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Metal-Free C–H Cross-Coupling toward Oxygenated Naphthalene-Benzene Linked Biaryls

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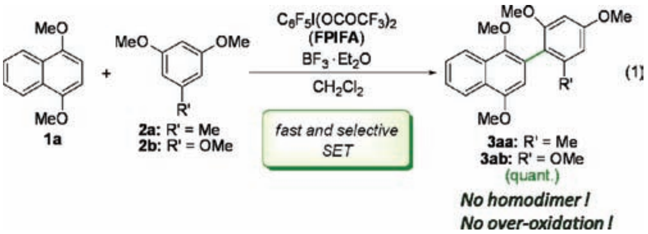
ABSTRACT



The intermolecular C–H cross-coupling between aromatic ethers has been achieved for the first time using perfluorinated hypervalent iodine(III) compounds as extreme single-electron-transfer (SET) oxidants. The demonstrations of this specific coupling could provide a direct route to valuable oxygenated mixed naphthalene-benzene biaryls 3 only, without formation of other biaryl-derived byproducts.

The oxidative coupling between arene C–H bonds is recognized as a straightforward and attractive approach that creates new C–C bonds of biaryl molecules without the use of prefunctionalized substrates, i.e., organometallic compounds or halides.[1] A recent breakthrough in this synthetic area by participation of transition metal chemistry has permitted direct access to a variety of mixed biaryl compounds containing heteroaromatic rings[2] and metal-coordinating directing groups[3] by C–H cross-couplings. On the other hand, oxidative cross-coupling between C–H bonds of aromatic hydrocarbons not containing directing groups, such as naphthalenes and benzenes, is still difficult in regard to the product selectivity and yield even after modern synthetic advances.[4] Previously, we reported the unprecedented success of the cross-coupling between naphthalenes and alkylbenzenes using phenyliodine bis(trifluoroacetate) (PIFA).[5] As a continuation of our

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research involving metal-free biaryl couplings using hypervalent iodine chemistry,[5−8] we now report the extremely specific C−H cross-coupling for a new combination of aromatic rings, that is, between aromatic ethers, to give the corresponding valuable oxygenated mixed biaryls (see examples in eq 1).

Highly oxygenated biaryl structures, which are frequently involved in many natural products, have been extensively utilized as the core components of pharmaceuticals, dyes, liquid crystals, organic devices, and conductors and for the design of ligands and catalysts in organic synthesis.[9] The intramolecular oxidative couplings of phenyl ether rings are widely used for the construction of the cyclic biaryl structures of these natural products and other useful compounds.[10] However, some difficulties emerge when performing intermolecular cross-coupling by the methods. The first commonly known problem is the coformation of an undesired homocoupling dimer together with a mixed biaryl product.[11,12] Another specific concern regarding the coupling of aromatic ethers is that the formed biaryls, that is, the oxidation-sensitive electron-rich compounds,[13] would be further oxidized and produce oligomers, quinone derivatives, and other byproducts, thus decreasing the yield of the coupling product. The intermolecular coupling for obtaining oxygenated mixed biaryls is believed to be very troublesome because of the chemoselective issues of both the substrates and products.

With respect to the excellent single-electron-transfer (SET) oxidizing ability of hypervalent iodine reagents to aromatic rings,[14] we first anticipated their possible use with the intermolecular cross-coupling between aromatic ethers employing PIFA. Indeed, the treatment of PIFA in the presence of the activator $BF_3 \cdot Et_2O$[5−7] in an attempt at the cross-coupling of the naphthalene and phenyl ethers **1a** and **2a** (eq 1) produced the expected naphthalene-benzene linked biaryl **3aa** in 63% yield (Table 1, entry 1). Nevertheless, PIFA caused homocoupling in this case, along with ca. 10% formation of the undesired dimer of methoxybenzene **2a**. Detailed screenings of the reaction conditions, such as the concentration, temperature, solvent, amounts of the reagent and activator, order of the reagent addition and their addition rate, were examined for the PIFA/$BF_3 \cdot Et_2O$ system for the purpose of suppressing the homodimer, the formation of which had not yet been eliminated. An alternative use of bromotrimethylsilane as an activator[8] was then investigated, which did not yield the mixed biaryl **3aa**. Instead, we found that a subtle change in the oxidant nature significantly affected the distribution of the coupling products, the cross-coupling biaryl **3aa** versus the homodimer of **2a**, as well as the reaction yield.

Table 1. Influence of the Structure of Hypervalent Iodine Reagents in the Cross-Coupling of **1a** and **2a** (eq 1)[a]

entry	oxidant Ar-I($OCOCF_3$)$_2$	mixed biaryl **3aa**[b] (%)	homocoupling of **2a**[c]
1	Ar = Ph (PIFA)	63	+ (10%)
2	Ar = 4-MeC_6H_4	14	+
3	Ar = 4-$MeOC_6H_4$	24	+
4	Ar = 2,4,6-MeC_6H_2	26	+
5	Ar = 4-$CF_3C_6H_4$	63	−
6	**Ar = C_6F_5 (FPIFA)**	**82**	−
7	**Ar = 4-$CF_3C_6F_4$**	**78**	−
8[d]	**(FPIFA)**	**>99**	−
9[d,e]	**(FPIFA)**	**96**	−

[a] Reactions were examined using **1a** (1 equiv) and **2a** (2 equiv) with oxidants (1 equiv) in the presence of $BF_3 \cdot Et_2O$ (2 equiv) at 0 °C. [b] Isolated yield of the pure product based on the substrate **1a** used. [c] The formation of the homodimer of **2a**, that is, 2,2′-dimethyl-4,4′,6,6′-tetramethoxybiphenyl, was checked by ^1H NMR, GC, and HPLC. [d] Reaction was performed at −40 °C. [e] 4 equiv of **2a**.

In comparison to PIFA, the relatively electron-rich aryl moieties in the oxidants Ar-I($OCOCF_3$)$_2$, where Ar = 4-Me, 4-MeO, and 2,4,6-Me, were less positive, and the product **3aa** was no longer formed in good yield (entries 2−4). In addition, formation of the homodimer of **2a** was observed. On the contrary, the oxidant having the CF_3 substituent as the electron-deficient group showed a degree of product formation similar to that of PIFA, while the homodimer was not detected (entry 5). With this perspective, we further evaluated the perfluorinated PIFA[15a−c]

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(FPIFA) and its CF$_3$-substituted derivative.[15d] Gratefully, both oxidants worked well as more effective promoters for the cross-coupling (entries 6 and 7). A more pronounced advantage of the perfluorinated oxidants was no formation of the homodimer, which is in clear contrast to PIFA. Further improvement of the product yield was achieved after optimization of the conditions, and the use of commercial FPIFA gave a perfect result (entry 8). It should be noted that the perfluorinated oxidant, FPIFA, did not induce the homodimer formation even in the presence of a greater excess amount of the methoxybenzene **2a** (entry 9). None of other typical chemical SET oxidants[10] [specifically, FeCl$_3$, MoCl$_5$, Mn(OAc)$_3$, Ce(NH$_4$)$_2$(NO$_3$)$_6$ (CAN), and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)] or anodic oxidations[11a] produced the cross-coupled **3aa** as the major product.

It became evident that selection of the oxidant is very important for successful cross-coupling. The consumuption of all of the naphthalene ether **1a** and the nearly perfect yield of **3aa** as the sole coupling product suggested the increased SET oxidation efficiency of the perfluorinated hypervalent iodine compounds over PIFA to quantitatively produce the naphthalene cation radical[14a] of **1a** (Figure 1, left), which was then trapped by the neutral **2a** to give the mixed biaryl **3aa**. The generation of the cation radical of **2a** that led to the homodimer did not occur. Hence, the Lewis acidity of the iodine atom in the FPIFA/BF$_3$·Et$_2$O adduct should just match the formation of the C-T complex with the naphthalene ether **1a** that was involved before starting the SET oxidation process. Similarly, overoxidation of the formed biaryl **3** can be ruled out. The reaction of the substrates **1a** (0.200 mmol) and **2a** (0. 40 mmol) or **2b** (R′ = OMe, 0.40 mmol) in the presence of the prepared **3aa** (0.200 mmol) or **3ab** (0.200 mmol) under the standard coupling conditions resulted in the recovery of 0.364 mmol (for **3aa**) and >0.399 mmol (for **3ab**) of the biaryls after isolation (see Supporting Information), which revealed the revival of at least 82% of the initially added biaryl **3aa** and over 99% of the biaryl **3ab** during the control experiments. This is also rationalized by considering the steric factor in the formed C-T complex (Figure 1, right). Apparently, the existence of the angular methoxybenzene ring in the products **3aa** and **3ab** forces the complexation with FPIFA to be unfavorable.

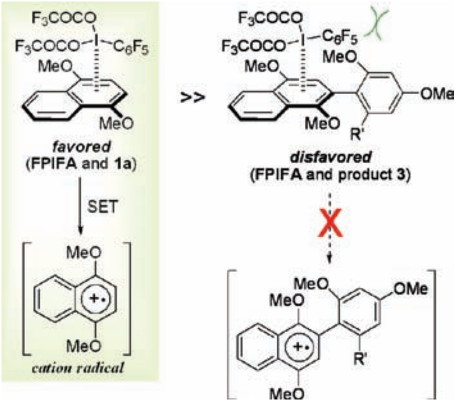
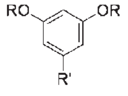
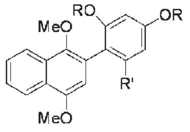
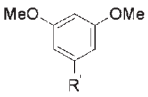
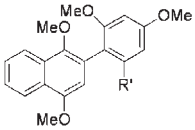
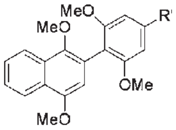


Figure 1. Selective C-T complex formation between FPIFA and **1a**.

Table 2. Examples of the Cross-Coupling Partners **2b**–**i**[a]

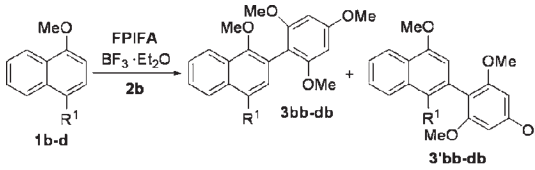
entry	arene **2**	mixed biaryl **3**, yield[b]
	 **2b-f**	 **3ab-af**
1	R = Me, R′ = OMe; **2b**	R = Me, R′ = OMe; **3ab**, >99%
2	R = Bn, R′ = OBn; **2c**	R = Bn, R′ = OBn; **3ac**, 87%
3	R = Me, R′ = CH$_2$OAc; **2d**	R = Me, R′ = CH$_2$OAc; **3ad**, 80%
4[c]	R = Me, R′ = C≡C-Bu; **2e**	R = Me, R′ = C≡C-Bu; **3ae**, 60%
5[c]	R = Me, R′ = H; **2f**	R = Me, R′ = H; **3af**, 65%
	 **2g-i**	 **3ag-ai** +  **3’ag-ai**
6	R′ = OBn; **2g**	R′ = OBn; **3ag**, 58%, **3’ag**, 41%
7	R′ = OH; **2h**	R′ = OH; **3ah**, nd, **3’ah**, 68%
8	R′ = NHTs; **2i**	R′ = NHTs; **3ai**, 4%, **3’ai**, 88%

[a] Reactions were perfomed using naphthalene ether **1a** (1 equiv) and **2b**–**d**,**g**–**i** (2 equiv) under the optimized conditions in Table 1 unless otherwise noted. [b] Isolated yield of the pure products based on the substrate **1a** used. [c] 4 equiv of **2e** and **2f** was used. nd = not determined (less than 3% yield formation). Ts = *p*-tosyl.

For these reasons, the extended series of the phenyl ethers **2b**–**i** could also be used as the coupling partners of the naphthalene ether **1a** with the optimized oxidant (Table 2). All coupling reactions proceeded to satisfactorily give the corresponding oxygenated mixed biaryls **3** without formation of the homodimer in these cases. Several protecting groups (benzyl, acetyl, etc.) and functionalities (alkyne, phenol, amine, and others) were acceptable as the coupling partners **2**. The phenyl ethers **2g**–**i** produced two separable cross-coupling products with preference of the biaryls, **3ag**, **3′ah**, and **3′ai**, by the *para*-reactions of the methoxy group or acidic substituents of **2h** and **2i** (entries 6–8). To our surprise, the oxidations of the phenol and aniline rings[16] were relatively slower than the cross-coupling with FPIFA (entries 7 and 8).

Regarding the naphthalene ring, the use of similar protecting groups and functionalities was also possible (Scheme 1). In **1c**, the couplings preferentially occurred at the less hindered position of the naphthalene ring. Curiously, the naphthalene ether **1d** selectively reacted at the *ortho* position of the methyl group to give only the biaryl **3′db**. On the other hand, interesting remote regioselectivity controls at the naphthalene rings were observed (Scheme 2). Particulary, the OTBDPS and halogen in **1f** and **1g** showed different regioselectivities to the OAc group in **1e**, which even overwhelmed the steric influence of the isobutyl group in substrate **1h**.

Scheme 1. Reactions of Naphthalene Ethers **1b–d**[a]



naphthalene	R^1	yield of the coupling product	
1b	O^tBu	**3bb** (49%)	**3'bb** (49%)
1c	OBn	**3cb** (53%)	**3'cb** (32%)
1d	Me	**3db** (nd)	**3'db** (60%)

[a] Reactions were performed using 2 equiv of **2b**.

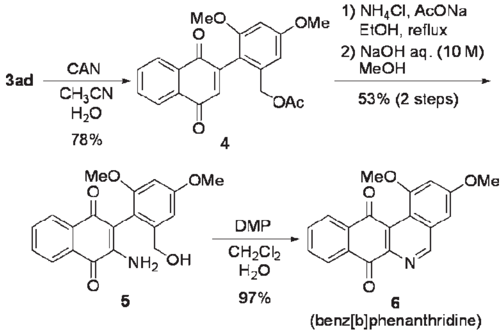
Scheme 2. Remote Regioselectivity Control in Naphthalenes[a]

naphthalene	R^1	R^2	yield (ratio of the regioisomers, **3** : **3'**)
1e	OMe	OAc	99% (**3eb** : **3'eb** = 72 : 28)
1f	OMe	OTBDPS	77% (**3'fb** only)
1g	OMe	Br	96% (**3gb** : **3'gb** = 10 : 90)
1h	O^tBu	OTBDPS	80% (**3'hb** only)

[a] TBDPS = *tert*-butyldiphenylsilyl

The oxygenated aryl naphthalenes **3** belong to a class of valuable synthetic intermediates that are the core structures of many useful compounds.[17] Their further oxidized aryl naphthoquinones are also versatile for divergent access to naturally occurring types of compounds. Accordingly, elaboration of the obtained biaryl in our method toward the benz[*b*]phenanthridine structure[18] was demonstrated (Scheme 3). The biaryl **3ad** was thus converted into the aryl naphthoquinone **4** by treatment of CAN[13b] followed by the installation of an amino group, and its cyclization could afford the target tetracyclic compound **6**. Considering the necessity of sacrificial functional groups, such as halogens, in order to construct the phenanthrizine structures via other synthetic routes, our metal-free C–H coupling method is capable of providing unique access toward molecules retaining such functional groups.

Scheme 3. Elaboration of the Biaryl Structure of **3ad**



In summary, we have reported for the first time the intermolecular C–H cross-coupling between the aromatic ethers **1** and **2**. The key point of the reaction success is the utilization of the excellent ability of hypervalent iodine reagents, especially the perfluorinated PIFAs, in the SET oxidation process. The remarkable high affinity of the reagents to the naphthalene ethers **1** over the phenyl ethers **2** as well as the formed mixed biaryl products **3** in the reactions can definitively exclude the undesired homocoupling and overoxidation of the biaryl products **3**, thus realizing the specific cross-coupling.

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

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