Pergamon

Tetrahedron 57 (2001) 345–352

TETRAHEDRON

Efficient oxidative biaryl coupling reaction of phenol ether derivatives using hypervalent iodine(III) reagents

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Received 23 March 2000; revised 30 May 2000; accepted 10 July 2000

Abstract—Oxidative biaryl coupling reaction of phenol ether derivatives with the hypervalent iodine reagent, phenyliodine(III) bis(trifluoroacetate) (PIFA), in the presence of $BF_3{\cdot}Et_2O$ gave a variety of substituted biphenyl and binaphthyl compounds in high yields. Replacement of PIFA with a more practical polymer-supported hypervalent iodine reagent has also been achieved.

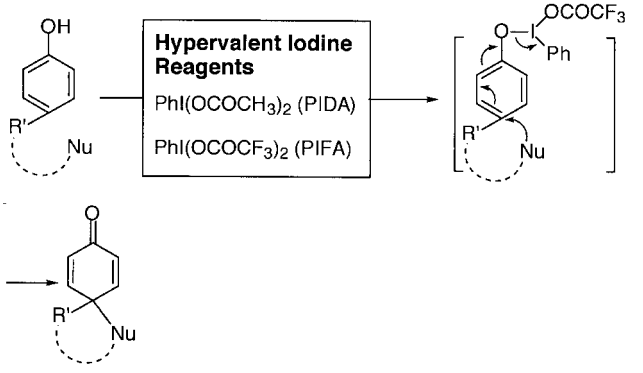
1. Introduction

The biaryl substructure is a central building block in a large number of natural products, such as polyketides, terpenes, lignanes, coumarins, flavonoids, tannins and many alkaloids.[1] Because of their interesting properties not only as bioactive natural products but also as chiral ligands in asymmetric reactions,[2] natural and unnatural biaryls are considered attractive synthetic targets. The reported methods for construction of these biaryl skeletons can be classified into two types: (1) the classical Ullmann reaction and other reductive processes; and (2) the oxidative (biomimetic) phenolic coupling reaction using a heavy metal oxidant.

The reductive processes include (1) the Ullmann coupling reaction of aryl halides using copper bronze as a reducing reagent,[3] (2) Semmelhack's method using Ni(0) complexes such as $[Ni(cod)_2]$ used in stoichiometric amounts to replace copper,[4] (3) a coupling reaction of aryl halides using a catalytic amount of low-valent nickel species which can be regenerated either electrochemically or by coreductants such as zinc or sodium hydride,[5] (4) a reaction of aryl-Grignard or organozinc compounds with aryl halides (the 'Kharash reaction') catalyzed by nickel or palladium derivatives,[6] (5) a palladium-catalyzed coupling reaction of arylboronic acids (or aryl tin compounds) with aryl halides (or triflates),[7] (6) the Meyers oxazoline method,[8] and (7) a cyanocuprate-mediated biaryl coupling reaction.[9]

On the other hand, the biomimetic syntheses of aporphine alkaloids, lignans and tannins were achieved using heavy metal oxidants, such as thallium(III), vanadium(V), ruthenium(IV) and iron(III) salts.[10] However, the unsatisfactory results obtained in the synthesis of highly functionalized symmetrical or unsymmetrical biaryl compounds using these reductive and oxidative methods have remained as problems. Moreover, heavy metal oxidants are highly toxic and must be handled very carefully. To solve these problems, we planned to use hypervalent iodine(III) reagents.

Hypervalent iodine(III) reagents are now extensively used in organic synthesis.[11] In particular, phenyliodine(III) diacetate (PIDA) and phenyliodine(III) bis(trifluoroacetate) (PIFA) have received a great deal of attention due to low toxicity, ready availability, easy handling, and reactivities similar to that of heavy metal reagents or anodic oxidation. Regarding the oxidation of phenol derivatives with PIDA or PIFA, in most cases, the reaction proceeds via the intermediate in which the phenolic oxygen reacts with the iodine center of the hypervalent iodine reagent followed by the nucleophilic attack of alcohol,[12] alkene,[13] amide,[14] carboxylic acid,[15] oxime,[16] fluoride ion,[17] water[18] or electron-rich aromatic ring[19] to give the cross-conjugated cyclohexadienone either by an inter- or intramolecular reaction pathway (Eq. (1)).



(1)

Keywords: biaryls; hypervalent elements; phenolics; coupling reactions.

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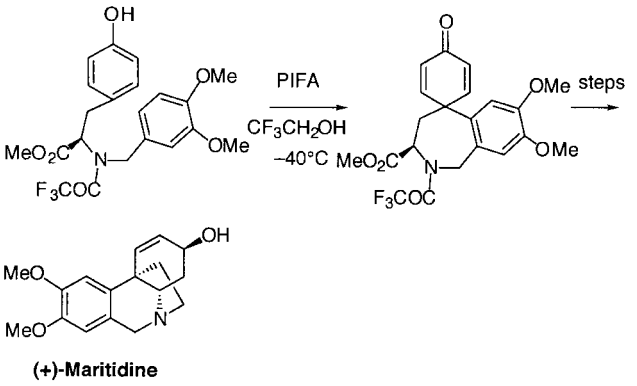
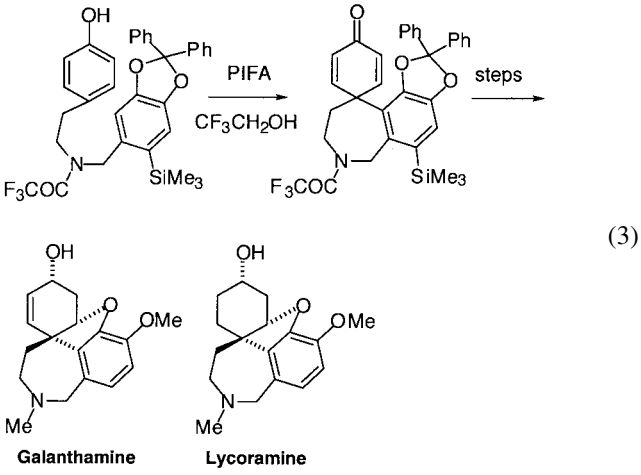
0040–4020/01/$ - see front matter
PII: S0040-4020(00)00941-8

We have successfully applied this pathway to the total syntheses of a variety of *Amaryllidaceae* alkaloid derivatives[20] (Eqs. (2) and (3)).

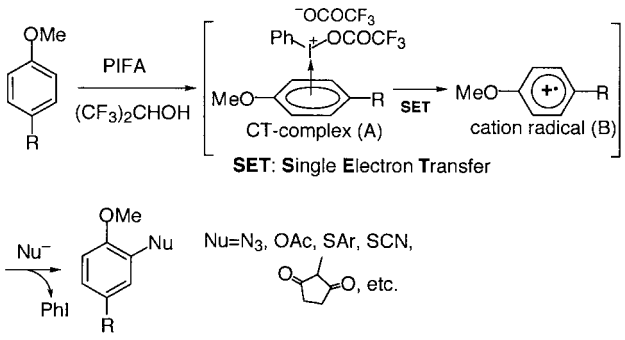


(2)



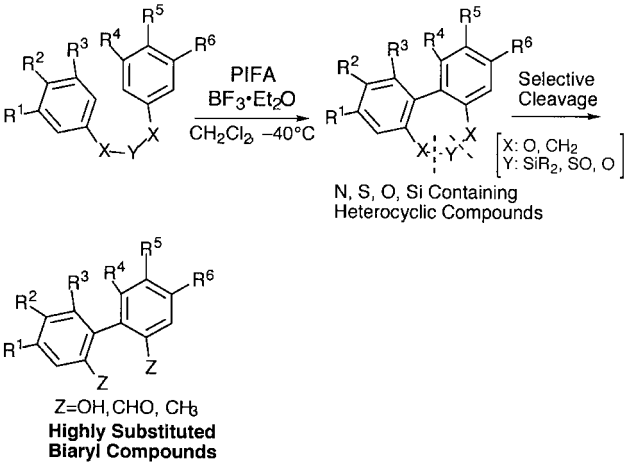
(3)

In contrast to the oxidation of phenol derivatives, reactions of phenol ethers with hypervalent iodine reagents have been limited and have yielded mostly iodonium salts. It is well-known that iodonium salts[21] are obtained by the reaction of unsubstituted or *meta*-substituted phenol ethers with hypervalent iodine reagents. However, in the case of *para*-substituted phenol ethers with PIFA, no iodonium salts were obtained. We found that the reaction of *p*-substituted phenol ethers with some nucleophiles in the presence of PIFA in polar and poorly nucleophilic solvents such as 2,2,2-trifluoroethanol (CF_3CH_2OH) and 1,1,1,3,3,3-hexafluoro-2-propanol ($(CF_3)_2CHOH$) caused nucleophilic substitution reactions. Thus, we explored a novel and straightforward nucleophilic substitution reaction on *p*-substituted phenol ethers with various nucleophiles (N_3^-,[22,23] AcO^-,[23] β-dicarbonyl compounds,[23] ArS^-,[24,25] and SCN^-[25]) using PIFA in CF_3CH_2OH or $(CF_3)_2CHOH$. This path involves an initial reaction of phenol ethers with the hypervalent iodine reagent and generates a cation radical intermediate [$ArH^{+\cdot}$] (Eq. 4).[23]



(4)

We have already found that the activated hypervalent iodine reagents such as PIFA–BF_3·Et_2O and PIFA–Me_3SiOTf are effective for the intramolecular reactions on phenol ether derivatives via SET (single electron transfer) process.[26] Although hypervalent iodine reagents have been used for several phenolic coupling reactions of substrates possessing free OH groups on the aromatic ring, biaryl coupling reaction of non-phenolic type substrates has not been reported. Thus, we developed a novel and efficient intramolecular oxidative biaryl coupling reaction of 1,3-diarylpropanes, *N*-benzyl-*N*-phenethylamines and *N*,*N*-dibenzylamines leading to the dibenzoheterocyclic compounds using PIFA–BF_3·Et_2O. Similar methods gave high yields of oxygen- and sulfur-containig dibenzoheterocyclic compounds, which were easily cleaved by known methods to give both symmetrical and unsymmetrical highly substituted biaryl compounds (Eq. 5).[27]



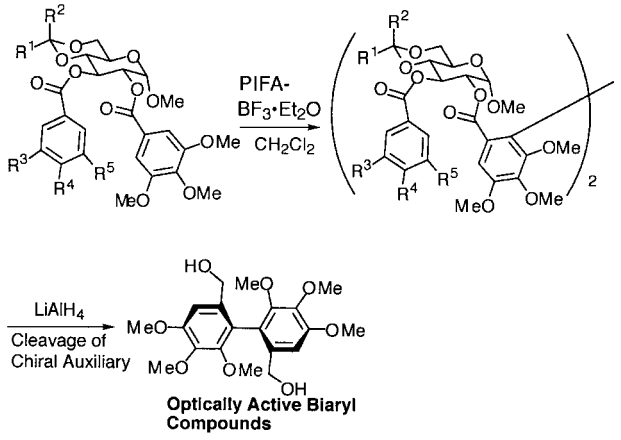
(5)

Furthermore, PIFA-induced oxidative phenolic coupling was applied to the synthesis of chiral biaryls. That is, the 1,2-diaroyl derivatives of protected α-D-glucose[28] underwent a smooth coupling reaction in the presence of PIFA–BF_3·Et_2O in a highly diastereoselective manner. The coupling product was treated with $LiAlH_4$ to yield the optically active biphenyl compound (>99% ee) quantitatively (Eq. 6).[29]

Table 1. Intermolecular biaryl coupling reaction using PIFA–BF_3·Et_2O

Entry	Substrate				Time (h)	Product	Yield (%)
	R^1	R^2	R^3				
1	OMe	OMe	OMe	(**1a**)	1.5		92
2	OMe	OMe	Me	(**1b**)	1.5		93
3	OMe	OMe	Br	(**1c**)	1.5		97
4	OMe	OMe	NO_2	(**1d**)	24		—a
5	OMe	Me	OMe	(**1e**)	1.5		92
6	OMe	Br	OMe	(**1f**)	1.5		91
7	Br	OMe	H	(**1g**)	3		72
	R^4	R^5	R^6	R^7			
8	H	H	H	OMe	(**1h**)	3	91
9	H	H	OMe	OMe	(**1i**)	1.5	61
10	Br	H	H	OMe	(**1j**)	1.5	98
11	H	OMe	H	H	(**1k**)	3	94
12	OMe	H	H	OMe	(**1l**)	3	82

a) no reaction



(6)

These intra- or intermolecular biaryl coupling reactions were found to be effective for preparing highly substituted biaryl compounds (hexa- to octa-substituted biaryls) though they required a final cleavage step (Eqs. (5) and (6)). Although the PIFA-induced intermolecular biaryl coupling reaction seems to be a direct route to multi-substituted (di- to hexa-substituted) biaryls and binaphthyls from phenol ethers and naphthol ethers, there is no report on the oxidative intermolecular biaryl coupling reaction. In this paper, we report our accomplishments on the intermolecular biaryl coupling reaction that directly leads to substituted biaryls and binaphthyls, which are useful precursors for a variety of biologically active natural products. In addition, a more practical preparation of biaryl compounds using a polymer-supported (diacyloxyiodo)benzene is also described.

2. Result and discussion

Compared to the abundant methods for biaryl coupling of phenols, methods for oxidative intermolecular biaryl coupling of phenol ether derivatives (non-phenolic compounds) are limited to heavy metal oxidation, anodic oxidation, and those using strong acids.[30] However, these methods still have drawbacks, such as (1) oxidants with high toxicity, (2) low to moderate yields, (3) low generality, or (4) vigorous reaction conditions. Thus, we investigated the use of PIFA–BF_3·Et_2O for the oxidative intermolecular biaryl coupling reaction.

2.1. Oxidative intermolecular biaryl coupling reaction using PIFA–BF_3·Et_2O

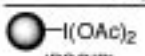
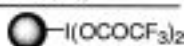
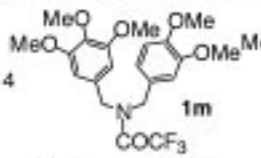
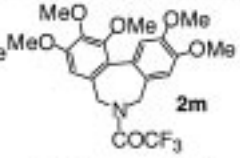
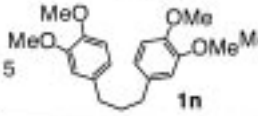
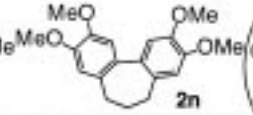
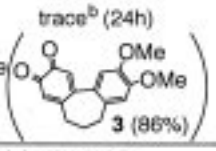
The intermolecular biaryl coupling reaction of 1,2,4-trimethoxybenzene (**1a**) was examined by treatment with PIFA–BF_3·Et_2O in CH_2Cl_2 at $-40°C$. The reaction proceeded smoothly to give the hexa-methoxylated biphenyl (**2a**) in 92% yield. Similarly, a variety of substituted phenol ethers (**1b**,**c**,**e**–**g**) were converted to the corresponding biaryls (**2b**,**c**,**e**–**g**) in excellent yields (Table 1). However, no reaction proceeded when using **1d** bearing a strong electron withdrawing NO_2 group.

Binaphthyl compounds (**2h**–**l**) were also obtained in good yields under these reaction conditions. Both the equivalency of the reagents and the reaction temperature remarkably affected the yields of biaryls. That is, in the oxidation of **1h**, the best yield was obtained using 0.55 equiv. PIFA, while the use of excess PIFA or higher reaction temperature ($>0°C$) gave oligomers or quinone derivatives as the by-products due to overoxidation.

2.2. Facile and practical biaryl coupling reaction using polymer-supported (diacyloxyiodo)benzene

Solid and polymer-supported reagents have applications in combinatorial chemistry, and the use of such operationally simple and environmentally benign reagents are becoming more and more important in the pharmaceutical and agrochemical industries. Several polymer-bound oxidants have been reported,[31] and polymer-supported hypervalent iodine reagents should be a welcome addition due to their versatility, low toxicity, and high yields. Recently, Togo et al.[32] and Ley et al.[33] demonstrated that polymer-supported

Table 2. Biaryl coupling reaction using polymer-supported (diacyloxyiodo)benzene

Entry	Substrate	Product	Reagent [Yield (%)]	
			 (PSDIB)	 (PSBTI)
1	**1a**	**2a**	77 (17h)	82 (3h)
2	**1b**	**2b**	75 (15h)	86 (3h)
3	**1h**	**2h**	trace[a] (24h)	89 (24h)
4	 **1m**	 **2m**	78 (48h)	80 (24h)
5	 **1n**	 **2n**	trace[b] (24h)  **3** (86%)	81 (24h)

a) A complex mixture was obtained. b) **3** was mainly obtained.

(diacetoxyiodo)benzene (PSDIB)[34] shows similar reactivity to (diacetoxyiodo)benzene and utilized it as a replacement for previously reported iodine(III) reagents. We reported a new and facile activation of PSDIB by the addition of KBr and developed an environmentally benign oxidation of alcohols in water.[35] As an extention of our studies on the practical utility of hypervalent iodine reagents, we proceeded to investigate the use of polymer-supported (diacyloxyiodo)benzene in the presence of $BF_3{\cdot}Et_2O$ for the oxidative biaryl coupling reaction. First, we examined the coupling reaction of **1a** with PSDIB–$BF_3{\cdot}Et_2O$, and **2a** was obtained in 77% yield, while the reaction proceeded slowly at −40°C due to the sparse solubility of PSDIB in CH_2Cl_2. On the other hand, polymer-supported bis(trifluoroacetoxyiodo)benzene (PSBTI), which is readily prepared by heating PSDIB in CF_3CO_2H or oxidation of polyiodostyrene with 30% H_2O_2–$(CF_3CO)_2O$, showed higher solubility in CH_2Cl_2 than that of PSDIB and demonstrated remarkable rate enhancement of the reaction. Furthermore, the coupling reaction of naphthyl ether **1h** also proceeded smoothly to give **2h** in 89% yield when using PSBTI although the reaction of **1h** with PSDIB gave a complex mixture (entry 3, Table 2). In addition, the overoxidation occurred in the reaction of **1n** with PSDIB to give **3** (86% yield) as the main product (entry 5, Table 2). Table 2 shows that PSBTI is more effective for both inter- and intramolecular biaryl coupling reactions than the use of PSDIB.

The recovery and recycling of the resin (polyiodostyrene) are easy. After quenching with saturated aqueous $NaHCO_3$, the resin was recovered nearly quantitatively by filtering the resulting mixture. The recovered resin was easily reoxidized to PSBTI via PSDIB by heating in CF_3CO_2H at 70°C, followed by precipitation by Et_2O. Thus, PSBTI can be used repeatedly without loss of activity. The reaction mechanism for the biaryl coupling reaction with PSDIB or PSBTI in the presence of $BF_3{\cdot}Et_2O$ possibly involves a one-electron oxidation step similar to that of PIFA.

3. Conclusion

A facile and efficient preparation of biaryl compounds has been developed by using the hypervalent iodine reagent, PIFA, activated by $BF_3{\cdot}Et_2O$. This method was found to be effective for the intermolecular biaryl coupling reaction as well as for our previously reported intramolecular reaction. Furthermore, we successfully improved this reaction to a more practical and general method by utilizing the polymer-supported hypervalent iodine reagent, PSBTI, under mild reaction conditions. Hence, hypervalent iodine reagents and their activated species show promise in replacing highly toxic heavy metal oxidants and should provide a useful tool for the syntheses of various biologically active natural products containing a biaryl structure.

4. Experimental

All melting points are uncorrected. Infrared (IR) absorption spectra (cm^{-1}) were recorded as KBr pellets. ^1H NMR (and ^{13}C NMR) spectra were recorded in $CDCl_3$ at 270 MHz (67.8 MHz) and 300 MHz (75.3 MHz) spectrometers with $SiMe_4$ as an internal standard. E. Merck silica gel 60 for column chromatography and E. Merck precoated TLC plates, silica gel F_{254} for preparative thin-layer chromatography were used. Organic layers were dried with anhydrous $MgSO_4$ or Na_2SO_4. PIFA is commercially available. $BF_3{\cdot}Et_2O$ was obtained from commercial suppliers and was used without further purification. Compounds **1a**–**h**, **1k**, and **1l** were purchased from Aldrich. Compounds **1j**, **1m**, and **1n** were prepared by known methods.[27b] Polymer-supported (diacyloxyiodo)benzene, PSDIB and PSBTI, were prepared by literature's procedures.[34]

4.1. General procedure for the intermolecular oxidative biaryl coupling reaction of 1a–l using PIFA–$BF_3{\cdot}Et_2O$

To a stirred solution of **1a**–**l** (0.2 mmol) in CH_2Cl_2 (5.0 ml)

was added dropwise to a solution of PIFA (0.11 mmol) and $BF_3{\cdot}Et_2O$ (0.22 mmol) in CH_2Cl_2 (5.0 ml) under nitrogen atmosphere at −40°C. The reaction mixture was stirred at −40°C for 1.5–3 h, then quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated. The residue was purified by column chromatography on silica gel (AcOEt–*n*-hexane) to give **2a–l** in yields shown in Table 1.

4.1.1. 2,4,5-Trimethoxy-1-(2,4,5-trimethoxyphenyl)benzene (2a). Colorless crystals, mp 248°C (decomp.) (hexane/AcOEt) (lit.[36] mp 248°C (decomp.)). IR (KBr) cm^{-1}: 2928, 1507, 1464, 1032, 814. ^1H NMR (300 MHz, $CDCl_3$) δ 3.69 (s, 6H), 3.78 (s, 6H), 3.86 (s, 6H), 6.56 (s, 2H), 6.75 (s, 2H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 56.1, 56.5, 56.9, 98.1, 115.1, 118.7, 142.7, 148.6, 151.0. MS *m/z* 334 (M^+), 288, 261, 167.

4.1.2. 2-Methyl-4,5-dimethoxy-1-(2-methyl-4,5-dimethoxyphenyl)benzene (2b).[37] Colorless crystals, mp 131°C (hexane/AcOEt). IR (KBr) cm^{-1}: 2851, 1674, 1651, 1609, 1507, 1213, 910. ^1H NMR (300 MHz, $CDCl_3$) δ 2.02 (s, 6H), 3.84 (s, 6H), 3.92 (s, 6H), 6.65 (s, 2H), 6.77 (s, 2H). ^{13}C NMR (75.3 MHz, $CDCl_3$) δ 19.3, 55.8, 56.0, 112.7, 112.9, 128.2, 133.3, 146.5, 147.7. MS *m/z* 302 (M^+), 257, 198, 158.

4.1.3. 2-Bromo-1-(2-bromo-4,5-dimethoxyphenyl)-4,5-dimethoxybenzene (2c). Colorless crystals, mp 160°C (benzene). (lit.[38] mp 157–159°C (benzene)). IR (KBr) cm^{-1}: 3002, 1603, 1505, 1173, 862. ^1H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 6H), 3.85 (s, 6H), 6.69 (s, 2H), 7.04 (s, 2H). ^{13}C NMR (75.3 MHz, $CDCl_3$) δ 56.1×2, 113.8×2, 115.0, 133.9, 147.9, 149.0. MS *m/z* 432 (M^++2), 257, 214. Anal. Calcd for $C_{16}H_{16}Br_2O_4$: C, 44.47; H, 3.73; Br, 36.98. Found: C, 44.57; H, 3.76; Br, 36.74.

4.1.4. 4-Methyl-2,5-dimethoxy-1-(4-methyl-2,5-dimethoxyphenyl)benzene (2e). Colorless crystals, mp 137°C (hexane/AcOEt). IR (KBr) cm^{-1}: 2994, 1497, 1210, 1048, 777. ^1H NMR (270 MHz, $CDCl_3$) δ 2.27 (s, 6H), 3.73 (s, 6H), 3.79 (s, 6H), 6.77 (2H, s), 6.81 (s, 2H). ^{13}C NMR (75.3 MHz, $CDCl_3$) δ 16.4, 56.0, 56.6, 113.8, 114.8, 125.5, 126.5, 150.6, 151.4. MS *m/z* 302 (M^+), 273, 242, 151. Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.30; H, 7.26.

4.1.5. 4-Bromo-1-(4-bromo-2,5-dimethoxyphenyl)-2,5-dimethoxybenzene (2f). Colorless crystals, mp 160°C (hexane/AcOEt) (lit.[39] mp 159–160°C). IR (KBr) cm^{-1}: 2998, 1727, 1487, 1215, 1067, 762. ^1H NMR (270 MHz, $CDCl_3$) δ 3.67 (s, 6H), 3.79 (s, 6H), 6.74 (s, 2H), 7.10 (s, 2H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 56.6, 56.9, 110.9, 115.1, 116.7, 126.5, 149.7, 151.0. MS *m/z* 432 (M^++2), 338, 257, 209. Anal. Calcd for $C_{16}H_{16}Br_2O_4$: C, 44.47; H, 3.73; Br, 36.98. Found: C, 44.56; H, 3.74; Br, 36.74.

4.1.6. 2-Bromo-4-(3-bromo-4-methoxyphenyl)-1-methoxybenzene (2g). Colorless crystals, mp 168°C (hexane/AcOEt). IR (KBr) cm^{-1}: 2840, 1601, 1482, 1250, 1059, 808. ^1H NMR (270 MHz, $CDCl_3$) δ 3.86 (s, 6H), 6.87 (d, 2H, *J*=8.6 Hz), 7.35 (dd, 2H, *J*=8.6, 2.3 Hz), 7.64 (d, 2H, *J*=2.3 Hz). ^{13}C NMR (75.3 MHz, $CDCl_3$) δ 56.3, 112.1×2, 126.6, 131.5, 133.4, 155.2. MS *m/z* 372 (M^++2), 328, 139. Anal. Calcd for $C_{14}H_{12}Br_2O_2$: C, 45.20; H, 3.25; Br, 42.95. Found: C, 45.14; H, 3.30; Br, 42.61.

4.1.7. 2-Methoxy-1-(2-methoxynaphthyl)naphthalene (2h). Colorless crystals, mp 199–202°C (hexane/toluene) (lit.[40] mp 200–204°C (hexane/toluene)). IR (KBr) cm^{-1}: 2838, 1507, 1246, 1069, 806. ^1H NMR (300 MHz, $CDCl_3$) δ 3.69 (s, 6H), 7.03 (d, 2H, *J*=7.9 Hz), 7.13 (t, 2H, *J*= 7.9 Hz), 7.23 (t, 2H, *J*=7.9 Hz), 7.38 (d, 2H, *J*=8.9 Hz), 7.79 (d, 2H, *J*=7.9 Hz), 7.90 (d, 2H, *J*=8.9 Hz). ^{13}C NMR (75.3 MHz, $CDCl_3$) δ 56.9, 114.2, 119.5, 123.5, 125.2, 126.3, 127.9, 129.2, 129.4, 134.0, 154.9. MS *m/z* 314 (M^+), 269, 141.

4.1.8. 2,3-Dimethoxy-1-(2,3-dimethoxynaphthyl)naphthalene (2i). Colorless crystals, mp 153–154°C (hexane/AcOEt) (lit.[41] mp 152–154°C). IR (KBr) cm^{-1}: 2938, 1597, 1464, 1420, 1252, 1117, 1042, 864, 749. ^1H NMR (270 MHz, $CDCl_3$) δ 3.53 (s, 6H), 3.97 (s, 6H), 6.96–7.04 (m, 4H), 7.22–7.29 (m, 4H), 7.69 (d, 2H, *J*=8.2 Hz). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 55.6, 60.7, 107.1, 123.9, 125.0, 125.6, 125.8, 126.4, 128.8, 131.0, 147.1, 152.1. MS *m/z* 374 (M^+), 328, 285, 107.

4.1.9. 6-Bromo-1-(6-bromo-2-methoxynaphthyl)-2-methoxynaphthalene (2j). Colorless crystals, mp 243–244°C (hexane/AcOEt). IR (KBr) cm^{-1}: 2938, 1586, 1495, 1266, 1071, 905. ^1H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 6H), 6.93 (d, 2H, *J*=8.9 Hz), 7.27 (dd, 2H, *J*=8.9, 1.8 Hz), 7.46 (d, 2H, *J*=8.9 Hz), 7.88 (d, 2H, *J*=8.9 Hz), 8.02 (d, 2H, *J*=1.8 Hz). ^{13}C NMR (75.3 MHz, $CDCl_3$) δ 56.7, 114.9, 117.4, 119.0, 126.9, 128.7, 129.7, 129.9, 130.2, 132.4, 155.1. MS *m/z* 473 (M^++3), 426, 361. Anal. Calcd for $C_{22}H_{16}Br_2O_2$: C, 55.96; H, 3.42; Br, 33.85. Found: C, 55.80; H, 3.55; Br, 33.54.

4.1.10. 4-Methoxy-1-(4-methoxynaphthyl)naphthalene (2k). Colorless crystals, mp 265°C (hexane/AcOEt) (lit.[30b] mp 264–265°C). IR (KBr) cm^{-1}: 2959, 1590, 1266, 1086, 764. ^1H NMR (300 MHz, $CDCl_3$) δ 4.07 (s, 6H), 6.91 (d, 2H, *J*= 7.9 Hz), 7.24–7.47 (m, 8H), 8.35 (d, 2H, *J*=8.5 Hz). ^{13}C NMR (75.3 MHz, $CDCl_3$) δ 55.6, 103.4, 122.0, 125.0, 125.5, 126.3, 126.4, 128.0, 130.7, 134.0, 155.0. MS *m/z* 314 (M^+), 268, 239, 119.

4.1.11. 2,6-Dimethoxy-1-(2,6-dimethoxynaphthyl)naphthalene (2l). Colorless crystals, mp 223°C (hexane/AcOEt). IR (KBr) cm^{-1}: 2838, 1595, 1507, 1252, 1092, 911, 735. ^1H NMR (270 MHz, $CDCl_3$) δ 3.65 (s, 6H), 3.81 (s, 6H), 6.82 (dd, 2H, *J*=9.2, 2.6 Hz), 6.94 (d, 2H, *J*=9.2 Hz), 7.09 (d, 2H, *J*=2.6 Hz), 7.34 (d, 2H, *J*=9.0 Hz), 7.77 (d, 2H, *J*=9.0 Hz). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 55.3, 57.1, 105.7, 114.9, 119.1, 120.0, 126.8, 127.8, 129.3, 129.9, 153.3, 155.8. MS *m/z* 374 (M^+), 328, 285, 164. Anal. Calcd for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92. Found: C, 76.69; H, 5.97.

4.2. Iodination of polystyrene

A mixture of polystyrene (5 g) (Mw=44,000, purchased from Aldrich), iodine (5 g), diiodine pentaoxide (2 g), carbon tetrachloride (10 ml), and 50% sulfuric acid (10 ml) in nitrobenzene (30 ml) was stirred at 90°C for

50 h. The reaction mixture was precipitated by adding AcOEt (100 ml) and filtered. The residue was dissolved in CH_2Cl_2 (120 ml), precipitated again by the addition of AcOEt, then filtered. The residue was washed with AcOEt and methanol. The resulting solid was collected and dried in vacuo to give poly iodostyrene (10.3 g). Elemental analysis (C, 43.87; H, 3.36; I, 51.65%) indicated that 87% of the phenyl ring in polystyrene was iodinated.

4.3. Preparation of PSDIB

Hydrogen peroxide (30%, 64.4 ml) was added dropwise to an acetic anhydride solution (233.6 ml) at 0°C. The solution was slowly warmed to room temperature and stirred overnight. To this solution, polystyrene (8.59 g) was added. Then, the solution was kept stirring at 40°C overnight. Et_2O was added and the mixture was filtered. The residue was washed with Et_2O to give PSDIB (12.6 g). Elemental analysis (C, 38.35; H, 3.57; I, 38.39%) indicated that 96% of the iodophenyl ring in poly(4-iodostyrene) was converted to a 4-(diacetoxyiodo)phenyl ring.

4.4. Preparation of PSBTI

PSDIB was heated in CF_3CO_2H at 70°C, then the mixture was precipitated by adding Et_2O, filtered, washed with Et_2O, and dried to give PSBTI.

4.5. General procedure for the biaryl coupling reaction of 1a,b using PSDIB–BF_3·Et_2O or PSBTI–BF_3·Et_2O

To a stirred suspension of **1a**,**b** (0.1 mmol) and PSDIB or PSBTI (0.15 mmol) in CH_2Cl_2 (5.0 ml) was added dropwise to BF_3·Et_2O (0.3 mmol) under nitrogen atmosphere at −40°C. The reaction mixture was stirred at −40°C for 3–24 h and then Et_2O was added and the resulting precipitate filtered off. The filtrate was washed with saturated aqueous $NaHCO_3$ and brine, dried, and evaporated. The residue was purified by column chromatography on silica gel (AcOEt–*n*-hexane) to give **2a**,**b** in yields shown in Table 2.

4.6. General procedure for the biaryl coupling reaction of 1h,m,n using PSDIB–BF_3·Et_2O or PSBTI–BF_3·Et_2O

To a stirred suspension of **1h**,**m**,**n** (0.1 mmol) and PSDIB or PSBTI (0.15 mmol) in CH_2Cl_2 (5 ml) was added dropwise to BF_3·Et_2O (0.3 mmol) in CH_2Cl_2 (5.0 ml) under nitrogen atmosphere at −40°C. The solution was slowly warmed to room temperature and stirred for 24–48 h and then Et_2O was added and the resulting precipitate filtered off. The filtrate was washed with saturated aqueous $NaHCO_3$ and brine, dried, and evaporated. The residue was purified by column chromatography on silica gel (AcOEt-*n*-hexane) to give **2h**,**m**,**n** in yields shown in Table 2.

4.6.1. 6-(Trifluoroacetyl)-1,2,3,9,10-pentamethoxy-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine (2m). A colorless solid, mp 142–144°C (hexane/AcOEt) (lit.[27b] mp 142–144°C). IR (KBr) cm^{-1}: 2940, 1684, 1464, 1248, 1129, 756. ^1H NMR (300 MHz, $CDCl_3$) δ 3.51–3.98 (m, 2H), 3.59 (s, 3H), 3.84–3.89 (m, 12H), 4.61 (dd, 1H, J=11.9, 9.9 Hz), 5.06 (dd, 1H, J=13.9, 11.9 Hz), 6.68 (d, 1H, J=47.6 Hz), 6.77 (d, 1H, J=47.6 Hz), 7.24 (m, 1H). HRMS (EI) Calcd for $C_{21}H_{22}F_3NO_6$ (M^+) 441.1397, found 441.1397. Anal. Calcd for $C_{21}H_{22}F_3NO_6$: C, 57.14; H, 5.02; N, 3.17. Found: C, 57.18; H, 5.14; N, 3.14.

4.6.2. 2,3,9,10-Tetramethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]-cycloheptene (2n). A colorless solid, mp 159–160°C (hexane/AcOEt) (lit.[27b] mp 153–155°C). IR (KBr) cm^{-1}: 2930, 1505, 1262, 1117, 752. ^1H NMR (270 MHz, $CDCl_3$) δ 2.20 (qui, 2H, J=7.0 Hz), 2.44 (t, 4H, J=7.0 Hz), 3.93 (s, 12H), 6.78 (s, 2H), 6.90 (s, 2H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 31.2, 34.0, 56.0, 56.2, 111.5, 111.8, 132.0, 132.8, 147.3, 147.7. HRMS (EI) Calcd for $C_{19}H_{22}O_4$ (M^+) 314.1519, found 314.1519.

4.6.3. 9,10-Bis(methoxy)-6,7-dihydro-2*H*-dibenzo[*a*,*c*]cycloheptene-2,3(5*H*)-dione (3). A red solid, mp 120°C (hexane/AcOEt). IR (KBr) cm^{-1}: 2936, 1657, 1510, 1279, 1127, 1017, 855, 733. ^1H NMR (270 MHz, $CDCl_3$) δ 1.90 (t, 2H, J=7.0 Hz), 2.32–2.37 (m, 2H), 2.67 (t, 2H, J= 6.8 Hz), 3.84 (s, 3H), 3.87 (s, 3H), 6.22 (s, 1H), 6.28 (s, 1H), 6.65 (s, 1H), 6.80 (s, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 25.2, 30.7, 32.2, 56.1, 56.2, 111.0, 112.2, 126.2, 126.9, 128.2, 131.5, 148.0, 151.2, 155.1, 156.3, 179.9, 180.3. Anal. Calcd for $C_{17}H_{16}O_4$·1/2H_2O: C, 69.61; H, 5.84. Found: C, 69.76; H, 5.73.

Acknowledgements

This research was financially supported in part by a Grant-in-Aid for Scientific Research (B) (No. 10470469) from the Ministry of Education, Science, Sports and Culture, Japan and a Grant-in-Aid for Encouragement of Young Scientists (No. 11771382) from Japan Society for the Promotion of Science.

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