

### Scheme 9. General problems in intermolecular oxidative C–C’ couplings

### Scheme 8. Synthesis of optically active biaryls utilizing chiral template.$^{22}$
examples of success, further development based on a new direct cross coupling system involving an alternative mechanistic conception, which permits other structural types of coupling combinations, is strongly required. For example, the preparation of a mixed biaryl of an aromatic hydrocarbon not having the heteroatom is still difficult.20 and even the novel method using a palladium catalyst with potassium persulfate in the presence of trifluoroacetic acid (TFA) was not practical because of its low yields, turnover numbers (TONs), and formation of a homocoupling product; the reaction of naphthalene with excess mesitylene in this system produced a large amount of 2-(3,5-dimethylbenzyl)-1,3,5-trimethylbenzene, a homocoupling product of mesitylene, together with the low yield of the desired mixed biaryl of naphthalene and mesitylene (Scheme 10).21,22 Furthermore, the catalyst combination of Pd(OOCF₃)₂ and Cu(OAc)₂ resulted in no reaction.

Scheme 10. Trial on the oxidative cross coupling of aromatic hydrocarbons using rare-metal catalyst.

4.1 Cross Couplings Using Hypervalent Iodine Reagent via SET Processes

Surprisingly, when the reaction of naphthalene and mesitylene in Scheme 10 was examined using the hypervalent iodine reagent, the desired cross coupling occurred in high yield! (Scheme 11). Contrary to the apprehension of forming the homodimer, the treatment of two aromatic hydrocarbons with PIFA gave only the mixed biaryl, even using an excess amount of mesitylene. To confirm the excellent behavior of the hypervalent iodine reagent, we tested a variety of other representative oxidants and conditions for this coupling. As the organic oxidants, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and even other hypervalent iodine reagents, such as C₅F₅I(OOCF₃)₂ and pentavalent Dess-Martin periodinane (DMP), caused the undesired formation of the homodimers of mesitylene, probably because the reactivities of the oxidants are too high to be selective. As a result, only Koser’s reagent (PhIOH)OTs, OTs=p-toluenesulfonate showed a comparable performance to PIFA as the hypervalent iodine reagent among the oxidants we tested. Ferric(III) chloride and thallium(III) trifluoroacetate could affect the cross coupling, but the yields of the mixed biaryls were too low (12% for FeCl₃ and 25% for Ti(OOCF₃)₂, respectively).

Scheme 11. Oxidative cross biaryl coupling using hypervalent iodine reagent.23

Other SET reagents, such as ceric ammonium nitrate (CAN) and molybdenum(V) chloride, were also screened as metal oxidants, but generally had more negative results than the hypervalent iodine reagents, while anodic oxidations induced the remarkable formation of the homodimers of both naphthalene and mesitylene.23b These results clearly suggest that the use of the organoiodine(III) oxidant is essential for the selective cross coupling and efficient reaction progress. We hypothesize that the new cross coupling first involves the generation of the naphthalene cation radical similar to the typical SET oxidation mechanism through the C–T complex (see Scheme 12). Subsequent in situ trapping of the resulting intermediate by the existing mesitylene (in which all of the naphthalene molecules were already consumed by taking advantage of the fast SET event) and the further one electron oxidation and deprotonation would furnish the aryl–aryl bond to give the mixed biaryl. For the realization of the cross coupling, the smooth and selective SET activation of naphthalene over mesitylene as well as effective trapping of the persistent naphthalene cation radical should occur in this order during the mechanism, otherwise the homodimer formation would occur. The estimated high nucleophilicity of mesitylene24-meets the latter requirement as a suitable coupling partner. Furthermore, the former can be experimentally expected by the measured oxidation potential of the aromatic compounds (naphthalene $E_{ox}$=1.64 V, mesitylene $E_{ox}$=1.83 V, respectively). However, the selectivity of the SET activation of the aromatic ring by PIFA cannot be simply determined by the oxidation potential of the aromatic compounds. To understand the reason for this result, the successful formation of a mixed biaryl from naphthalene and pentamethylbenzene in the reaction should be noted. Thus the undesired homocoupling hardly occurred, and neither the homodimer of naphthalene nor pentamethylbenzene was detected (checked by GC). The successful coupling of these two aromatics is remarkable because the selective activation of one of these aromatic compounds is difficult due to the very close relationship regarding their oxidation potentials (naphthalene $E_{ox}$=1.64 V vs. pentamethyl benzene $E_{ox}$=1.58 V). This unusual phenomenon accounts for the fact that PIFA would not form the C–T complex with multi-substituted aromatic compounds, i.e., mesitylene and pentamethylbenzene, because of the steric factor, whose unique characteristics could also attenuate the selectivity of the SET oxidation process over the feasibility of the aromatic rings toward oxidation that is suggested by the oxidation potential. Similarly, the over-oxidation of the formed biaryl would not occur during the hypervalent iodine–induced cross coupling due to

Scheme 12. A plausible explanation for hypervalent iodine induced oxidative cross coupling mechanism.
slower reaction rate of the biaryl toward the SET oxidation, which was confirmed by performing control experiments on the reactivities of the biaryl vs. naphthalene, resulting in the observed exclusive SET oxidation of naphthalene to start the reactions.

This rationalization should provide a general guideline for a novel direct approach to the cross coupling. The reaction would become particularly effective if the selected two aromatic compounds have quite different oxidation potentials and the SET-insensitive partner shows a higher nucleophilicity compared to the other one. Actually, the selection of sterically hindered aromatic hydrocarbons possessing high oxidation potentials as one of the ultimate coupling partners enabled the extended cross coupling. The results in Scheme 13 reveal the generality of the cross coupling for a series of aromatic compounds via the SET oxidation process, and good yields were obtained for the coupling of a number of substituted naphthalenes. Typically, the biaryl bond formations occurred at the sterically less hindered site on the aromatic nucleophiles. The halogen functionality, which allowed further elaboration of the obtained mixed biaryl structures, was the best and most versatile directing group to control the reaction position of the naphthalenes. A high selectivity was thus observed for bond formation on the more electron-rich ring as shown in the results of the bromonaphthalene. On the other hand, the high reactivity of the reaction intermediates allowed the construction of highly congested biaryls, which are difficult to synthesize by other methods. In fact, the naphthalene cross coupling with 1,3,5-tri(isopropyl)benzene could afford the highly congested biaryl in 70% yield after purification (entry 8). Hence, we have succeeded in the first successful examples of the selective and efficient cross coupling between unfunctionalized aromatic hydrocarbons, which largely relies on the unique SET selectivity of the hypervalent iodine reagent for the generation of aromatic cation radicals. Recently, we have found that this method is potentially applicable to oxidative C–H cross coupling leading to highly oxygenated mixed naphthalene–benzene type biaryls.

4.2 The New Iodonium Salts-Mediated Strategy

We then attempted to extend the original SET method of cross coupling to heteroaromatics, such as thiophenes, pyroles, and indoles, but the developed strategy did not work well since the heteroaromatic compounds could easily dimerize to homodimers and even oligomerize under the stated reaction conditions. Unfortunately, the heteroaromatic compounds are too sensitive to selectively react even by the SET oxidation.
processes using the hypervalent iodine reagents. On the other hand, the reported C–H cross coupling methods using transition metal catalysts are rather effective for heteroaromatic compounds, which is a marked contrast to our method. The metal–catalyzed strategies for heteroaromatic compounds usually consider the presence of σ-aryl metal intermediates in the reaction mechanisms, while the evident use of σ-aryl high-valent non-metal elements as key intermediate of metal–free cross coupling has never appeared. At the same time, we have just developed a method for the synthesis of aryliodonium(III) salts by the dehydrative condensation of heteroaromatic compound and the hypervalent iodine reagent. Utilization of the σ–heteroaromatic iodonium(III) species as intermediate in development of a new cross coupling has thus been envisioned.

Preliminary investigation using isolatable σ-thienyl iodonium(III) salt A–OTs having a tosylate anion under the conditions already stated and by adding acid activators (BF₃·Et₂O, TMSOTf, HPAs, and solid clay catalysts such as M–K10) with or without heating were all ineffectual for the aromatic substitution reaction with the methoxynaphthalene, and the stable salt A–OTs was recovered from the reaction mixtures in most cases (Scheme 14). The extensive screening of acid activators almost failed to obtain any biaryl product, while when specifically using bromotrimethylsilane (TMSBr), the reaction of the iodonium salt A–OTs led to the trace formation of a mixed biaryl product of the thiophene and naphthalene. This is quite surprising as the iodonium salt is generally inert under such conditions in the absence of a metal catalyst and never reacts with an aromatic compound. This result, albeit in very low yield, implied for the first time the possible use of an aryliodonium salt in developing new C–H cross couplings to biaryl without activation by a metal catalyst. Strongly encouraged by this finding, we then evaluated fluoroalcohol solvents using TMSBr, among which the yield of the obtained mixed biaryl was dramatically improved, and to our delight, reached an 87% yield in the case of HFIP. Curiously, the use of over two equivalents of TMSBr regarding the iodonium salt A–OTs was essential for a smooth reaction progress, otherwise the use of one equivalent only mainly produced the iodonium bromide A–Br. On the other hand, the isolated bromide A–Br could also work as a cross coupling partner of the methoxynaphthalene in the cross coupling upon the addition of a further equivalent of TMSBr, and even in the presence of other acids, such as BF₃·Et₂O, TMSOTf, and HPAs. Therefore, the essential use of TMSBr in the newly developed cross coupling should be for the in situ preparation of the iodonium bromide A–Br as an intermediate. To realize the C–H cross coupling from unfunctionalized aromatic compounds, we finally improved the transformation in Scheme 14 to produce a reaction in a one–pot manner from thiophene, by preparing the iodonium salt A–OTs in situ in the fluoroalcohol using Ph(OH)OTs (HTIB) before starting the cross coupling triggered by TMSBr (Scheme 15).

Fortunately, this challenge based on the unusual reactivity of the σ–aryl trivalent iodine intermediates can lead to an extensive range of heteroaryl–involved mixed biaryl syntheses using the hypervalent iodine reagent. The treatment of various heteroaromatic compounds with electron–rich aromatic partners under the cross coupling conditions produced the corresponding mixed biaryls in very good yields as the sole coupling products without any formation of a homodimer (Scheme 16).

Especially, thiophenes and pyrroles, which are known to smoothly form aryliodonium salts, can work as good substrates. As the to smoothly form aryliodonium salts, can work as good substrates. As the coupling partners to these salts, the nucleophilic characteristics of the aromatic rings are the most important factor, and thus various aromatic nucleophiles, i.e., phenyl ethers and nucleophilic heteroaromatic compounds, could be used. In the thiophene–pyrrole cross couplings, the reactants would couple with each α-position of the heteroaryl rings to give α–linked biaryls. The new iodonium-mediated cross coupling method apparently has several synthetic advantages over other reported methods using metal catalysts. One is that the intermediacy of the stable iodine intermediates like the A–OTs (see, above) enables selective cross couplings between closely related arene molecules. Even in the coupling reactions between thiophenes or pyrroles, the desired mixed biaryls were successfully obtained as represented by the coupling products 8ce and 8ef. Owe to the mild oxidation character of the hypervalent iodine reagents and reaction conditions, halogen functionalities remained unreacted during the reactions as seen in the product 8fg, which allowed further elaboration of the
obtained mixed biaryl structures using well-known modern bond-forming technologies.

One of the intriguing features of this cross coupling is the regioselectivity, that is, the thiophenes having one substituent at their β-position exclusively coupled with another aromatic partner at the remote α-position of the thiophene atom (see product 8cb in Scheme 16). This unique selectivity that has not appeared in other metal catalyzed C–H cross coupling methods is explained by the following possible reaction mechanism (Scheme 17). The reaction of 3–alkylthiophene should start by the selective condensation with HTIB at the reactive 2–position of the heteroaromatic ring to form the stable iodonium salt, A–OTs. The formed A–OTs salt was transferred to the more reactive bromide A–Br by treatment of TMSBr, which was further activated by the persistent TMSBr to induce the cross coupling, probably through the formal hydroarylation with the aromatic nucleophiles 7 in HFIP utilizing the thermodynamically favored formation of iodobenzene as well as the cleavage of the weak I(III)–Br bond as the driving force, where the introduction of the aromatic nucleophiles would occur at the remote position of the activated thienyliodonium salt A–Br rather than at the ipso-position of the iodine(III) leaving group, resulting in the observed unique regioselectivity of the mixed biaryl products in the case of the 3–alkylthiophenes. Nonetheless, the detailed reaction mechanism depends on the coupling combination of aromatic compounds and the reaction conditions, especially concerning the activator of the bromide A–Br, and unusual ipso-substitution of the diaryliodonium bromides could occur using stronger Lewis acids and very SET-sensitive aromatic compounds.32

Scheme 17. A plausible reaction mechanism for the metal-free cross coupling using TMSBr as activator.

Based on this preference of site selectivity, we anticipated that a variety of unsymmetrical dimers might be synthesized by the substituted thiophenes without formation of other regioisomers via the iodonium salt. As a result, a novel direct method for the synthesis of head–to–tail (H–T) bithiophenes has been realized for the first time using the hypervalent iodine reagent (Scheme 18). The reactions could smoothly proceed in a variety of alkyl and alkoxy–substituted thiophenes and gave the corresponding H–T bithiophenes in high yields as a single biaryl isomer. The strategy relies upon the reactivity of thienyliodonium intermediates that exclusively activate the 5–position of the substituted thiophenes are inherently more reactive at the 2–position and would typically couple at the position to form H–H dimers under oxidation. Thus, we have named this approach for obtaining unsymmetrical dimers as ‘Selectivity Switching, a Concept’ for modulating the reactivity of heteroaromatic compounds based on the involvement of the iodonium salts.

Scheme 19 is a summary of the representative mixed biaryl products obtained by our newly developed two types of the C–H cross couplings using hypervalent iodine reagents. The novel intermolecular C–H cross coupling strategies have the following characteristics and various synthetic merits, such as (i) a metal catalyst–free method, (ii) mild reaction conditions (the use of an organoiodine oxidant, ambient conditions), (iii) high yields and regioselectivities of the obtained mixed biaryl, (iv) no oligomer formations, and (v) no requirement of using an excess amount of arenes. The use of a recyclable alternative to the hypervalent iodine reagent was also possible and could improve the reactions to be more practical ones.32 The electron-rich mixed heteroaromatic biaryls prepared by these methods should be promising synthetic precursors in many scientific fields, and utilization of the obtained mixed biaryls as building blocks of organic materials is now in progress for commercialization.33

5. Concluding Remarks and Future Perspectives

In this paper, we have introduced our development of the hypervalent iodine–induced metal–free C–H cross couplings that was started in the 1990’s. By extending the initial discovery of the SET oxidation ability of the hypervalent iodine reagent, a series of metal–free C–H functionalizations of aromatic rings using the hypervalent iodine oxidants have been realized. In particular, the biaryl–constructing cross coupling strategies that can effectively utilize unfunctionalized C–H bonds have now opened new metal–free synthetic areas in organic synthesis. The prospective role of the hypervalent iodine reagent in the previous century was a simple replacement of the heavy metal oxidants, which goes beyond being alternatives to even the rare–metals as much as the unique reactivities and selectivities have been pioneered. The aim of our research is to expand...
the utility of the hypervalent iodine reagent as a future replacement for metal-using methods. Under such considerations, the chemistry of hypervalent iodines will continue to make an impact in the 21st century of organic synthesis.

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References and Notes


PROFILE

Yasuyuki Kita was born in 1945 in Osaka, Japan. He received his Ph.D (1972) from Osaka University and subsequently was a member of the faculty of the Pharmaceutical Sciences of the University. After two years (1975–1977) of postdoctoral work with Professor G. Büchi at MIT, he moved back to Osaka University, and was promoted to Associate Professor in 1983. Since 1992, he had been Full Professor of Osaka University. He took retirement from Osaka University in March 2008 and is now a dean of College of Pharmaceutical Sciences, Ritsumeikan University and a Professor emeritus (Osaka University). He received the PSJ Award for Young Scientists (1986), the PSJ Award for Divisional Scientific Contributions (1997), the PSJ Award (2002) and the Society of Iodine Science (SIS) Award (2007). His research interests extend to development of new synthetic methods including asymmetric synthesis and total synthesis of biologically active natural products.

Toshifumi Dohi received his Ph.D in 2005 (Y. Kita), subsequently became Assistant Professor at Osaka University. Since 2008, he has also been Assistant Professor at Ritsumeikan University, Kusatsu. He received the IUPAC-ICOS 15 Poster Award for most excellent presentation (2004), the Pharmaceutical Society of Japan (PSJ) Award for Young Scientists at the Kinki Branch Office (2006) and the PSJ Award for Young Scientists (2009). His current research into organic synthesis is focused on hypervalent iodine chemistry.

Koji Morimoto received his Ph.D in 2009 from Osaka University. He is Postdoctoral fellow at Ritsumeikan University, Kusatsu. He received the Pharmaceutical Society of Japan (PSJ) Award for Young Scientists at the Kinki Branch Office (2010). He is involved in the development of new methodologies in oxidative coupling reaction by utilizing hypervalent iodine reagent.