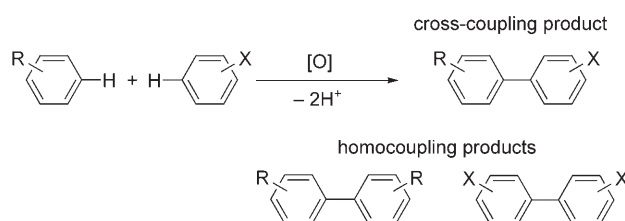


Oxidative Cross-Coupling of Arenes Induced by Single-Electron Transfer Leading to Biaryls by Use of Organoiodine(III) Oxidants**

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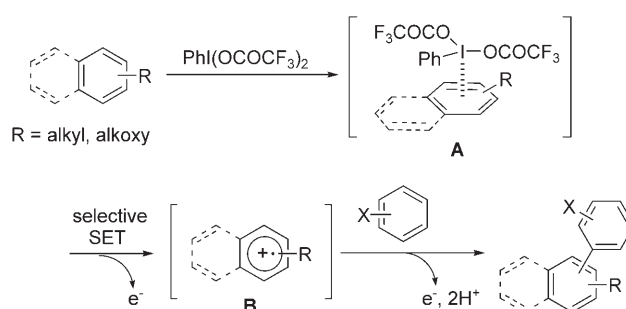
The scientific importance and value of biaryls are easily recognized from the broad industrial utilization of these compounds as versatile building blocks for liquid crystals, organic devices and conductors, dyes, ligands for metal catalysts, and even in medical fields, since these structures are ubiquitous in biologically active, naturally occurring products.^[1] Above all, many synthetic efforts have already been devoted to the practical access of these biaryls and the resolution of specific problems during their syntheses.^[2,3] Considering current pressure to reduce the number of synthetic steps and the production of waste, the most ideal and attractive route to biaryl compounds appears to be the direct oxidative coupling of two non-activated arenes.^[4–9] Heavy-metal oxidants (i.e. V^V, Mn^{III}, Mo^V, Fe^{III}, Tl^{III}, and Pb^{IV}) in strong acids,^[4] nitric acid based oxidants,^[5] and anodic oxidations^[6] have typically been employed for direct access to biaryl compounds. More recently, hypervalent iodine(III) reagents^[7] and combinations of palladium catalysts and oxidants^[8] have been used. However, the majority of these methods still have limited applications owing to the difficulty in obtaining cross-coupling products, because the undesired competitive formation of homocoupling dimers occurs (Scheme 1). To address this issue, solutions have recently been provided by Stuart and Fagnou^[10] and by Canesi and co-workers^[11] regarding selective indole or aniline cross-couplings by two-electron oxidative activation utilizing the nitrogen functionalities. Despite a few examples of unprecedented direct cross-couplings,^[12,13] there remains a strong demand for the further development of new direct cross-coupling systems involving alternative mechanistic conceptions, which permit other structural types of coupling combinations. Herein, we report a novel direct oxidative approach for the cross-coupling of naphthalenes and mesity-



Scheme 1. Biaryl products for the oxidative cross-coupling reaction.

lenes, with the latter representing a selection of the ultimate nucleophilic partners. This is the first successful example of selective cross-coupling between unfunctionalized arenes induced by single-electron transfer (SET) oxidation, taking advantage of the unusual selectivity for the generation of aromatic cation radical intermediates using hypervalent iodine(III) reagents.

Our working hypothesis for the design of a new cross-coupling method involves the generation of aromatic cation radicals **B** as key intermediates (Scheme 2). Thus, using the



Scheme 2. Working hypothesis for oxidative cross-coupling.

appropriate oxidant, generation of radicals **B** would occur by the SET oxidation of electron-rich arenes as the first event, through the charge-transfer complexes **A**.^[14] Subsequent in situ trapping of the resulting intermediates **B** by other existing aromatic molecules and subsequent further one-electron oxidation and deprotonation would lead to aryl–aryl bond formation to give the corresponding mixed biaryls. For the realization of the effective cross-coupling mechanism without any undesired formation of homodimers, the following points should be considered: 1) smooth and selective SET activation of specific aromatic compounds by a suitable oxidant in the presence of another aromatic coupling partner, and, at the same time, 2) the coupling partner must have a nucleophilicity sufficiently higher than that of the specific aromatic compound being activated in order to act as an

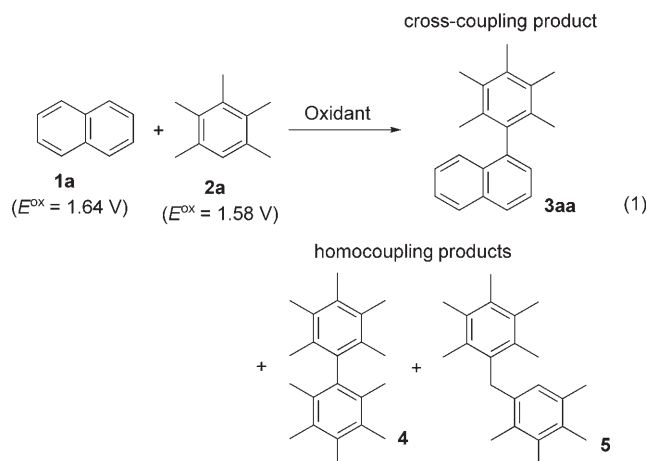
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effective nucleophile. With these aspects in mind, we selected the hypervalent iodine(III)-induced oxidative coupling of naphthalenes with mesitylenes, assuming the high affinity of the hypervalent iodine(III) oxidants toward non-nucleophilic naphthalenes as well as the excellent nucleophilicity of mesitylenes^[15] as suitable coupling partners.

In fact, for the treatment of naphthalene **1a** and pentamethylbenzene **2a** with phenyliodine bis(trifluoroacetate) (PIFA) [Eq. (1)],^[16] the cross-coupling reaction afforded the



desired unsymmetrical biaryl **3aa** in high yields, even using a slight excess of **2a**^[17] (Table 1, entries 1 and 2). Remarkably, in spite of the difficulty in the selective activation of naphthalene **1a** in the presence of **2a**, which has an oxidation potential close to that of **1a**, the undesired homocoupling reaction hardly occurred under the stated conditions, and the homodimers of **1a** and **2a** were not detected (confirmed by GC). One plausible reason for the observed high selectivity of PIFA for naphthalene **1a** is the steric hindrance of **2a**. We then compared the present method to a variety of other organic and representative metal oxidants. Using the PIFA derivative $C_6F_5I(OCOCF_3)_2$, the undesired homodimer **4** was formed along with the cross-coupling product **3aa**, probably because the reactivity of the oxidant is too high (Table 1, entry 3). The Koser reagent $PhI(OH)OTs$ ($OTs = p$ -toluenesulfonate)^[18] provided an inferior result to PIFA when using

1.5 equivalents of **2a**, but it selectively afforded **3aa** (Table 1, entries 4 and 5). On the other hand, the pentavalent DMP and DDQ caused the formation of the homodimer **5** instead of the cross-coupling product (Table 1, entries 6 and 7). Iron(III) (Table 1, entry 8), thallium(III) (Table 1, entry 9), $[Ce(NH_4)_2(NO_3)_6]$ (CAN, Table 1, entry 10), $Mn(OAc)_3$, and $MoCl_5$ were then screened as metal-based oxidants^[4,5] with generally negative results (0–25% yields of **3aa**). In these cases, problems with the halogenation,^[4b] metalation,^[4c] and nitration of **1a** and **2a** occurred. Furthermore, anodic oxidations^[6] induced the remarkable formation of the homodimers of **1a** and mesitylenes **2**, while the catalyst combination of $Pd(OCOCF_3)_2$ and $Cu(OAc)_2$ ^[10] resulted in no reaction. These results clearly indicated that the use of organoiodine(III) oxidants is essential for the selective activation of naphthalene **1a** and efficient reaction progress.

The scope of this cross-coupling reaction was investigated, and selected examples are summarized in Table 2. For the PIFA-induced cross-coupling, we found that the halogen functionality is the best and most versatile directing group, which allowed control of the regioselectivity and further elucidation of the mixed biaryl products, such as the results of C–C, C–O, and C–N bond formations (Table 2, entries 1–4). Thus, the reaction of **1b–d** gave the mixed biaryl **3bb–3db** as the sole products, the regioselectivities of which were determined by X-ray crystal structure analysis (see below) or by comparing them to the authentic samples. In contrast, the presence of an electron-withdrawing group changed the regioselectivity, and an alternative regioisomer **3eb'** was produced in preference to **3eb** (Table 2, entry 5); this result suggests that the resonance effect of the halogen atom is important for the regioselective couplings. As an example of substitution at the 1-position, we performed the reaction using 1-phenyl naphthalene (**1f**), which exclusively produced a 1,4-diarylated product **3fb** (Table 2, entry 6). A variety of nucleophilic partners **2** were also applicable (Table 2, entries 7–9). The aryl–aryl bond formations occurred at the less sterically hindered site of the aromatic nucleophiles **2**.

Aryl–aryl bond formation at the sterically hindered carbon atom of the 1,3-disubstituted benzenes is the most challenging task now being assessed by modern coupling strategies.^[19] One positive feature of our new biaryl synthetic method is the high reactivity of the intermediates, which

overcomes the steric influence of the starting materials. For sterically hindered nucleophiles **2**, the method was found to be optimal for the coupling reaction. Accordingly, the reaction of **1b** with 1,3,5-tri(isopropyl)benzene (**2f**) using PIFA and $BF_3 \cdot Et_2O$ afforded the highly congested biaryl **3bf** in 70% yield of isolated product after purification.^[20] Single crystals of **3bf** suitable for a crystallographic analysis were obtained by recrystallization from hexane (Figure 1).^[21] It was revealed that the naphthalene ring and the other aromatic ring in

Table 1: Product distribution for representative oxidants.^[a]

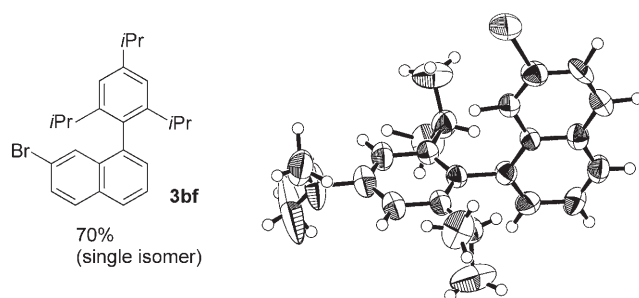
Entry	Oxidant	Conditions	3aa [%] ^[b]	Homodimer 4 or 5 [%] ^[b]
1	PIFA	$BF_3 \cdot Et_2O$, ^[c] CH_2Cl_2 , $-78^\circ C$	88 (82) ^[d]	–
2 ^[e]	PIFA	$BF_3 \cdot Et_2O$, ^[c] CH_2Cl_2 , $-78^\circ C$	60	–
3	$C_6F_5I(OCOCF_3)_2$	$BF_3 \cdot Et_2O$, ^[c] CH_2Cl_2 , $-78^\circ C$	64	4 : 26
4	$PhI(OH)OTs$	$BF_3 \cdot Et_2O$, ^[c] CH_2Cl_2 , $-78^\circ C$	85	–
5 ^[e]	$PhI(OH)OTs$	$BF_3 \cdot Et_2O$, ^[c] CH_2Cl_2 , $-78^\circ C$	31	–
6	DMP	$BF_3 \cdot Et_2O$, ^[c] CH_2Cl_2 , RT	0	5 : 11
7	DDQ	$BF_3 \cdot Et_2O$, ^[c] Benzene, RT	0	5 : 34
8	$FeCl_3$	Benzene, RT	12	–
9	$Tl(OCOCF_3)_3$	$BF_3 \cdot Et_2O$, ^[c] CH_2Cl_2 , RT	25	–
10	CAN	$BF_3 \cdot Et_2O$, ^[c] CH_2Cl_2 , $0^\circ C$	0	– ^[f]

[a] Reactions were performed using three equivalents **2a** and one equivalent oxidant. [b] Yield was determined by GC. [c] Two equivalents relative to **1a**. [d] Yield of isolated product. [e] 1.5 equivalents of **2a**. [f] Nitration products of **2a** were obtained. DMP = Dess–Martin periodinane, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, CAN = $Ce(NH_4)_2(NO_3)_6$.

Table 2: Scope of PIFA-induced oxidative cross-coupling.^[a]

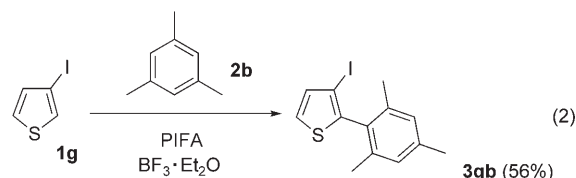
Entry	Arene 1 ^[b]	Nucleophile 2 ^[c]	Mixed biaryl 3	Yield [%] ^[d]
1	1a	2b	3ab	63
2	1b	2b	3bb	99
3	1c	2b	3cb	82
4	1d	2b	3db	57
5 ^[e]	1e	2b	3eb + 3eb'	51 (3eb / 3eb' = 1:5.5)
		2b^[f]	3fb	56
7	1b	2c	3bc	87
8	1b	2d	3bd	92
9	1b	2e	3be	86

[a] All reactions were performed using three equivalents of **2** unless otherwise noted. [b] **1a** $R^1 = R^2 = R^3 = H$; **1b** $R^1 = Br$, $R^2 = R^3 = H$; **1c** $R^1 = Br$, $R^2 = Me$, $R^3 = H$; **1d** $R^1 = Br$, $R^2 = H$, $R^3 = Me$; **1e** $R^1 = CO_2Me$, $R^2 = H$, $R^3 = H$; [c] **2c** $R^4 = Et$, $R^5 = H$, $R^6 = Et$; **2d** $R^4 = Me$, $R^5 = H$, $R^6 = tBu$; **2e** $R^4 = Me$, $R^5 = Ph$, $R^6 = Me$; [d] Yield of isolated product based on arene **1**. [e] Two equivalents PIFA and four equivalents $BF_3 \cdot Et_2O$. [f] Ten equivalents **2b**.


Figure 1. Structural formula and X-ray crystal structure of the highly congested biaryl **3bf**.

3bf are exactly perpendicular to each other along the biaryl axis. The conformational rigidity of **3bf** derived from the bulky isopropyl *ortho* substituents makes a difference in the environment around the methyl groups, leading to induction of a remarkable magnetic shield effect on the neighboring benzyl proton (confirmed by 1H NMR spectroscopic analysis).

Further investigations using other electron-rich arenes and heteroarenes, for example thiophenes [Eq. (2)] and phenylethers, would imply the possibility



of extending of the cross-coupling method (see the Supporting Information). Research towards enhancing the practicability of this novel oxidative cross-coupling method and utilization of the newly obtained biaryl compounds are now in progress.

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