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A novel and efficient oxidative biaryl coupling reaction of phenol ether derivatives using a combination of hypervalent iodine(III) reagent and heteropoly acid

Hiromi Hamamoto, Gopinathan Anilkumar, Hirofumi Tohma and Yasuyuki Kita*

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6, Yamada-oka, Suita, Osaka 565-0871, Japan. E-mail: kita@phs.osaka-u.ac.jp

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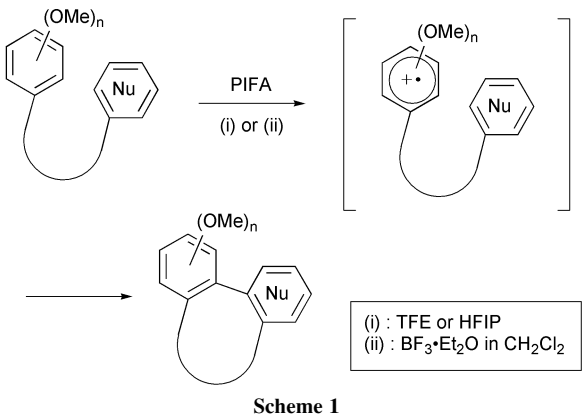
A novel and efficient oxidative biaryl coupling reaction of phenol ether derivatives using a combination of hypervalent iodine(III) reagent, phenyliodine(III) bis(trifluoroacetate) (PIFA), and heteropoly acid has been developed.

The biaryl unit is a key building block in the structure of a large number of important natural products, such as polyketides, terpenes, lignanes, coumarins, flavonoids, tannins and many alkaloids.[1] These can be synthesized by oxidative biaryl coupling reaction using heavy metal oxidizing reagents such as thallium(III), vanadium(V), or ruthenium(IV) salts.[2] However, these oxidants are highly toxic and must be handled with great care. Over several years, hypervalent iodine(III) reagents have received much attention because they have low toxicity and are readily available and their reactivities are similar to those of heavy metal reagents.[3] The hypervalent iodine(III) reagent-induced biaryl coupling reaction of phenol ether derivatives involving aromatic cation-radical intermediates was originally developed by us[4,5,6] and applied to the synthesis of some useful heterocycles by Moreno *et al.*[7] The commonly used conditions for oxidative biaryl coupling reactions using phenyliodine(III) bis(trifluoroacetate) (PIFA) are as follows: (i) in polar but poorly nucleophilic solvents such as 2,2,2-trifluoroethanol (TFE) or 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) and (ii) in the presence of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 (Scheme 1).

Currently, due to the world-wide concern over environmental safety, organic reactions using two equivalents of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 or the use of expensive trifluoro or hexafluoroalcohol as a solvent is not recommended. In this communication, we describe a novel use of a readily available, inexpensive, easily handling, noncorrosive, nonvolatile and odourless solid heteropoly acid for oxidative biaryl coupling reaction with PIFA in CH_3CN.

As a representative reaction, conversion of *N*-benzyl-*N*-phenylethylamine derivative **1a** to the dibenzazocine derivative **4a** is shown in Table 1. Four heteropoly acids (HPAs), $H_3[PW_{12}O_{40}]$, $H_3[PMo_{12}O_{40}]$, $H_4[SiW_{12}O_{40}]$, and $H_4[SiMo_{12}O_{40}]$,[8,9] were examined for activation of PIFA in a biaryl coupling reaction and all were found to give **4a** in excellent yields under homogeneous conditions (entries 1–4). On the other hand, without a HPA, **4a** was obtained only in 4% yield and the starting material was recovered even after a long reaction time (entry 5). The reaction did not proceed when $H_3[PMo_{12}O_{40}]$, which has the highest oxidation potential among the four heteropoly acids, was used in the absence of PIFA (entry 6). These results suggest that the heteropoly acid does not work as an oxidant but as an activator of PIFA in oxidative coupling reactions.[10]

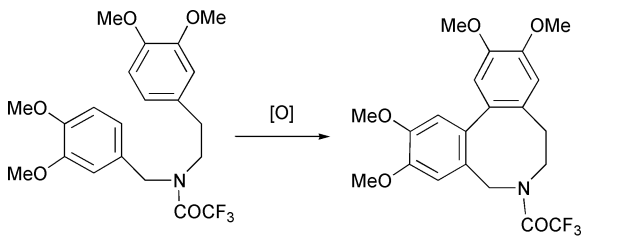


Scheme 1

In order to find the best coupling method, cyclization was also carried out under various conditions: (a) PIFA in the presence of $BF_3{\cdot}Et_2O$ in CH_2Cl_2,[4b] (b) PIFA in HFIP,[4b] (c) thallium(III) tris(trifluoroacetate) (TTFA) [prepared *in situ* by combination of thallium(III) oxide with trifluoroacetic acid and its anhydride],[2e] (d) ruthenium(IV) tetrakis(trifluoroacetate) (RUTFA) [prepared *in situ* by combination of ruthenium(IV) oxide with trifluoroacetic acid and its anhydride],[2f] and (e) vanadium(V) oxytrifluoride (entries 7–11).[2b] Although a considerable yield of the biaryl coupling product **4a** was obtained in some cases, no other condition gave higher yield than that given by PIFA in the presence of a HPA. These results clearly indicate that a reagent system of PIFA–HPA is the best condition for the oxidative biaryl coupling reaction.

One possible explanation for the remarkable control exerted by a HPA is that HPAs play important roles not only in the activation of PIFA but also in stabilizing the cation radical intermediate due to the greater softness of heteropoly anions.[11] The better yield with one-electron oxidant, VOF_3, which would smoothly give the cation radical intermediate, than the two

Table 1 Intramolecular oxidative coupling reaction of **1a**



1a **4a**

Entry	Reagents and solvents	Temp.	Time	Yield (%)[a]
1	PIFA, $H_3[PW_{12}O_{40}]$,[b] CH_3CN	−20–0 °C	40 min	97
2	PIFA, $H_3[PMo_{12}O_{40}]$,[b] CH_3CN	−20–0 °C	40 min	94
3	PIFA, $H_4[SiW_{12}O_{40}]$,[b] CH_3CN	−20–0 °C	40 min	94
4	PIFA, $H_4[SiMo_{12}O_{40}]$,[b] CH_3CN	−20–0 °C	40 min	97
5	PIFA, CH_3CN	−20 °C–rt	24 h	4
6	$H_3[PMo_{12}O_{40}]$,[c] CH_3CN	−20 °C–rt	24 h	NR
7	PIFA, $BF_3{\cdot}Et_2O$, CH_2Cl_2	−40 °C	10 min	68
8	PIFA, HFIP	0 °C	6 h	77
9	Tl_2O_3, $BF_3{\cdot}Et_2O$, TFA,TFAA, CH_2Cl_2	0 °C	2 h	56
10	RuO_2, $BF_3{\cdot}Et_2O$, TFA,TFAA, CH_2Cl_2	0 °C	8 h	45
11	VOF_3, TFA,TFAA, CH_2Cl_2	−20 °C	4 h	89

[a] Yield of isolated **4a**. [b] 200 mg mmol^{-1}. [c] 2 g mmol^{-1}.

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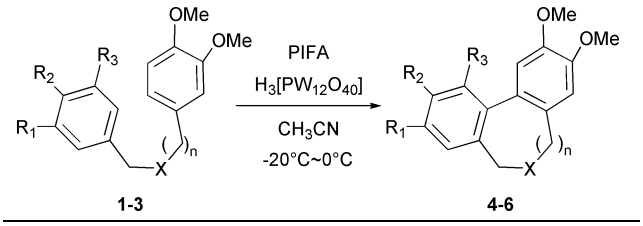
Table 2 Intramolecular oxidative coupling reaction of **1–3** with PIFA–$H_3[PW_{12}O_{40}]$



1-3 **4-6**

Entry	Substrate	R_1	R_2	R_3	X	*n*	Product	Yield (%)[a]
1	**1a**	OMe	OMe	H	$NCOCF_3$	2	**4a**	97
2	**1b**	OMe	OMe	OMe	$NCOCF_3$	2	**4b**	93
3	**2a**	OMe	OMe	H	$NCOCF_3$	1	**5a**	95
4	**2b**	OMe	OMe	OMe	$NCOCF_3$	1	**5b**	92
5	**2c**	$-OCH_2O-$		H	$NCOCF_3$	1	**5c**	94
6	**3a**	OMe	OMe	H	CH_2	1	**6a**	99
7	**3b**	OMe	OMe	OMe	CH_2	1	**6b**	96
8	**3c**	$-OCH_2O-$		H	CH_2	1	**6c**	99

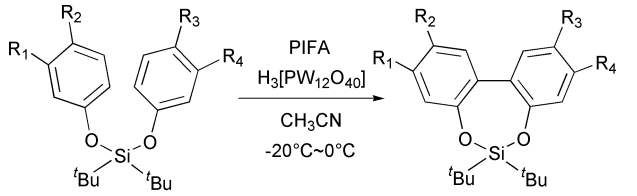
[a] Yield of isolated product.

electron oxidants such as thallium(III), ruthenium(IV), and hypervalent iodine(III), supports this explanation.

Similarly reactions of other substrates such as *N*-benzyl-*N*-phenylethylamine derivative **1b**, *N*,*N*-dibenzylamine derivatives **2a–c**, and 1,3-diarylpropanes **3a–c** with PIFA and tungsto(VI) phosphoric acid, $H_3[PW_{12}O_{40}]$, which has the highest thermal and hydrolytic stability and the lowest oxidation potential among the four HPAs, gave the corresponding biaryl compounds, **4b**, **5a–c**, **6a–c**, in excellent yield (Table 2).

The best result obtained with the reaction of diaryl substrates **1–3** prompted us to extend our procedure to silaketal derivatives **7a–c**, the resulting product could be easily converted into the 2,2′-substituted biaryl compounds possessing hydroxy groups after hydrolysis by the known method.[4b] Treatment of silaketal derivatives **7a–c** with PIFA activated by $H_3[PW_{12}O_{40}]$ afforded

Table 3 Intramolecular oxidative coupling reaction of silaketals **7** with PIFA–$H_3[PW_{12}O_{40}]$



7a-c **8a-c**

Entry	Substrate	R_1	R_2	R_3	R_4	Product	Yield (%)[a]
1	**7a**	OMe	OMe	OMe	OMe	**8a**	94
2	**7b**	OMe	OMe	$-OCH_2O-$		**8b**	86
3	**7c**	$-OCH_2O-$		$-OCH_2O-$		**8c**	93

[a] Yield of isolated **8**.

the corresponding coupling products **8a–c** in high yields (Table 3). It is noteworthy that the silaketal moiety of **8a–c** was not cleaved during the reaction.

A typical experimental protocol for biaryl coupling reaction with PIFA activated by HPA is as follows: to a stirred solution of open-chain precursor **1–3**, **7** (0.1 mmol) in MeCN (4 ml) was added HPA (20 mg) and PIFA (43 mg, 0.1 mmol) at −20 °C. Stirring was continued for 40 min (or as required according to GC-MS) at −20–0 °C. The solution was then filtered through a short column of basic alumina and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel gave the corresponding biaryl coupling product **4–6**, **8**.

Further studies on the oxidative biaryl coupling reaction of various phenol ether derivatives and detailed investigation of the reaction mechanism are in progress.

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