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Novel and efficient oxidative biaryl coupling reaction of alkylarenes using a hypervalent iodine(III) reagent

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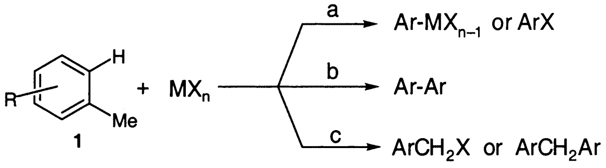
Abstract—First facile and efficient oxidative coupling reaction of alkylarenes leading to alkylbiaryls using a combination of hypervalent iodine(III) reagent, phenyliodine(III) bis(trifluoroacetate) (PIFA), and $BF_3 \cdot Et_2O$ has been developed. © 2002 Elsevier Science Ltd. All rights reserved.

Biaryl compounds serve as key structures of bioactive natural products and chiral ligands for asymmetric reactions, and as precursors for electroconductive materials due to their interesting properties.[1] This makes these compounds attractive synthetic targets. A direct and efficient route to biaryl compounds is via oxidative electron transfer of arenes. Several methods for oxidative biaryl coupling of phenol derivatives using toxic heavy metal oxidants[2] such as Pb^{IV}, Tl^{III}, V^{V}, Ru^{IV}, Mo^{V} and Fe^{III} salts, which often require vigorous reaction conditions, and anodic oxidation reactions[3] have been reported thus far. Over this decade, use of hypervalent iodine(III) reagents[4] has gained importance as a safe alternative to heavy metal reagents for performing a variety of organic transformations. In our continuous studies on hypervalent iodine chemistry,[5,7d] we have recently developed mild and high yielding biphenyl coupling reactions of phenol ether derivatives via aromatic cation radical intermediates[6] using a combination of either phenyliodine(III) bis(trifluoroacetate) (PIFA) and $BF_3 \cdot Et_2O$[7] or PIFA and heteropolyacid (HPA).[8] As a new stage of our studies on biaryl synthesis, we report herein the first facile and efficient oxidative coupling reaction of alkylarenes, which are less electron-rich than phenol ether derivatives, using PIFA–$BF_3 \cdot Et_2O$.

In contrast to biaryl syntheses from phenols and phenol ether derivatives, oxidation of alkylarenes often gave low to moderate yields of biaryls along with some unsatisfactory byproducts when using the typical oxidants such as heavy metal salts and nitric acid.[9] Exceptions are limited examples of anodic oxidation reactions.[3] Such results may be due to at least three major reactions that have been identified in the oxidation of alkylbenzene derivatives by metal oxidants (MX_n): namely (a) aromatic-nuclear substitution; (b) biaryl coupling, and (c) side-chain substitution (Scheme 1).

These side reactions as well as higher oxidation potentials[10] of alkylarenes compared to phenol derivatives have prevented the practical utility of oxidative coupling leading to alkylbiaryls.

Therefore, preparative methods for alkylarene dimers have been limited to metal-catalyzed coupling reactions[1] such as Ullmann, Suzuki, Heck, Stille, and Negishi reactions via halogenated and/or other functionalized alkylarenes. Despite their utility, these methods have several drawbacks in their yields of multi-substituted alkylbiaryls, especially in the preparation of tetra-*ortho*-substituted biaryls, except for a few successful examples.[11] In addition, they generally also require highly reactive organometallic reagents in the preparation of nucleophilic compounds (i.e. boronic or tin derivatives).



Scheme 1. Oxidation of alkylarenes with metal oxidants (MX_n).

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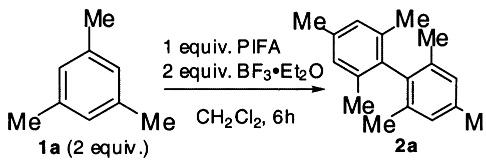
Table 1. Oxidative biaryl coupling of mesitylene (**1a**) with PIFA



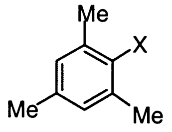
Entry	Temp. (°C)	Conc. PIFA (M)	Yield[a] (%)
1	rt	0.05	6[b]
2	0	0.05	8[b]
3	−40	0.05	52
4	−78	0.05	70
5	−78	0.02	45
6	−78	0.4	94
7	−78	0.4	No reaction[c]

[a] Yields are based on GC analyses with *n*-tetradecane as the internal standard. Yields are based on consumed PIFA.

[b] ca. 1 equiv. of **1a** was recovered. **3** and **4** were also obtained.

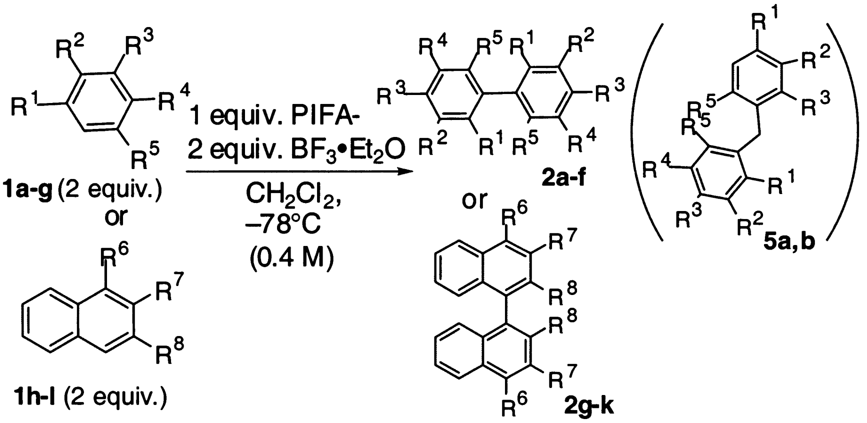
[c] In the presence of galvinoxyl.

In order to develop a facile and efficient synthesis of biaryls directly from alkylarenes (type (b) reaction), we examined PIFA-induced oxidative coupling reaction of mesitylene (**1a**) under various reaction conditions.[12] Consequently, 2,2′,4,4′,6,6′-hexamethylbiphenyl (**2a**) was the major product when using PIFA–BF_3·Et_2O (Table 1), a reagent which we have previously developed for biaryl synthesis from phenol ethers. On the other hand, no reaction occurred either in the absence of additives or in the presence of heteropolyacid, $H_3[PW_{12}O_{40}]$, and complex mixtures involving **3** and **4** but not **2a** were obtained when the reactions were carried out in $(CF_3)_2CHOH$ or CF_3CO_2H.



3: X=$OCOCF_3$
4: X=I

Table 2. Oxidative biaryl coupling of alkylarene (**1**) with PIFA–BF_3·Et_2O

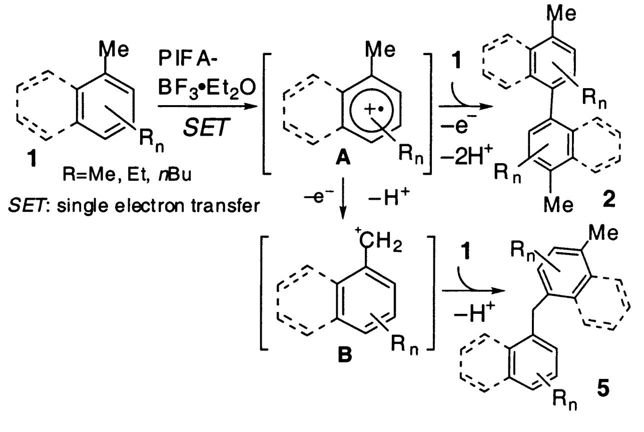


Entry	Substrate	R¹	R²	R³	R⁴	R⁵	Reaction time (h)	Product	Yield (%)[a]
1	**1a**	Me	H	Me	H	Me	6	**2a**	90
2	**1b**	Et	H	Et	H	Et	6	**2b**	74
3	**1c**	Me	H	Me	H	H	3	**2c**	75[b]
4	**1d**	Me	H	Me	H	I	6	**2d**	84
5	**1e**	Me	Me	Me	H	H	6	**2e**	64[c]
6	**1f**	Me	Me	H	Me	Me	6	**5a**	46
7	**1g**	Me	Me	Me	Me	Me	6	**2f**+**5b**	20 (**2f**) 43 (**5b**)
			R⁶	R⁷	R⁸				
8	**1h**		Me	H	H		6	**2g**	82
9	**1i**		Et	H	H		4	**2h**	89
10	**1j**		^{n}Bu	H	H		4	**2i**	80
11	**1k**		Me	Me	H		3	**2j**	94
12	**1l**		Me	H	Me		3	**2k**	96

[a] Isolated yields.

[b] 10 equiv. of **1c** was used at −40°C.

[c] 10 equiv. of **1e** was used at 0°C.



Scheme 2. Plausible reaction mechanism.

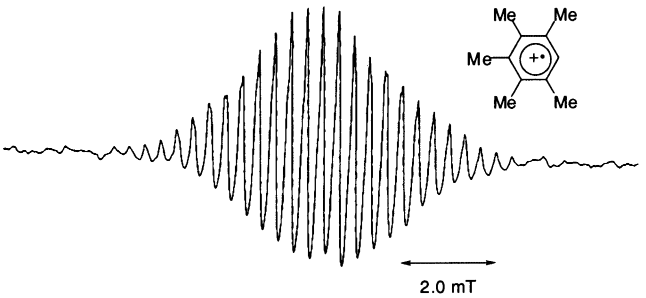


Chart 1. ESR spectra of cation radical of **1g** generated by PIFA–$BF_3 \cdot Et_2O$.

After improving the reaction conditions (temperature and the concentration of PIFA), we finally obtained **2a** in 94% yield (GC) with perfect control of the possible side reactions (entry 6, Table 1).

Typical experimental procedure is as follows: $BF_3 \cdot Et_2O$ (2.0 mmol) and PIFA (1.0 mmol) were added sequentially to a stirred solution of alkylbenzene or alkylnaphthalene (**1**) (2.0 mmol) in CH_2Cl_2 (2.5 mL) at −78°C under a nitrogen atmosphere. The mixture was stirred for 6h under the same reaction conditions. Aqueous work-up with saturated $NaHCO_3$ at 0°C followed by column chromatography (SiO_2/*n*-hexane) gave the corresponding biphenyl or binaphthyl compound **2**.

This reaction was applicable to various alkylbiphenyl and binaphthyl syntheses. The results are summarized in Table 2. Although oxidation of inactive monoalkylbenzenes such as toluene and *t*-butylbenzene did not proceed under the improved conditions, reactions of mesitylene (**1a**), triethylbenzene (**1b**), xylene (**1c**), and alkylnaphthalenes (**1h**–**l**) with PIFA–$BF_3 \cdot Et_2O$ proceeded smoothly to afford the corresponding biphenyl and binaphthyl compounds including tetra-*ortho*-substituted biaryls in moderate to high yields (entries 1–5, and 8–12, Table 2). On the other hand, in the reaction of durene **1f** and pentamethylbenzene **1g** with PIFA–$BF_3 \cdot Et_2O$, the corresponding diarylmethane **5** was mainly obtained probably due to steric hindrance (entries 6 and 7), while, surprisingly, minor product **2f** was also obtained in 20% yield even when using **1g**.

A plausible reaction mechanism is shown in Scheme 2. Cation radical **A** is initially formed from **1**, then a second molecule of **1** attacks **A** under the reaction conditions in a manner analogous to those of our previously developed PIFA-induced reactions[6–8] or typical heavy metal oxidations[9] yielding aromatic cation radicals. Formation of **A** was supported by effective inhibition of the reaction of **1a** to form **A** in the presence of galvinoxyl, which is an efficient radical scavenger (entry 7, Table 1).

Furthermore, a cation radical of **1g**,[9g] which was formed by mixing PIFA and **1g** in CH_2Cl_2 at −20°C ~ 0°C in the presence of $BF_3 \cdot Et_2O$ after degassing, was detected by electron spin resonance (ESR) spectroscopy (Chart 1).

On the other hand, in the reactions of durene (**1f**) or pentamethylbenzene (**1g**) with PIFA, nucleophilic attack of a second molecule of **1f** or **1g** yielded diarylmethane **5** as the major product. Product **5** will be formed via benzylic cation **B** rather than via the more unstable cation radical **A**.

In conclusion, we have developed a novel and efficient non-metallic oxidative biaryl coupling reaction of alkylarenes using PIFA–$BF_3 \cdot Et_2O$ under mild reaction conditions. This methodology provides a facile and direct route to alkylbiaryl compounds without introducing any directing groups into alkylarenes before the coupling reaction. Further optimization and application of this reaction to the syntheses of various biaryls and oligoaryls that may have utility as artificial bioactive molecules and electroconductive materials are now underway.

Acknowledgements

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12. Besides unsuccessful results when using the typical heavy metal oxidants, we also examined oxidative coupling reaction of **1a** with $NaNO_2$–CF_3SO_3H, which has been reported for efficient binaphthyl syntheses.[9i] However, the reaction did not proceed at all even after 6 h.