Iodinated Biaryls Synthesized by the Direct Dehydrodimerization of Iodoarenes Using Phenyliodine(III) Bis(trifluoroacetate) (PIFA)

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Abstract: Multiply iodinated biaryls can be prepared in yields up to 75% by direct oxidative coupling reaction of the iodinated arenes. The PIFA-mediated dehydrodimerization is superior to all other known methods. The developed protocol is reliable and easy to perform.

Keywords: biaryls; C–C coupling; hypervalent iodine reagents; iodoarenes; synthetic methods

Introduction

Iodoarenes represent valuable precursors in the synthesis of biaryl compounds. Due to the excellent leaving group properties of the iodo moiety, this particular substituent is lost under reductive coupling reaction conditions.[1] The oxidative coupling process of electron-rich aryls mediated by phenyliodine(III) bis(trifluoroacetate) (PIFA), a hypervalent iodine reagent, was intensively studied by Kita and co-workers.[2] Usually, PIFA is activated by strong Lewis acids and acts as a two-electron-acceptor. This particular reagent has found wide application in organic synthesis.[3]

Multiply iodinated biaryls are generally obtained by linear multi-step syntheses and have recently attracted attention as novel contrast media for X-ray diagnostics.[4] The direct oxidative coupling of iodoarenes to iodinated biaryls usually fails yielding deiodinated products.[5] Generally, highly toxic thallium(III) or lead(IV) reagents are used to perform the dehydrodimerization without loss of the valuable iodo substituent.[6] Recently, we reported an environmentally friendly alternative by using $MoCl_5$ for the oxidative dimerization of iodoveratrole derivatives.[7] Application of this methodology to substrate **9** even allows a direct synthesis of a 2,2′,6,6′-tetraiodobiphenyl. To improve the solubility of the multiply iodinated biaryls for further purposes, the introduction of solubilizing groups in the alkoxy side chains is of great interest. Surprisingly, the $MoCl_5$-mediated dehydrodimerization, e.g., of **1**, provided not the desired biaryls but led rather to a highly selective chlorination of the iodoarenes, directed by the alkoxycarbonylmethyl side chain.[8]

Here, we describe the dehydrodimerization of iodoarenes mediated by PIFA in combination with $BF_3 \cdot Et_2O$ as Lewis acid additive. The reaction occurs without loss of the iodo moiety and tolerates a broad scope of substrates leading to multiply iodinated biaryls. The protocol for the transformation is highly reliable and easy to perform.

Results and Discussion

Synthesis of Iodoarenes

The syntheses of diiodobenzenes **1** and **2** from guaiacol (**19**) were performed as published.[8] The synthesis of **3** started with the known alkylation of catechol (**17**)[9] in good yields followed by iodination with iodine monochloride, providing 48% of the desired product (Scheme 2). Substrate **4** was obtained by alkylation of the corresponding phenol **20**, that was accessible from guaiacol applying known procedures.[10]

Diiodoarenes **5** and **6** were prepared according to Scheme 2. The first and common step involved the described multiple iodination of guaiacol providing the instable intermediate **21**.[11] Without further purification the subsequent transformations gave on the one hand by alkylation with (2-chloroethyl)tosylate product **5** in a good yield and on the other hand demethylation and direct formation of the dioxolane moiety afforded the benzodioxole derivative **6** which was obtained in a total yield of 24%. Compounds **8** and **16** were constructed similarly to described protocols,[12] while iodoarenes **7** and **9–15** are known.[13] All employed substrates were obtained and used for further studies in analytically pure form.

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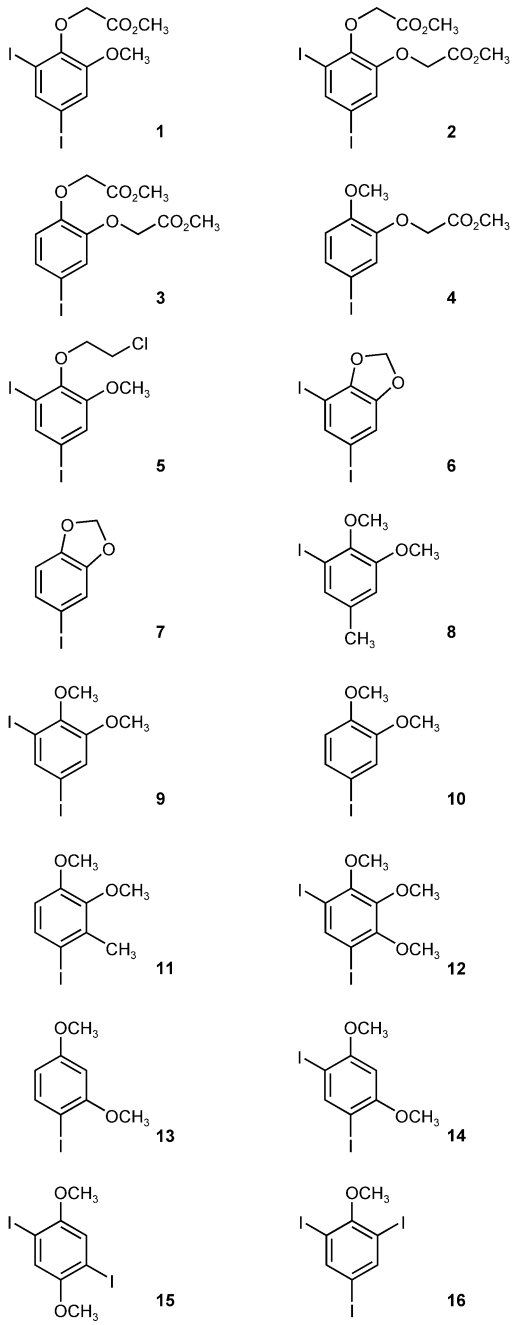


Scheme 1. Employed substrates.

Dehydrodimerization of Iodoarenes

The dehydrodimerization of iodoarenes using PIFA/$BF_3 \cdot Et_2O$ as oxidizing mixture leads directly to multiply iodinated biaryls (Scheme 3). When applying the standard reaction conditions[2] on substrate **1**, the corresponding biaryl **1a** was obtained in 55% besides 26% of non-converted starting material (Table 1, entry 1). The reaction was carried out for 90 minutes at $-40\,^{\circ}C$. After warming up to room temperature, the volatile components were evaporated and the products were directly subjected to column chromatography. Using that particular substrate, the reaction conditions were investigated. Quenching of the reaction mixture with $NaHCO_3$ solution at $-40\,^{\circ}C$ and $0\,^{\circ}C$, respectively, demonstrates that there is almost no conversion at lower temperatures (entries 2 and 3). Mainly substrate **1** was recovered under these conditions. In contrast to the literature, we anticipate that the oxidative coupling process occurs at room temperature. The dehydrodimerization reaction with PIFA seems to be very fast since the proto-deiodination process on arenes is known to be slow and was not observed in these studies. By running the reaction at $25\,^{\circ}C$ for a few minutes, 56% of the desired product and 31% of **1** could be isolated (entry 4). The best results were obtained by slow addition of the oxidizing mixture at room temperature. Removal of the solvent and separation by column chromatography on silica provided 61% of the biaryl and 31% of the iodoarene (entry 5). Elevated temperatures, prolonged reaction times, or using an excess of the coupling agent decreased the amount of the desired product since over-oxidation takes place.

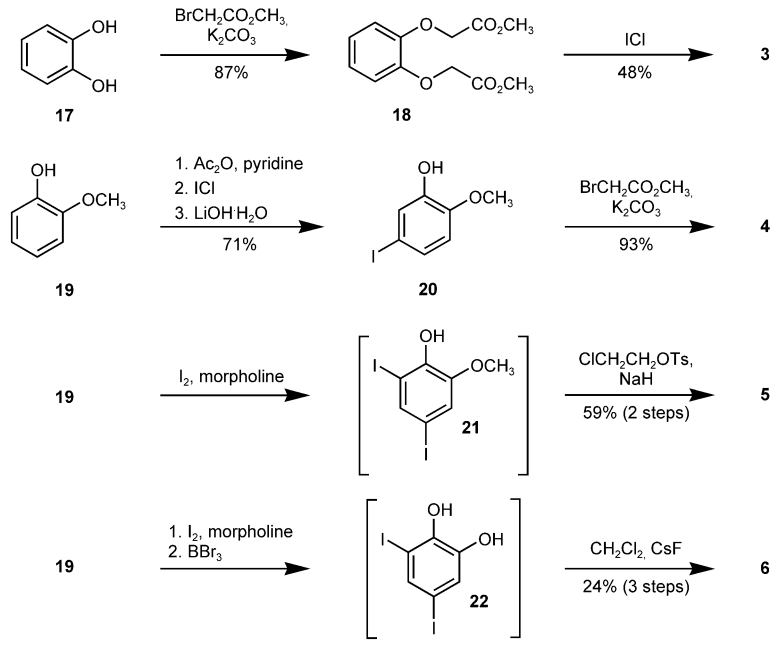
These ameliorated reaction conditions were applied on a variety of iodoarenes (Scheme 1). The conversion of these substrates was performed in synthetically interesting yields up to 75%. Generally, the amount of product is significant higher when 2,2′,6,6′-tetrasubstituted biaryls are formed compared to the yield of only 2,2′-disubstituted biaryls (Table 2). The synthetic potential of the PIFA/$BF_3 \cdot Et_2O$ mixture is apparent in the conversion of **9** which provides remarkably better results than the $MoCl_5$-mediated process (entry 8).[7] By applying slightly milder reaction conditions, substrates with benzodioxole moieties are successfully subjected to the dehydrodimerization process (entries 5 and 6).

The multiply iodinated biaryls are obtained as colorless solids that are stable towards light and heat. The coupling reaction usually occurs *para* to an alkoxy substituent in spite of the steric demand of the iodine moieties. Under the applied reaction conditions no side reactions were observed. This fact also makes the PIFA-mediated oxidation superior compared to the $MoCl_5$ methodology.[8] The solid state structure of **6a** reveals

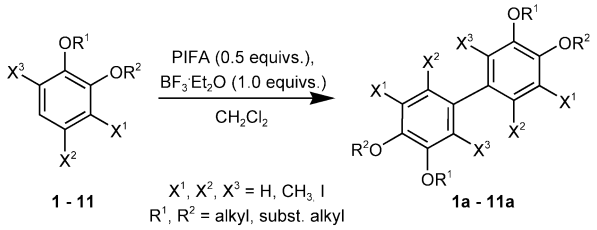
Table 1. Investigation of the reaction conditions for the conversion of **1**.

Entry	*T*	Time	Recovered **1**	Yield of biaryl **1a**
1	$-40\,^{\circ}C$	90 min	26%	55%
2	$-40\,^{\circ}C$	90 min[a]	82%	7%
3	$0\,^{\circ}C$	90 min[a]	74%	12%
4	$25\,^{\circ}C$	5 min	31%	56%
5	$25\,^{\circ}C$	30 min[b]	31%	61%

[a] The reaction mixture was quenched with $NaHCO_3$ solution.
[b] Slow addition of PIFA/$BF_3 \cdot Et_2O$.



Scheme 2. Synthesis of iodoarenes.



Scheme 3. Dehydrodimerization of iodoarenes.

Table 2. Dehydrodimerization of iodoarenes.

Entry	Substrate	Recovered substrate	Yield of biaryl
1	**2**	23%	66% (**2a**)
2	**3**	39%	37% (**3a**)
3	**4**	6%	40% (**4a**)
4	**5**	17%	69% (**5a**)
5	**6**	39%	46%[a] (**6a**)
6	**7**	49%	38%[a] (**7a**)
7	**8**	20%	60% (**8a**)
8	**9**	13%	75% (**9a**)
9	**10**	23%	66% (**10a**)
10	**11**	37%	34% (**11a**)

[a] Addition of PIFA/$BF_3 \cdot Et_2O$ at 0 °C, stirring at 25 °C for 1–2.5 h.

the orthogonality of the aromatic planes (Figure 1). Furthermore, the iodo substituents are shielded by those of the other aryl portion and also by the other aromatic plane, which might explain the unusual stability of such compounds.

Surprisingly, the electron-rich substrate **12** was not converted to the corresponding biaryl under these conditions. Instead, a transiodination occurred leading to triiodotrimethoxybenzene (**23**). The transiodination product was achieved in 42% by using a two-fold excess of the oxidizing agent. Iodoarene **13** was also transiodinated yielding **14** in 16%. The conversion of **15** and **16** showed no formation of a defined product, only starting material could be recovered in 51% and 71%, respectively, whereas subjecting **14** to the protocol led to complete decomposition.

Conclusion

Multiply iodinated biaryls can be prepared in synthetically interesting yields up to 75% by applying a very simple protocol employing a PIFA/$BF_3 \cdot Et_2O$ mixture for the dehydrodimerization reaction. The valuable iodo substituents are not lost during the procedure. The developed PIFA-mediated protocol is superior to other

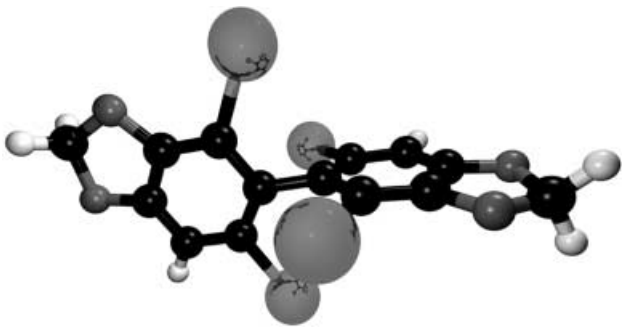


Figure 1. Solid state structure of **6a**.

known methods since the reagent mixture is considered as environmentally benign and no side reactions are observed. The broad scope of this transformation in the substitution pattern of the arenes as well as in the side chains offers a wide range of applications for the multiply iodinated biaryls.

Experimental Section

General Remarks

All reagents used were of analytical grade. Solvents were desiccated if necessary by standard methods. Column chromatography was performed on silica gel 60 (particle size 63–200 μm) using mixtures of cyclohexane and EtOAc as eluents. Melting points were determined on a MFB 595 Gallenkamp apparatus (UK) and are uncorrected. Microanalyses were performed using a Vario EL III (Elementar-Analysensysteme, Hanau, Germany). NMR spectra were recorded at 25 °C on a Bruker ARX 300 using TMS as an internal standard. Chemical shifts (δ) are reported in parts per million (ppm) relative to TMS. Mass spectra were obtained on a MAT8200 system (Finnigan-MAT, Bremen, D) (EI) or on a Quattro LC-Z (Micromass, Manchester, UK) (ESI). Exact mass was determined with a GC-TOF (Micromass, Manchester, UK).

Methyl (4-Iodo-2-methoxycarbonylmethoxy-phenoxy)acetate (3)

Catechol (10.00 g, 91.0 mmol) was dissolved in DMF. K_2CO_3 (40.0 g, 290 mmol) and methyl bromoacetate (26.0 mL, 272 mmol) were added. After stirring at 25 °C overnight, Et_2O (200 mL) was added and the mixture was washed several times with water and brine, dried over anhydrous $MgSO_4$ and concentrated under vacuum. Compound **18** was obtained as a colorless oil, which was used without further purification; yield: 20.03 g (78.8 mmol, 87%).

Compound **18** (7.53 g, 29.4 mmol) was dissolved in CH_3CN (100 mL) and treated with ICl (1.5 mL, 29.4 mmol) at 25 °C for 24 h under light exclusion. The reaction mixture was concentrated under vacuum and treated with $Na_2S_2O_3$ solution (50 mL, 10%) and Et_2O (50 mL). The aqueous layer was re-extracted with Et_2O (50 mL) and the combined organic layers were washed with water (2×50 mL) and brine and dried over anhydrous $MgSO_4$. After removal of the solvent, the crude product was purified by distillation under high vacuum to give **3** as a colorless oil, that crystallizes immediately; yield: 5.36 g (14.0 mmol, 48%); bp 155–157 °C/2.7×10^{-2} mbar; mp 77 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.71 (s, 2H, CH_2), 4.72 (s, 2H, CH_2), 6.66 (d, 1H, $^3J_{5,6}$ = 8.4 Hz, 6-H), 7.19 (d, 1H, $^4J_{3,5}$ = 2.1 Hz, 3-H), 7.27 (dd, 1H, $^3J_{5,6}$ = 8.4 Hz, $^4J_{3,5}$ = 2.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.92 (OCH_3), 51.95 (OCH_3), 66.25 (CH_2), 66.40 (CH_2), 83.94 (C4), 117.15 (C6), 124.39 (C3), 131.33 (C5), 147.95 (C1), 148.52 (C2), 168.61 (CO), 168.76 (CO); MS (EI, 70 eV): *m/z* (%) = 380 (100) [M^+], 321 (3) [$M^+ - CO_2CH_3$], 307 (9) [$M^+ - CH_2CO_2CH_3$], 249 (34) [$307 - CO_2CH_3$]; anal. calcd. for $C_{12}H_{13}IO_6$ (380.13): C 37.92, H 3.45; found: C 37.97, H 3.21.

Methyl (5-Iodo-2-methoxy-phenoxy)acetate (4)

Guaiacol (11.1 mL, 100 mmol), pyridine (17.1 mL, 220 mmol) and DMAP (0.61 g, 5.0 mmol) were dissolved in CH_2Cl_2 (200 mL). At 0 °C acetic acid anhydride (10.4 mL, 110 mmol) was added dropwise. After stirring for 1 h, the reaction mixture was brought to 25 °C and acidified with 1 M H_3PO_4 solution (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2×60 mL) and the combined organic layers were washed with brine, dried over anhydrous $CaCl_2$ and concentrated under vacuum. Distillation under high vacuum furnished the protected guaiacol as a colorless oil; yield: 16.04 g (96.5 mmol, 97%); bp 64 °C/1.2×10^{-2} mbar.

The acetylguaiacol (15.62 g, 94.0 mmol) was dissolved in CH_2Cl_2 (150 mL) and treated dropwise with a solution of ICl (5.7 mL, 113 mmol) in CH_2Cl_2 (60 mL). The reaction mixture was stirred at 25 °C under light exclusion for 7 d. The reaction progress was controlled by GC. After addition of $Na_2S_2O_3$ solution (100 mL, 10%) and standard work-up (see 3) the crude product was dissolved in a 1:1 mixture of MeOH/THF (180 mL) and a solution of lithium hydroxide monohydrate (15.78 g, 376 mmol) in water (30 mL) was added. After stirring at 25 °C for 5 d, the mixture was acidified with 2 N HCl solution (160 mL) and extracted with Et_2O (2×100 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under vacuum. After purification by column chromatography, the deprotected phenol **20** was obtained; yield: 17.14 g (68.6 mmol, 73%).

Phenol **20** (4.64 g, 18.6 mmol) was treated with methyl bromoacetate (2.6 mL, 27.9 mmol) and K_2CO_3 (5.00 g, 36.2 mmol) as described for compound 3. Standard work-up and purification by column chromatography afforded **4** as colorless crystals; yield: 5.55 g (17.2 mmol, 93% from **20**); mp 97 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.66 (s, 2H, CH_2), 6.65 (d, 1H, $^3J_{3,4}$ = 8.4 Hz, 3-H), 7.10 (d, 1H, $^4J_{4,6}$ = 2.1 Hz, 6-H), 7.26 (dd, 1H, $^3J_{3,4}$ = 8.4 Hz, $^4J_{4,6}$ = 2.1 Hz, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.18 (OCH_3), 55.95 ($ArOCH_3$), 66.52 (CH_2), 81.80 (C5), 114.06 (C3), 123.57 (C6), 131.53 (C4), 148.00 (C2), 149.89 (C1), 168.84 (CO); MS (EI, 70 eV): *m/z* (%) = 322 (100) [M^+], 263 (10) [$M^+ - CO_2CH_3$], 249 (26) [$M^+ - CH_2CO_2CH_3$]; anal. calcd. for $C_{10}H_{11}IO_4$ (322.10): C 37.29, H 3.44; found: C 37.27, H 3.15.

2-(2-Chloroethoxy)-1,5-diiodo-3-methoxybenzene (5)

Iodine (23 g, 90.6 mmol) was dissolved in EtOH (120 mL) and treated dropwise with morpholine (24 mL, 180 mmol). After stirring for an additional hour guaiacol (**19**) (2.5 mL, 22.6 mmol) was added. The reaction mixture was stirred at 25 °C overnight under light exclusion and then concentrated under vacuum. Saturated NH_4Cl solution (250 mL) was added and the aqueous phase was extracted with Et_2O (3×100 mL). The combined organic layers were washed with $Na_2S_2O_3$ solution (250 mL, 10%) and brine, dried over anhydrous $MgSO_4$ and concentrated under vacuum.

Without further purification the crude product **21** was dissolved in DMF (90 mL) and deprotonated with NaH (651 mg, 27.1 mmol; 60% in oil). After stirring at 25 °C for 30 min, 2-chloroethyl tosylate (4.9 mL, 27.1 mmol) was injected. The reaction mixture was stirred at 90 °C for 4 h. After cooling to 25 °C, EtOAc (200 mL) was added and the mixture was

washed with water (3×100 mL) and brine, dried over anhydrous $MgSO_4$ and concentrated under vacuum. Purification by column chromatography furnished **5** as colorless crystals; yield: 5.88 g (13.4 mmol, 59%); mp 70 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.83$ (t, 2H, $^3J_{CH_2CH_2}=6.3$ Hz, CH_2Cl), 3.83 (s, 3H, OCH_3), 4.21 (t, 2H, $^3J_{CH_2CH_2}=6.3$ Hz, OCH_2), 7.14 (d, 1H, $^4J_{4,6}=1.8$ Hz, 4-H), 7.67 (d, 1H, $^4J_{4,6}=1.8$ Hz, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=42.22$ (CH_2Cl), 56.29 (OCH_3), 72.57 (OCH_2), 88.02 (C1), 93.43 (C5), 122.14 (C4), 138.35 (C6), 147.80 (C3), 152.69 (C2); MS (EI, 70 eV): *m/z* (%) = 438, 440 (100, 33) [M^+], 375 (60) [$M^+ - CH_2CH_2Cl$]; anal. calcd. for $C_9H_9ClI_2O_2$ (438.43): C 24.66, H 2.07; found: C 24.68, H 1.84.

4,6-Diiodobenzo[1,3]dioxole (6)

The iodination of guaiacol (**19**) (5.8 mL, 52.3 mmol) was performed according to the synthesis of compound **5**. The crude product **21** was dissolved in 150 mL anhydrous CH_2Cl_2 and chilled to −78 °C. BBr_3 (5.9 ml, 62.9 mmol) was added dropwise. The mixture was stirred for 30 min at −78 °C and 4 h at −12 °C. After addition of Et_2O (100 mL), the mixture was brought to 25 °C, water (200 mL) was added and the aqueous layer was extracted with EtOAc (2×100 mL). The combined organic layers were washed with $Na_2S_2O_3$ solution (10%) and brine, dried over anhydrous $MgSO_4$ and concentrated under vacuum.

The crude product **22** was dissolved in DMF (100 mL), anhydrous CH_2Cl_2 (4.0 mL, 62.8 mmol) and CsF (39.7 g, 262 mmol) were added. The reaction mixture was refluxed for 90 min. After cooling to 25 °C, water (100 mL) was added, followed by an extraction with Et_2O (2×100 mL). The combined organic layers were washed with water (3×100 mL) and brine, dried over anhydrous $MgSO_4$ and concentrated under vacuum. Column chromatography gave **6** as colorless crystals; yield: 4.64 g (12.4 mmol, 24%); mp 108 °C (EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=6.01$ (s, 2H, CH_2), 7.05 (d, 1H, $^4J_{5,7}=1.8$ Hz, 7-H), 7.75 (d, 1H, $^4J_{5,7}=1.8$ Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=71.70$ (C4), 83.00 (C6), 101.01 (C2), 117.52 (C7), 137.69 (C5), 147.28 (C7a), 149.86 (C3a); MS (EI, 70 eV): *m/z* (%) = 374 (100) [M^+], 247 (5) [$M^+ - I$]; anal. calcd. for $C_7H_4I_2O_2$ (373.91): C 22.49, H 1.08; found: C 22.81, H 1.08.

Dehydrodimerization with PIFA; General Procedure

The respective substrate (1.50 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL). A solution of PIFA (323 mg, 0.75 mmol) and $BF_3\cdot Et_2O$ (0.19 mL, 1.50 mmol) in CH_2Cl_2 (5 mL) was added in small portions over a period of 15 minutes at 25 °C. After stirring for additional 15 min the solvent was evaporated under vacuum and without further work-up the crude mixture was directly subjected to column chromatography. All biaryls formed as colorless crystalline solids immediately upon evaporation of the solvents. The products were dried under high vacuum.

2,2′,6,6′-Tetraiodo-4,4′-dimethoxy-3,3′-bis(methoxycarbonylmethoxy)-biphenyl (1a): mp 175 °C (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.84$ (s, 6H, OCH_3), 3.90 (s, 6H, Ar-OCH_3), 4.65 (s, 4H, CH_2), 7.45 (s, 2H, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=52.12$ (OCH_3), 56.27 ($ArOCH_3$), 68.97 (CH_2), 92.99 (C2), 98.06 (C6), 122.57 (C5), 147.15, 147.56 (C1, C4), 151.32 (C3), 168.82 (CO); MS [ESI (ES+), Cap: 0.84 V; Cone: 52 V]: *m/z* = 917 [$M+Na^+$]; anal. calcd. for $C_{20}H_{18}I_4O_8$ (893.97): C 26.87, H 2.03; found: C 26.80, H 2.11.

2,2′,6,6′-Tetraiodo-3,3′,4,4′-tetrakis(methoxycarbonylmethoxy)-biphenyl (2a): mp 204 °C (EtOAc); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta=3.72$ (s, 6H, OCH_3), 3.73 (s, 6H, OCH_3), 4.70 (s, 4H, CH_2), 4.98 (s, 4H, CH_2), 7.63 (s, 2H, 5-H); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta=51.72$ (OCH_3), 51.90 (OCH_3), 65.19 (CH_2), 68.51 (CH_2), 93.65 (C2), 98.66 (C6), 123.19 (C5), 146.73, 147.17 (C1, C4), 148.84 (C3), 168.26 (CO), 168.54 (CO); MS (EI, 70 eV): *m/z* (%) = 1010 (100) [M^+]; anal. calcd. for $C_{24}H_{22}I_4O_{12}$ (1010.04): C 28.54, H 2.20; found: C 28.44, H 2.00.

2,2′-Diiodo-4,4′,5,5′-tetrakis(methoxycarbonylmethoxy)-biphenyl (3a): mp 125–126 °C (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.78$ (s, 6H, OCH_3), 3.83 (s, 6H, OCH_3), 4.70 (s, 4H, CH_2), 4.75 (s, 4H, CH_2), 6.69 (s, 2H, 6-H), 7.33 (s, 2H, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=52.27$ (OCH_3, OCH_3), 66.44 (CH_2), 66.70 (CH_2), 89.68 (C2), 116.75 (C6), 125.11 (C3), 142.52 (C1), 147.80 (C4, C5), 168.78 (CO), 168.83 (CO); MS (EI, 70 eV): *m/z* (%) = 758 (100) [M^+], 631 (41) [$M^+ - I$], 499 (18) [$M^+ - I - CH_2CO_2CH_3 - CO_2CH_3$]; anal. calcd. for $C_{24}H_{24}I_2O_{12}$ (758.25): C 38.02, H 3.19; found: C 37.94, H 2.85.

2,2′-Diiodo-5,5′-dimethoxy-4,4′-bis(methoxycarbonylmethoxy)-biphenyl (4a): mp 196 °C (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.83$ (s, 6H, OCH_3), 3.86 (s, 6H, OCH_3), 4.72 (s, 4H, CH_2), 6.75 (s, 2H, 6-H), 7.28 (s, 2H, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=52.25$ (OCH_3), 56.11 (Ar-OCH_3), 66.51 (CH_2), 87.48 (C2), 113.92 (C6), 125.89 (C3), 142.87 (C1), 147.21 (C5), 149.63 (C4), 168.83 (CO); MS (EI, 70 eV): *m/z* (%) = 642 (100) [M^+], 515 (61) [$M^+ - I$]; anal. calcd. for $C_{20}H_{20}I_2O_8$ (642.18): C 37.41, H 3.14; found: C 37.16, H 2.93.

3,3′-Bis(2-chloroethoxy)-2,2′,6,6′-tetraiodo-4,4′-dimethoxy-biphenyl (5a): mp 170 °C (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.87$ (t, 4H, $^3J_{CH_2CH_2}=6.3$ Hz, CH_2Cl), 3.92 (s, 6H, OCH_3), 4.29 (t, 4H, $^3J_{CH_2CH_2}=6.3$ Hz, OCH_2), 7.45 (s, 2H, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=42.25$ (CH_2Cl), 56.29 (OCH_3), 72.46 (OCH_2), 92.68 (C2), 98.74 (C6), 122.57 (C5), 147.18 (C1), 148.17 (C4), 151.67 (C3); MS (EI, 70 eV): *m/z* (%) = 874, 876, 877 (100, 70, 25) [M^+], 811 (27) [$M^+ - CH_2CH_2Cl$], 63, 65 (23, 7) [$CH_2CH_2Cl^+$]; anal. calcd. for $C_{18}H_{16}Cl_2I_4O_4$ (874.84): C 24.71, H 1.84; found: C 24.65, H 1.68.

4,4′,6,6′-Tetraiodo-[5,5′]bi(benzo[1,3]dioxolyl) (6a): The oxidizing reagent mixture was added at 0 °C. After stirring for 30 min at 0 °C, the reaction mixture was brought to 25 °C, stirred for additional 2 h and purified following the general protocol; mp 215 °C (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=6.13$ (s, 4H, CH_2), 7.34 (s, 2H, 7-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=75.92$ (C4), 88.48 (C6), 101.45 (C2), 118.17 (C7), 145.67 (C5), 146.27 (C7a), 150.92 (C3a); MS (EI, 70 eV): *m/z* (%) = 746 (100) [M^+], 492 (34) [$M^+ - 2\,I$]; HRMS: *m/z* calcd. for $C_{14}H_6I_4O_4$ (M^+): 745.6445; found: 745.6403.

6,6′-Diiodo-[5,5′]bi(benzo[1,3]dioxolyl) (7a):[14] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=6.02$ (s, 4H, CH_2), 6.67 (s, 2H, 4-H), 7.32 (s, 2H, 7-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=88.59$ (C6), 101.82 (C2), 110.25 (C4), 118.06 (C7), 142.25 (C5), 148.01, 148.14 (C3a, C7a); MS (EI, 70 eV): *m/z* (%) = 494 (100) [M^+], 367 (57) [$M^+ - I$], 240 (58) [$M^+ - 2\,I$]; anal. calcd. for $C_{14}H_8I_2O_4$ (494.02): C 34.04, H 1.63; found: C 34.43, H 1.62.

2,2′-Diiodo-3,3′,4,4′-tetramethoxy-6,6′-dimethylbiphenyl (8a): mp 233–234 °C (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.96 (s, 6H, CH_3), 3.85 (s, 6H, OCH_3), 3.92 (s, 6H, OCH_3), 6.82 (s, 2H, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.23 (CH_3), 55.92 (OCH_3), 60.42 (OCH_3), 100.29 (C2), 114.23 (C5), 133.24 (C6), 140.16 (C1), 147.40 (C3), 151.51 (C4); MS (EI, 70 eV): *m/z* (%) = 554 (100) [M^+], 427 (23) [$M^+ - I$]; anal. calcd. for $C_{18}H_{20}I_2O_4$ (554.16): C 39.01, H 3.64; found: C 39.30, H 3.48.

2,2′-Diiodo-4,4′,5,5′-tetramethoxybiphenyl (10a):[15] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.86 (s, 6H, OCH_3), 3.91 (s, 6H, OCH_3), 6.73 (s, 2H, 6-H), 7.31 (s, 2H, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.04 (OCH_3), 56.17 (OCH_3), 88.14 (C2), 113.26 (C6), 120.91 (C3), 141.45 (C1), 149.00 (C4, C5); MS (EI, 70 eV): *m/z* (%) = 526 (100) [M^+], 399 (58) [$M^+ - I$], 257 (30) [$M^+ - 2\,I - CH_3$].

2,2′-Diiodo-4,4′,5,5′-tetramethoxy-3,3′-dimethylbiphenyl (11a):[6a] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.46 (s, 6H, CH_3), 3.80 (s, 6H, OCH_3), 3.81 (s, 6H, OCH_3), 6.64 (s, 2H, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.38 (CH_3), 55.87 (OCH_3), 60.49 (OCH_3), 96.58 (C2), 111.70 (C6), 135.54 (C1, C3), 146.54 (C4), 152.26 (C5); MS (EI, 70 eV): *m/z* (%) = 554 (68) [M^+], 427 (100) [$M^+ - I$].

1,2,3-Triiodo-4,5,6-trimethoxybenzene (23): mp 118 °C (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.85 (s, 6H, OCH_3), 3.87 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 60.77 (OCH_3), 60.92 (OCH_3), 100.67 (C1, C3), 114.15 (C2), 144.54 (C5), 155.19 (C4, C6); MS (EI, 70 eV): *m/z* (%) = 546 (100) [M^+]; anal. calcd. for $C_9H_9I_3O_3$ (545.88): C 19.80, H 1.66; Found: C 20.03, H 1.42.

X-Ray Crystallographic Study

X-ray crystal structure analysis of 6a: formula $C_{14}H_6I_4O_4 \cdot 0.5\,CH_2Cl_2$, M = 788.25, yellow crystal 0.50 × 0.30 × 0.10 mm, a = 20.020(1), b = 11.681(1), c = 17.336(1) Å, β = 111.10(1)°, V = 3782.3(4) Å^3, $\rho_{calcd.}$ = 2.769 g cm^{-3}, μ = 67.47 cm^{-1}, empirical absorption correction ($0.133 \leq T \leq 0.552$), Z = 8, monoclinic, space group *C*2/c (No. 15), λ = 0.71073 Å, T = 198 K, ω and φ scans, 8111 reflections collected ($\pm h$, $\pm k$, $\pm l$), [(sinθ)/λ] = 0.66 Å^{-1}, 4479 independent (R_{int} = 0.042) and 3450 observed reflections [$I \geq 2\,\sigma(I)$], 213 refined parameters, R = 0.044, wR^2 = 0.115, max. residual electron density 1.78 (−1.71) e Å^{-3} close to iodine, hydrogens calculated and refined as riding atoms.

The data set was collected with a Nonius KappaCCD diffractometer, equipped with a rotating anode generator Nonius FR591. Programs used: data collection COLLECT (Nonius B. V., 1998), data reduction Denzo-SMN (Z. Otwinowski, W. Minor, *Methods in Enzymology*, **1997**, *276*, 307–326), absorption correction SORTAV (R. H. Blessing, *Acta Cryst.* 1995, *A51*, 33–37; R. H. Blessing, *J. Appl. Cryst.* **1997**, *30*, 421–426), structure solution SHELXS-97 (G. M. Sheldrick, *Acta Cryst.* 1990, *A46*, 467–473), structure refinement SHELXL-97 (G. M. Sheldrick, Universität Göttingen, **1997**), graphics SCHAKAL (E. Keller, Universität Freiburg, **1997**).

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-229654. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336–033; E-mail: deposit@ccdc.cam.ac.uk].

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