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Dehydrodimerization of iodobenzenes to iodinated biaryls

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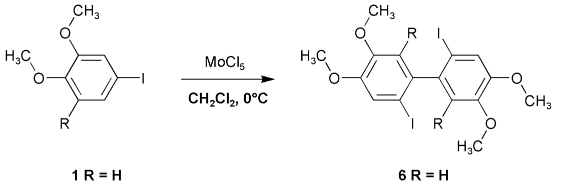
The molybdenum pentachloride-mediated oxidative coupling of iodo-substituted electron rich benzenes without the loss of the iodo-substituents is reported. The presented methodology is an environmentally friendly alternative to known thallium(III)- and lead(IV)-reagents. Even 2,2′,6,6′-tetraiodobiphenyl derivatives are easily accessible.

Since iodo substituents offer the straightforward installation of various functionalities, iodoaryls represent valuable precursors for the synthesis of organic molecules. Due to that particular reactivity the iodo substituent is lost during most reaction conditions.[1] However, for specific applications the iodo moiety has to be introduced later on. While the oxidative coupling reaction of bromoaryls successfully occurs, it usually fails when employing substrates containing iodo-substituents, yielding the deiodinated products.[2] Only when using the highly toxic thallium(III)- or lead(IV)-reagents there are oxidative coupling reactions reported wherein no release of the iodo moiety is observed.[3] Multiply iodo-substituted aromatic systems are applied as contrast media for X-ray diagnostics.[4] Recent developments include polyiodinated biaryls which have to be constructed in a linear multi-step synthesis.[5] We report the molybdenum pentachloride-mediated coupling reaction of electron rich iodobenzenes without the loss of the iodo moiety. Molybdenum pentachloride is an inexpensive, commercially available reagent for the dehydrodimerization of alkoxy-substituted aryls,[6] leading to novel structures for supramolecular chemistry.[7]

The employed substrates were synthesized according to known procedures.[8] The conversion with molybdenum pentachloride proceeds in a smooth and rapid way, wherein the evolution of hydrogen chloride is observed. It is noteworthy that for the coupling reaction only a single solvent is required. The above mentioned thallium reagents depend on mixtures of solvents and Lewis acids.



1 R = H
2 R = CH$_3$
3 R = I

6 R = H
7 R = CH$_3$
8 R = I

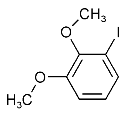
Firstly, 4-iodoveratrole, which was successfully dehydrodimerized with thallium(III)-reagents, was reacted in high yield to the biaryl **6**. For good conversions a minimum amount of two equivalents of molybdenum pentachloride for each C–C-bond formation was required, demonstrating that molybdenum pentachloride acts as a single electron acceptor.[9] During the reaction the biphenyl precipitates and is collected, after recrystallization from ethyl acetate, in an analytically pure form. The conversion of compound **2**† gives a product that remains in solution during the reaction. Interestingly, using less molybdenum pentachloride of course decreases the yield in biaryl but efficiently avoids the deiodinated by-products. Even the diiodobenzene derivative undergoes the dehydrodimerization in the presence of molybdenum pentachloride yielding a 2,2′,6,6′-tetraiodobiphenyl structure. In order to keep the deiodinated by-products to less than 5%, it is advantageous to add the molybdenum pentachloride in small portions. The purification was accomplished by crystallization. The structure and connectivity was verified by an X-ray analysis of **8** (Fig. 1).

Table 1 Isolated yields in the oxidative coupling reaction of iodobenzenes

Entry	Substrate	MoCl$_5$ (eq.)	% Yield
1	**1**	1.2	81 (**6**)
2	**2**	1.2	58 (**7**)
3	**3**	0.7	29 (**8**)
4	**3**	0.8	34 (**8**)
5	**3**	0.7	47 (**8**)[a]
6	**4**	1.2	53 (**9**)[b]
7	**5**	0.7	6 (**10**)

1.8 mmol substrate in 15 mL CH$_2$Cl$_2$ was treated with molybdenum pentachloride for 40 min at 0 °C. Washing the organic phase with water and Na$_2$S$_2$O$_3$ solution results in the raw material which was recrystallized. [a] Addition of molybdenum pentachloride in small portions over 25 min. [b] Mixture of oligomers.[10]

In general, the coupling reaction occurs in the position *para* to a methoxy substituent. Even the steric demand of four iodo-substituents adjacent to the biaryl moiety does not interfere! In the solid state structure the planes of the aromatic systems are perpendicular. Compound **8** forms colorless crystals which exhibit an unusual high stability towards light and heat. No photolytic liberation of iodine during exposure to sunlight over several days was observed. However, the steric demand of the adjacent iodo-substituents and the other aromatic system seems to form a protective pocket for the substituent of interest.



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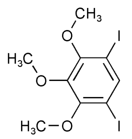

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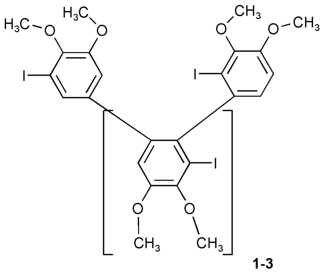

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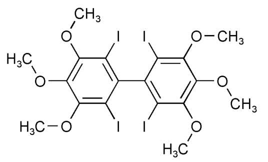

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The conversion of 3-iodoveratrole **4** leads, besides some traces of dimeric material, to a mixture of oligomeric coupling products **9**.[10] Since two activated *para*-positions are available,

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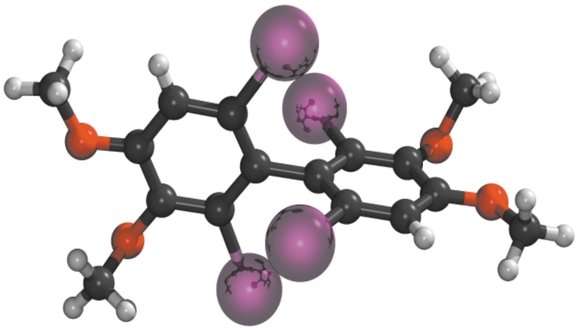

Fig. 1 Solid state structure of 2,2′,6,6′-tetraiodobiphenyl **8**.

higher aggregates are formed. Because of the bulkiness of the iodo substituents, a cyclization to a triphenylene structure is avoided and linear oligomers are favored. Using less molybdenum pentachloride does not improve the reaction outcome. If more electron rich substrates, like **5**, are applied to the molybdenum pentachloride-mediated oxidative coupling reaction, the deiodination process is favored and only small amounts of the known compound **10** are obtained.[11]

We compared the oxidative coupling potential of molybdenum pentachloride with common reagents for the dehydrodimerization of electron rich benzenes. The oxidative coupling reaction of 3,5-diodobenzene to the biaryl **8** was applied.

While molybdenum pentachloride reacts smoothly, no conversion was observed with the corresponding vanadium tetrachloride (Table 2, Entry 2). The more reactive vanadyl halides exhibit less synthetic use. Only a large excess of the expensive vanadyl fluoride resulted selectively in the tetraiodo derivative. Since ferrous chloride initiates the release of the iodo substituent, we applied combinations exhibiting better oxidation qualities. Remarkably, the ferrous chloride reagents also offer the access to the desired biaryl beside some deiodination products. Molybdenum pentachloride represents the most reactive transition metal reagent for the oxidative coupling reaction of electron rich iodobenzenes.

In conclusion, the oxidative coupling reaction of iodobenzenes bearing two methoxy substituents succeeds with molybdenum pentachloride without the release of the iodo substituent. Therefore, molybdenum pentachloride is an environmental friendlier alternative to the highly toxic thallium(III)- or lead(IV)-reagents. Molybdenum pentachloride seems to be the superior reagent among the transition metal halides. For the reaction only dichloromethane as a single solvent is required. The direct dehydrodimerization of electron rich iodobezenes gives an efficient and direct access to multiply iodinated biraryls that usually require multi-step syntheses. Despite the steric demand of the iodo substituents, 2,2′,6,6′-tetraiodobiphenyls are formed. The dehydrodimerization of iodobenzenes will be applied to the construction of complex structures and will be reported in due course.

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Table 2 Comparison of different transition metal reagents in the direct synthesis of **8**

Entry	Reagent	% Yield
1	1.5 eq. $MoCl_5$	47
2	1.5 eq. VCl_4	0
3	1.5 eq. $VOCl_3$	0
4	1.5 eq. VOF_3	3
5	15 eq. VOF_3	20
6	2 eq. $FeCl_3/H_2SO_4$	dec
7	2 eq. $FeCl_3$/HOAc	18

All reactions were performed on a 4 mmol scale at 25 °C (except entry 1 at 0 °C) for 1 h. Purification was done by column chromatography on silica.

Notes and references

† Analytical data for **7**: mp. 233 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.93 (s; 6H; CH_3), 3.82 (s; 6H; OCH_3), 3.88 (s; 6H; OCH_3), 6.79 (s; 2H; CH); ^{13}C NMR(75 MHz, $CDCl_3$, 25 °C, TMS): δ = 21.23, 55.91, 55.94, 60.40, 60.45, 100.30, 114.26, 133.24, 140.17, 147.42, 151.50; MS (70 eV): *m*/*z* (%): 553.8 (100) [M$^+$], 428 (20) [M$^+$ − I]; micro analysis (%): calcd. for $C_{18}H_{20}I_2O_4$ (554.16): C 39.10, H 3.64; found: C 39.30, H 3.48. Analytical data for **8**: mp. > 300 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.71 (s; 6H; OCH_3), 3.88 (s; 6H; OCH_3), 7.57 (s; 2H; CH); ^{13}C NMR(75 MHz, $CDCl_3$, 25 °C, TMS): δ = 56.51, 60.06, 94.27, 99.50, 122.44, 146.62, 149.01, 151.84; MS (70 eV): *m*/*z* (%): 777 (100) [M$^+$], 107(60)[M$^+$ − I], 524(10)[M$^+$ − 2I]; micro analysis (%): calcd. for $C_{16}H_{14}I_4O_4$ (777.9): C 24.70, H 1.81; found: C 24.89, H 1.71. X-ray crystal structure analysis of **8**: formula $C_{16}H_{14}I_4O_4$, M = 777.87, colourless crystal 0.25 × 0.25 × 0.03 mm, a = 18.540(1), b = 8.482(1), c = 14.637(1) Å, β = 115.31(1)°, V = 2080.8(3) Å^3, ρ calc = 2.483 g cm^{-3}, μ = 60.06 cm^{-1}, absorption correction *via* SORTAV (0.315 $\leqslant T \leqslant$ 0.840), Z = 4, monoclinic, space group $C2/c$ (No. 15), λ = 0.71073 Å, T = 198 K, ω and φ scans, 4069 reflections collected (±h, ±k, ±l), $[(\sin\theta)/\lambda]$ = 0.66 Å^{-1}, 2466 independent (Rint = 0.036) and 1832 observed reflections [$I \geqslant 2\sigma(I)$], 111 refined parameters, R = 0.041, $wR2$ = 0.109, max. residual electron density 1.61 (−1.38) e Å^{-3}, hydrogens calculated and refined as riding atoms. 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), absorption correction SORTAV (R. H. Blessing, *Acta Cryst.*, 1995, **A51**, 33; R. H. Blessing, *J. Appl. Cryst.* 1997, **30**, 421), structure solution SHELXS-97 (G.M. Sheldrick, *Acta Cryst.* 1990, **A46**, 467), structure refinement SHELXL-97 (G.M. Sheldrick, Universität Göttingen, 1997), graphics SCHAKAL (E. Keller, Universität Freiburg, 1997). CCDC 176882. See http://www.rsc.org/suppdata/cc/b2/b202841g/ for crystallographic data in .cif or other electronic format.

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9 The nature of the resulting molybdenum species is not known. The observed stoichiometry is in contradiction to ref. 6.

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