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Metal-Free Oxidative Cross-Coupling of Unfunctionalized Aromatic Compounds

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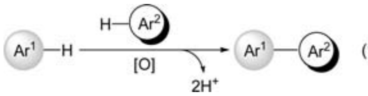
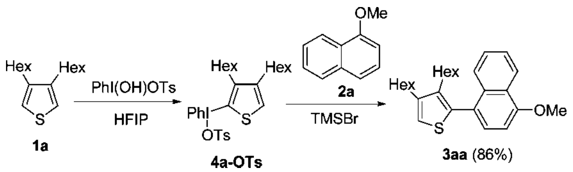
The oxidative cross-coupling reaction between two unfunctionalized arenes [oxidative C−H/C−H cross-coupling] has been widely accepted as a new and environmentally benign method for the direct synthesis of extremely important biaryls involving heteroaryls as electronic materials and devices (eq 1), by which the conventional stepwise approaches through prefunctionalizations of arenes, such as halides or metals, would be partially replaced.[1] On the contrary, the number of the selective cross-coupling methods is yet limited due to the difficulty of suppressing the undesired homodimer formations. The successful methods include σ-aryl palladiums,[1,2] phenoxy copper species,[3] anilenium ions,[4] and aromatic cation radicals[5] as the key intermediates.



(1)

Among the methods, the palladium-catalyzed procedures in combination with the stoichiometric terminal oxidants can be one of the most important strategies, especially for performing selective cross-coupling of heteroaromatic compounds, to which σ-heteroaryl palladiums are successfully introduced as the general key intermediates in the reaction mechanisms. Although continuous efforts have been devoted to using the well-defined σ-aryl palladium chemistries for the development of new direct C−H/C−H cross-couplings,[2] no reports focusing on the utilization of other reactive σ-aryl high-valent elements as key intermediates of the cross-couplings, to the best of our knowledge, have yet appeared in the literature. In this paper, we report an excellent metal-free cross-coupling of heteroaromatic compounds that provides a variety of useful mixed biaryls.

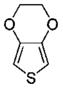
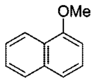
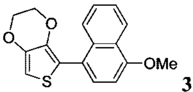
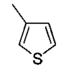
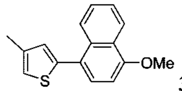
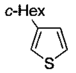
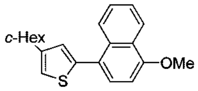
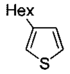
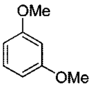
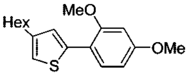
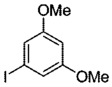
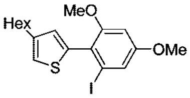
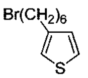
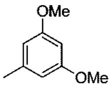
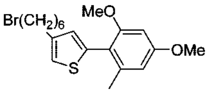
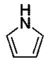
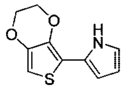
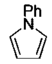
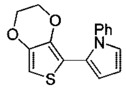
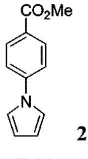
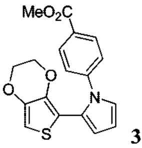
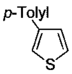
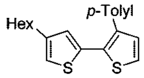
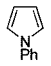
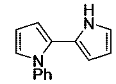
Scheme 1. Cross-Coupling Reaction of Thiophene **1a** with 1-Methoxynaphthalene **2a**



Recently, we have reported the direct synthesis of diaryl iodonium(III) salts in fluoroalcohol media.[6] We now have found that thiophene **1a** also afforded the corresponding α-thienyl iodonium(III) salt **4a-OTs** under the same conditions and sequential addition of 1-methoxynaphthalene **2a** and TMSBr to the resulting mixture selectively produced the cross-coupling biaryl **3aa** in excellent yield (Scheme 1). This is surprising since the cross-coupling heterobiaryl was selectively obtained without use of any metal catalyst. These interesting results in the present unique reaction systems strongly prompted us to survey the potential of the σ-thienyl iodine(III) species as a metal-free oxidative cross-coupling method of heteroaromatics with other aryl compounds.

The generality of the metal-free cross-coupling reactions is shown in Table 1.[7] Owing to the mild oxidation characters of the

Table 1. Metal-Free Cross-Coupling Reactions[a]

entry	thiophene	arene	biaryl	yield[b]
1	 **1b**	 **2a**	 **3ba**	88
2	 **1c**	**2a**	 **3ca**	98
3	 **1d**	**2a**	 **3da**	74
4	 **1e**	 **2b**	 **3eb**	85
5	**1e**	 **2c**	 **3ec**	60
6	 **1f**	 **2d**	 **3fd**	72
7	**1b**	 **2e**	 **3be**	51
8	**1b**	 **2f**	 **3bf**	78
9	**1b**	 **2g**	 **3bg**	60
10	**1e**	 **2h**	 **3eh**	60
11[c]	 **1g**	**2e**	 **3ge**	42

[a] Reactions were performed using PhI(OH)OTs (1.05 equiv), arenes **2** (1.5 equiv), and TMSBr (2 equiv) in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) at room temperature for 3 h. [b] Isolated yield based on **1**. [c] $PhI(OAc)_2$ was used instead of PhI(OH)OTs.

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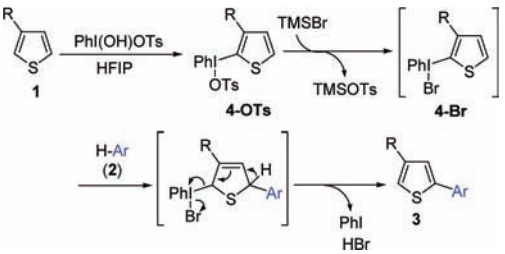
hypervalent iodine(III) reagents[8] and reaction conditions, the method showed a broad scope of functional group compatibility. As the coupling partners **2**, the nucleophilic characteristics of the aromatic rings were found to be the most important factor, and thus various aromatic nucleophiles, i.e., phenyl ethers, pyrroles, and thiophene, could be used for the transformations. In the thiophene−pyrrole cross-couplings, the pyrrole nucleophiles **2e**−**g** were introduced with a high degree of product selectivities (entries 7−9). These unknown types of mixed biaryls would become the potential core structures for a variety of new thiophene−pyrrole hybrid materials by extending the π-conjugated systems.

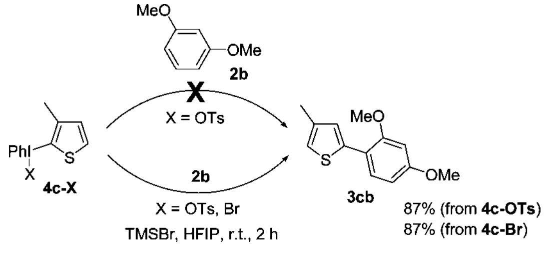
The new iodine(III)-mediated cross-coupling method apparently has several synthetic advantages over other reported methods. The most intriguing feature is that the intermediacy of the stable iodine(III) intermediates like **4**-**OTs** (see, below) in the mechanism enables selective cross-couplings between two arene molecules having closely related structures. Even in the coupling reactions between thiophenes (entry 10) or pyrroles (entry 11), the desired mixed biaryls were successfully obtained. Furthermore, the aryl−aryl bond was exclusively formed at the 2-position of the thiophene ring of **2h** (entry 10).[9]

Regarding the mechanism, the transformations mainly consist of two sequential steps (Scheme 2). First, the electron-rich heteroaromatic compounds **1** could selectively react at the 2-positions with the iodine oxidant, PhI(OH)OTs, to form the stable iodonium(III) salts, **4**-**OTs**. The process rapidly occurred with the aid of the fluoroalcohol solvent.[6] The formed **4**-**OTs** salts are usually inert toward the neutral aromatic nucleophiles **2** but are activated by the added TMSBr in hexafluoroisopropanol (HFIP) to induce further reactions and provide the mixed biaryl products **3**, probably through the formal hydroarylation with nucleophiles **2** and successive elimination of iodobenzene. The intermediacy and unique reactivities of **4**-**OTs** and **4**-**Br** leading to the products **3** were confirmed by the following control experiments using the isolated iodine(III) **4c**-**X** (Scheme 3). Thus, both **4c**-**OTs** and **4c**-**Br** reacted with **2b** in the presence of TMSBr to produce **3cb** in comparable yields under the same reaction conditions,[10] though **4c**-**OTs** did not react with **2b** in the absence of TMSBr. Based on these observations, the iodine(III) bromides **4**-**Br** could be involved in the reactions.[11]

Scheme 2. Possible Reaction Mechanism



Scheme 3. Metal-Free α-Arylation of **4c-X** with Arene **2b**



In conclusion, we now suggest a novel metal-free selective cross-coupling method for thiophenes and pyrroles based on the unusual reactivities of the σ-aryl trivalent iodine intermediates **4**-**Br** developed in fluoroalcohol media in the presence of TMSBr. Our biaryl synthetic procedure has the following characteristic features and various synthetic merits such as (i) a metal catalyst-free method, (ii) mild reaction conditions (the use of trivalent organoiodine oxidants, room temperature), (iii) high yields and regioselectivities of the obtained mixed biaryls, (iv) no oligomer formations, (v) a broad scope of substrate availability that allows the use of a wide range of heteroaromatic compounds **1** and aromatic nucleophiles **2**, and (vi) no required excess amount of arenes. This is the first successful example of a cross-coupling between two molecules of unfunctionalized heteroaromatic compounds with high product selectivities. The new α-free electron-rich mixed heteroaromatic biaryls effectively obtained by the method should be promising synthetic precursors in many scientific fields, and hence utilization of the new mixed biaryls will be expected to appear in the near future.

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Supporting Information Available: The experimental procedures and detailed spectroscopic data of the products **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) We have confirmed that the addition of several Lewis acids such as TMSOTf or TMSBr could accelerate the reaction of **4c**-**Br** with the arene nucleophile **2b**. On the other hand, treatment of the corresponding **4c**-**OTs** with **2b** did not react even in the presence of these Lewis acids.
(11) We have checked the exchange process between the OTs and Br using **4c**-**OTs** by treatment with 1 equiv of TMSBr in HFIP (**4c**-**Br**: 79% isolated yield).

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