Oxidative Coupling Reactions Mediated by $MoCl_5$ Leading to 2,2′-Cyclolignans: The Specific Role of HCl

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The scope and performance of oxidative coupling reaction using $MoCl_5$ can be significantly improved by employing Lewis-acidic additives such as $TiCl_4$, $SnCl_4$, or $SiCl_4$. Since the by-product, HCl, plays a particular function as an inhibitor for $MoCl_5$ by forming chloro complexes, exploiting typical chloride scavengers, like silver salts or molecular sieves, is also successful.

A variety of differently substituted 1,4-diarylbutanes **4a**–**g**, which were easily synthesized by a modular approach, were subjected to the dehydrodimerization reaction. For the oxidative coupling reaction, a *para*-substitution pattern — with a donor group on the aryl system — is pivotal for allowing access to the 2,2′-cyclolignans **5a**,**e**–**g**.

Introduction

Eight-membered biaryl compounds, such as the 2,2′-cyclolignans, are widely occurring natural products. The most prominent method for the construction of these moieties employs an oxidative coupling reaction. Recently, we described a total synthesis of (+)-detigloyloxysteganolide in which the key step was accomplished by a molybdenum pentachloride mediated oxidative coupling reaction.[1] For the selective eight-membered ring formation in the 2,2′-cyclolignan synthesis, we believe that a preceding preorganization occurs of the electron-rich aryl components with the Lewis-acidic molybdenum pentachloride. While variations in the substitution pattern of the butylidene bridge support this hypothesis, the exact nature of the pre-complex is still unclear. It turns out that the dehydrodimerization reaction involving molybdenum pentachloride prefers a 1,2-disubstitution pattern of donor substituents on the aryl components.[2] In addition, the oxidative coupling reaction is not limited to methoxy-substituted arenes. Recently, we developed several protective groups for the phenolic oxygen atom that are compatible with the reaction conditions.[3] Furthermore, this methodology has been exploited successfully for the construction of particular scaffolds that are usually only accessible by multi-step procedures.[4−6]

Since the naturally occurring 2,2′-cyclolignans exhibit highly diverse substitution patterns on the biaryl moiety, we focused our attention on the scope of the dehydrodimerization involving a number of differently substituted 1,4-diarylbutanes. Furthermore, we investigated additives that we expected to support the molybdenum pentachloride mediated oxidative coupling reaction.

Results and Discussion

The synthesis of the precursors for the oxidative cyclization to 2,2′-cyclolignans started with the readily available 3,4-dimethoxycinnamic acid, which provided, after several standard transformations, the iodo derivative **1**[7,8] that was converted into the phosphonium salt **2**. The straightforward synthetic sequence, which involved a Wittig olefination followed by a hydrogenation with a heterogeneous catalyst, afforded the 1,4-diarylbutanes **4a**−**g** in good yields (Scheme 1, Table 1). The formed triphenylphosphane oxide and the accompanying salts were removed yielding a crude mixture of olefinic isomers that were subjected directly to the catalytic reduction. The compounds **4a**−**g** were obtained in an analytically pure state. The modular approach to the 1,4-diarylbutanes gave ready access to a variety of differently substituted starting materials for the oxidative cyclization reaction.

The oxidative coupling reaction employing molybdenum pentachloride as the sole reagent gave the desired eight-membered ring system in significant amounts only with substrate **4e**; the substitution pattern was similar to that used in previous experiments.[1] Applying this methodology to other substrates resulted in almost no conversion. Only **4a** was converted into the 2,2′-cyclolignan **5a** in moderate yield (Scheme 2), which might be explained by the high oxidation potential of the anisole moiety. In all cases, elevated

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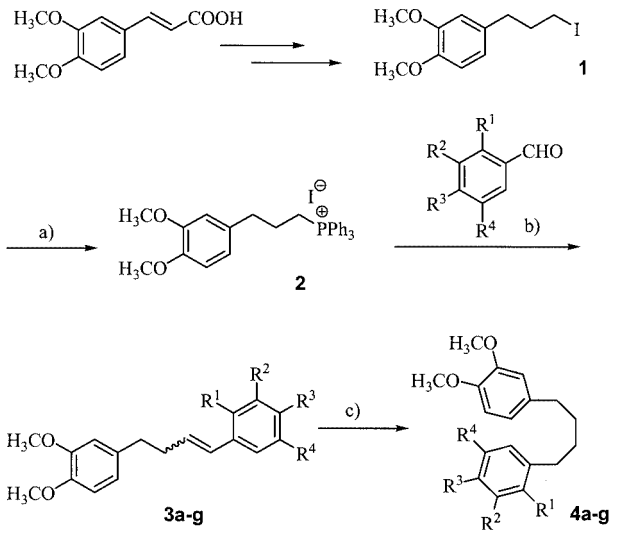


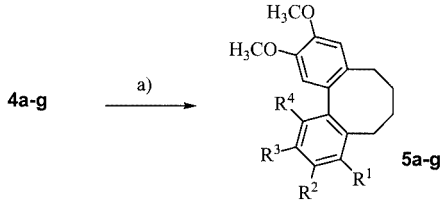
Scheme 1. a) PPh_3, DMF, reflux; b) i. KO*t*Bu, THF, 0 °C, ii. benzaldehyde derivative; c) Pd/C, H_2, THF, room temp.

Table 1. Synthesis of 1,4-diarylbutanes

Entry	Compound	R^1	R^2	R^3	R^4	Yield [%][a]
1	**4a**[9]	H	OCH_3	H	H	85
2	**4b**	OCH_3	H	H	H	79
3	**4c**	H	OCH_3	H	OCH_3	78
4	**4d**	OCH_3	H	H	OCH_3	77
5	**4e**	H	O−CH_2−O		H	89
6	**4f**	OCH_3	OCH_3	H	H	83
7	**4g**	OCH_3	OCH_3	OCH_3	H	87

[a] Refers to analytically pure material obtained over two steps from **2**.

temperatures, prolonged reaction times and higher amounts of $MoCl_5$ did not improve the outcome of the reaction, and led mostly to degradation of the substrates.[10]



Scheme 2. a) $MoCl_5$, additive, CH_2Cl_2, 0 °C

Lewis acids are usually added to enhance the power of oxidizing agents,[11] because they affect the removal of a ligand or substituent from the oxidatively active material. The resulting electrophilic species is then more capable of mediating the redox process. Therefore, we screened several Lewis-acidic additives in the oxidative coupling transformations of **4a**−**g**. We used equimolar amounts of additives relative to $MoCl_5$ and monitored the reactions by GC. The best reagent combination was then used for the synthesis on a larger scale and displayed a good correlation with the screening experiments.[12] The Lewis acidity of $MoCl_5$ is not known precisely, since common NMR spectroscopy techniques are not compatible with its paramagnetic nature.[13−15] Based on the Lewis acid catalyzed reactions, $MoCl_5$ is considered as active as $TiCl_4$.[16] Initially, we anticipated that a strong Lewis acid would activate the remaining molybdenum chloride clusters and, therefore, mediate the oxidative coupling reactions. The tested additives are known not to react with $MoCl_5$ at ambient temperature.[17] When NaCl is treated with a mixture of $AlCl_3$ and $MoCl_5$, the more Lewis-acidic aluminum center assumes the chloride anion, to generate the tetrachloroaluminate anion, while the molybdenum chloride remains unchanged.[18] During the oxidative coupling reaction, hydrogen chloride is formed as a by-product that might deactivate the molybdenum reagent by forming chloro complexes with $MoCl_5$. The $[MoCl_6]^-$ system is known, but it is considered to be a complex having low stability.[19,20]

Using very strong Lewis acids, like $SbCl_5$, resulted in an immediate decomposition and chlorination of all substrates, forming a sluggish reaction mixture. Employing $AlCl_3$ led to a significant increase in reactivity, except for the substrate **4a**, which resulted in a lower yield. Using a mixture containing boron trifluoride−diethyl ether gave very similar results to those of $AlCl_3$. A vast improvement was obtained by the addition of $TiCl_4$ to the $MoCl_5$-mediated oxidative coupling reactions, which led to ameliorated yields of 2,2′-cyclolignans. Alternative additives for substrates that are especially electron-rich, such as **4g**, are $SiCl_4$ and $SnCl_4$, the use of which result in cleaner reaction mixtures and excellent yields. Less electron-rich substrates, like **4a** and **4f**, suffer, however, even under these conditions, from low conversions. It became clear that the excess of hydrogen chloride had to be eliminated from the reaction mixture. Common additives based on amines resulted in no reactivity at all, since either the amines would coordinate directly to the molybdenum center and decrease its electrophilic behavior[21,22] or the molybdenum center was directly reduced because of the low oxidation potentials of amines. Addition of inert amines, such as 2,2,6,6-tetramethylpiperidine, disfavored the dehydrodimerization reaction in all cases. Only a low conversion was observed when the most successful substrate, **4g**, was allowed to react in the presence either of the co-reagent 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Switching to typical chloride scavengers, like silver salts, improved the transformation and gave good yields. Using molecular sieves as hydrogen chloride trapping agents had a similar effect, and had the advantages of a simple workup and cost effectiveness. Performing the $MoCl_5$-mediated oxidative coupling reaction in the presence of 0.5 equiv. of LiCl resulted in a decrease in reactivity, which is demonstrated by the very low conversions, even with substrate **4e**. This finding clearly supports the particular inhibitor function of chloride anions in the $MoCl_5$-mediated oxidative coupling reaction (Figure 1).

The detailed screening experiments reveal that the by-product, hydrogen chloride, plays a significant role in the reactivity of the dehydrodimerization reaction performed by

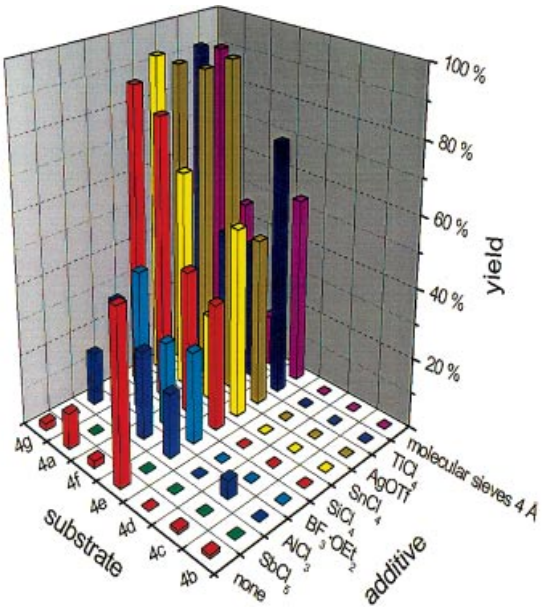


Figure 1. Screening for additives in the $MoCl_5$-mediated oxidative coupling reaction

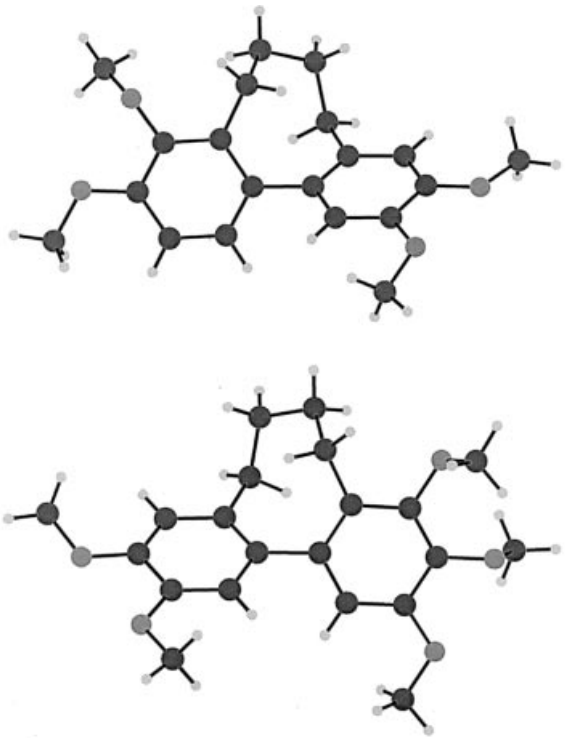


Figure 2. Structures of **5f** (top) and **5g** (bottom) in the crystal

$MoCl_5$. For a successful oxidative coupling reaction leading to the desired 2,2′-cyclolignans, a *para*-substitution pattern with donor functions is pivotal. Despite involving two electron-rich arene systems, **4c** and **4d** were not suitable substrates for the oxidative cyclization reaction. More importantly, an activated *para* position on the arene gives rise to the formation of the eight-membered ring system. Other oxidative coupling products, such as dimers or six-membered rings, were not found in the reaction mixtures. The 2,2′-cyclolignan **5a** had properties identical with those reported in the literature.[9] The other isolated cyclolignans, **5e**−**5g**, were fully characterized. All NMR spectroscopic signals were clearly assigned by NOE and COSY experiments, which are described in detail for **5f**, that consistently support the exclusive formation of the eight-membered ring systems. This feature was verified by X-ray crystallographic analyses of single crystals of **5f** and **5g** that revealed, in both cases, the same twist-boat-chair conformation,[23] which is considered to be the preferred conformation for 2,2′-cyclolignans.[24] The biaryl moieties are twisted by 64° in **5f** and 60° in **5g** (Figure 2).

Conclusion

The by-product, hydrogen chloride, limits the performance of $MoCl_5$-mediated oxidative coupling reactions. Additives consisting of simple Lewis acids, such as $TiCl_4$, $SnCl_4$, or $SiCl_4$, improve the transformation remarkably. Furthermore, chloride scavengers like Ag^+ or molecular sieves also lead to a significant amelioration in reactivity, which is of particular synthetic interest. The appropriate substitution pattern of the donor groups on the arene entities is decisive in the formation of 2,2′-cyclolignans: the oxidative coupling reaction fails completely in the absence of a *para*-substitution pattern.

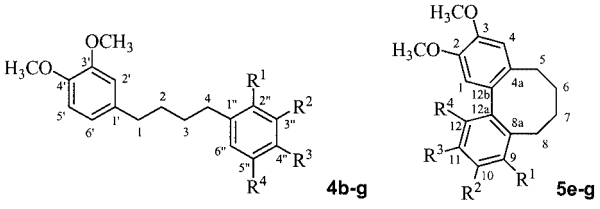
Experimental Section

General Remarks: Tetrahydrofuran and dichloromethane were dried with sodium wire and CaH_2, respectively. Subsequent distillation and handling was carried out under argon. Column chromatography was performed on silica gel with a particle size of 63−200 μm from Merck KGaA (Darmstadt, Germany). All benzaldehyde derivatives were used directly as purchased from Aldrich. Melting points were determined with an MFB 595 Gallenkamp apparatus (UK) and are uncorrected. Microanalysis was performed using a Vario EL III (Elementar-Analysensysteme, Hanau, Germany). NMR spectra were recorded with a Bruker ARX 300, AM 360 or AMX 400 spectrometer using TMS as an internal standard. EI Mass spectra were obtained using an MAT8200 system (Finnigan-MAT, Bremen, Germany); ESI mass spectra were obtained using a Quattro LCS (Waters-Micromass, Manchester, UK). Exact mass was determined using a GC-TOF spectrometer (Micromass, Manchester, UK).

[3-(3,4-Dimethoxyphenyl)propyl]triphenylphosphonium Iodide (2): 4-(3′-Iodopropyl)-1,2-dimethoxybenzene (**1**)[7,8] (10.0 g, 0.033 mol) was combined with triphenylphosphane (8.8 g, 0.033 mol) in DMF (50 mL) and the reaction mixture was heated under reflux over a period of 4 h. Removal of the solvent by short-path distillation and subsequent recrystallization provided pure colorless **2** (14.9 g, 84%). M.p. 161−162 °C (from MeOH/Et_2O). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.86−1.97 (m, 2 H, CH_2-CH_2-P), 2.93 (t, $^3J_{H,H}$ = 7 Hz, 2 H, $CH_2-CH_2-CH_2$), 3.59−3.68 (m, 2 H, aryl−CH_2-CH_2), 3.80 (s, 6 H, OCH_3), 6.71−6.82 (m, 3 H, $H_{arom.}$), 7.60−7.78 (m, 15 H, $P(C_6H_5)_3$] ppm. ^{13}C NMR ($CDCl_3$, 75 MHz):

δ = 21.7 (d, $^2J_{C,P}$ = 51 Hz, $CH_2-CH_2-CH_2$), 24.6 (aryl$-CH_2-CH_2$), 34.9 (d, $^2J_{C,P}$ = 15 Hz, CH_2-CH_2-P), 55.9, 56.3 (OCH_3), 111.4 (C-3), 117.4 (C-6), 118.6 (C-5), 120.7 (C-4), 130.3, 130.5, 132.5, 133.5, 133.6, 135.0 [$P(C_6H_5)_3$], 147.5 (C-1), 149.0 (C-2) ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = 25.0 ppm. MS (ESI): *m/z* = 441.3 $[M - I]^+$. $C_{29}H_{30}IO_2P$ (586.1): calcd. C 61.28, H 5.32; found C 61.23, H 5.16.

General Procedure for Preparation of 1,4-Diarylbutanes 4a−g: A chilled suspension of the phosphonium salt **2** (12 mmol) in dry THF (25 mL) was treated with potassium *tert*-butoxide (12 mmol) at 0 °C. The orange suspension was stirred at 0 °C for 2 h before the substituted benzaldehyde (12 mmol) was added. After stirring overnight, the turbid reaction mixture was filtered and the triphenylphosphane oxide washed with diethyl ether. The solvents were evaporated in vacuo. The residue was fractionated between diethyl ether (3 × 150 mL) and brine (100 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure and then purified by column chromatography on silica (cyclohexane/ethyl acetate). Subsequent hydrogenation of the furnished substrates provided colorless oils or solids in pure form. The substrates were dissolved in THF (25 mL) and Pd/C (10% Pd, 0.2 g) was suspended in the solution. These mixtures were stirred at room temperature under H_2 for 12 h. The catalyst was filtered off and the solvent was evaporated. The different 1,4-diarylbutane derivatives **4a−g** were synthesized in overall yields of 77−89%. For systematic numbering of the carbon atoms see Scheme 3.



Scheme 3. Systematic numbering of the carbon atoms in the 1,4-diarylbutanes and 2,2′-cyclolignans

1,2-Dimethoxy-4-[4-(2-methoxyphenyl)butyl]benzene (4b): Colorless crystals (2.84 g, 79%). M.p. 49 °C (from MeOH). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.66 (m, 4 H, 2-, 3-*H*), 2.62 (t, $^3J_{H,H}$ = 7 Hz, 2 H, 1-*H*), 2.68 (t, $^3J_{H,H}$ = 7 Hz, 2 H, 4-*H*), 3.83, 3.87, 3.89 (s, 9 H, OCH_3), 6.74−6.92 (m, 5 H, 2′-, 5′-, 6′-, 3′′-, 5′′-H), 7.14−7.21 (m, 2 H, 4′′-, 6′′-H) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 29.4 (C-4), 29.9 (C-2), 31.4 (C-3), 35.3 (C-1), 55.1, 55.8, 55.9 (OCH_3), 110.2 (C-3′′), 111.2 (C-2′), 111.8 (C-5′), 120.1 (C-5′′), 120.3 (C-6′), 126.8 (C-1′′), 129.7 (C-4′′), 130.9 (C-6′′), 135.5 (C-1′), 147.0, 148.7 (C-3′, C-4′), 157.4 (C-2′′) ppm. MS (EI, 70 eV): *m/z* (%) = 300.1 (100) $[M]^+$, 151.1 (81) $[veratryl]^+$, 121.0 (14) $[OCH_3-C_6H_4-CH_2]^+$. $C_{19}H_{24}O_3$ (300.1): calcd. C 75.97, H 8.05; found C 75.72, H 8.05.

1,2-Dimethoxy-4-[4-(3,5-dimethoxyphenyl)butyl]benzene (4c): Colorless crystals (3.09 g, 78%). M.p.: 48−50 °C (from MeOH). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.64 (quint, $^3J_{H,H}$ = 3, $^3J_{H,H}$ = 7 Hz, 4 H, 2-, 3-*H*), 2.57 (t, $^3J_{H,H}$ = 7 Hz, 4 H, 1-, 4-*H*), 3.74, 3.75, 3.83, 3.85 (s, 12 H, OCH_3), 6.28−6.33 (m, 3 H, 2′′-, 4′′-, 6′′-H), 6.68−6.78 (m, 3 H, 2′-, 5′-, 6′-H) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 30.6 (C-2), 31.1 (C-3), 35.2, 36.0 (C-1, C-4), 55.0, 55.1, 55.7, 55.8 (OCH_3), 97.5 (C-4′′), 106.4 (C-2′′, C-6′′), 111.2, 111.8 (C-2′, C-5′), 120.1 (C-6′), 135.1 (C-1′), 144.9 (C-1′′), 147.0, 148.7 (C-3′, C-4′), 160.6, 160.8 (C-3′′, C-5′′) ppm. MS (EI, 70 eV): *m/z* (%) = 330.1 (100) $[M]^+$, 151 (70) $[veratryl]^+$. $C_{20}H_{26}O_4$ (330.1): calcd. C 72.70, H 7.93; found C 72.30, H 7.77.

1,2-Dimethoxy-4-[4-(2,5-dimethoxyphenyl)butyl]benzene (4d): Colorless oil (3.05 g, 77%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.73−1.84 (m, 4 H, 2-, 3-*H*), 2.72, 2.74 (tt, $^3J_{H,H}$ = 7, $^3J_{H,H}$ = 7 Hz, 4 H, 1-, 4-*H*), 3.87, 3.89 (s, 6 H, 2′′-, 5′′-OCH_3), 3.97, 3.98 (s, 6 H, 3′-, 4′-OCH_3), 6.79−6.91 (m, 6 H, $H_{arom.}$) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 29.4 (C-4), 30.0 (C-2), 31.3 (C-3), 35.3 (C-1), 55.5, 55.6, 55.7, 55.8 (OCH_3), 110.6 (C-4′′), 111.2, 111.3, 111.9, 114.7 (C-2′, C-5′, C-3′′, C-6′′), 120.2 (C-6′), 132.3 (C-1′′), 135.4 (C-1′), 147.0, 148.8 (C-3′, C-4′), 151.7, 153.4 (C-2′′, C-5′′) ppm. MS (EI, 70 eV): *m/z* (%) = 330.1 (100) $[M]^+$, 151.1 (64) $[veratryl]^+$. $C_{20}H_{26}O_4$ (330.1): calcd. C 72.70, H 7.93; found C 72.47, H 7.99.

5-[4-(3,4-Dimethoxyphenyl)butyl]benzo[1,3]dioxole (4e): Colorless crystals (3.36 g, 89%). M.p. 64 °C (from EtOH). ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.59−1.64 (m, 4 H, 2-, 3-*H*), 2.52−2.58 (m, 4 H, 1-, 4-*H*), 3.83, 3.85 (s, 6 H, OCH_3), 5.89 (s, 2 H, $O-CH_2-O$), 6.59−6.79 (m, 6 H, $H_{arom.}$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 31.0 (C-4), 31.2 (C-2), 35.3 (C-3), 35.4 (C-1), 55.8, 55.9 (OCH_3), 100.6 (O-CH_2-O), 108.0, 108.8 (C-2′′, C-5′′), 111.3, 111.8 (C-2′, C-5′), 120.2, 121.0 (C-6′, C-6′′), 135.2 (C-1′′), 136.4 (C-1′), 145.5, 147.1 (C-3′, C-4′), 148.5, 148.8 (C-2′′, C-3′′) ppm. MS (EI, 70 eV): *m/z* (%) = 314.2 (100) $[M]^+$, 151.1 (99) $[veratryl]^+$, 135.1 (48) $[O-CH_2-O-C_6H_3-CH_2]^+$. $C_{19}H_{22}O_4$ (314.2): calcd. C 72.59, H 7.05; found C 72.63, H 7.19.

1,2-Dimethoxy-4-[4-(2,3-dimethoxyphenyl)butyl]benzene (4f): Colorless oil (3.29 g, 83%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.66, 1.68 (tt, $^3J_{H,H}$ = 5, $^3J_{H,H}$ = 5 Hz, 4 H, 2-, 3-*H*), 2.61 (t, $^3J_{H,H}$ = 7 Hz, 2 H, 1-*H*), 2.68 (t, $^3J_{H,H}$ = 7 Hz, 2 H, 4-*H*), 3.82, 3.85, 3.86, 3.88 (s, 12 H, OCH_3), 6.72−6.80 (m, 5 H, 2′-, 5′-, 6′-, 5′′-, 6′′-H), 6.96−7.00 (m, 1 H, 4′′-H) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 29.6 (C-4), 30.2 (C-2), 31.4 (C-3), 35.3 (C-1), 55.6, 55.7, 55.8, 55.9 (OCH_3), 110.1 (C-4′′), 111.3, 111.9 (C-2′, C-5′), 120.2 (C-6′), 121.8, 123.6 (C-5′′, C-6′′), 135.3 (C-1′′), 136.3 (C-1′), 147.0, 147.1 (C-3′, C-4′), 148.8, 152.7 (C-2′′, C-3′′) ppm. MS (EI, 70 eV): *m/z* (%) = 330.2 (100) $[M]^+$, 151.1 (71) $[veratryl]^+$. $C_{20}H_{26}O_4$ (330.1): calcd. C 72.70, H 7.93; found C 72.53, H 8.19.

[4-(3,4-Dimethoxyphenyl)butyl]-2,3,4-trimethoxybenzene (4g): Colorless oil (3.76 g, 87%). ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.57−1.69 (m, 4 H, 2-, 3-*H*), 2.55−2.61 (m, 4 H, 1-, 4-*H*), 3.83, 3.84, 3.85, 3.86, 3.88 (s, 15 H, OCH_3), 6.60 (s, 1 H, 4′-H), 6.69−6.83 (m, 2 H, $H_{arom.}$), 6.76−6.81 (m, 2 H, $H_{arom.}$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 29.1 (C-1), 29.5 (C-3), 30.5 (C-2), 35.4 (C-4), 55.8, 55.9, 56.0, 60.7, 60.9 (OCH_3), 107.3 (C-5′), 111.4, 112.0 (C-2′′, C-5′′), 120.3 (C-1′), 123.7 (C-6′, C-6′′), 135.5 (C-1′′), 142.4 (C-3′), 151.9 (C-2′, C-4′, C-3′′, C-4′′) ppm. MS (EI, 70 eV): *m/z* (%) = 360.2 (100) $[M]^+$, 181.1 (90) $[(OCH_3)_3C_6H_2CH_2]^+$, 151.1 (99) $[veratryl]^+$. $C_{21}H_{28}O_5$ (360.2): calcd. C 69.98, H 7.83; found C 69.82, H 8.17.

General Procedure for the Oxidative Coupling Reaction: A solution of substrates **4a−g** (5 mmol) in dry CH_2Cl_2 (20 mL) was placed in a well-dried flask. After the temperature had been adjusted to 0 °C, $MoCl_5$ (10.5 mmol) and the corresponding additive (10.5 mmol) were added at once. The reaction mixture was stirred for a period of 30−60 min and then it was quenched with saturated aqueous $NaHCO_3$ (50 mL). The mixture was extracted with EtOAc (3 × 100 mL). The combined organic fractions were washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), and then concentrated to provided a crude product that was purified either by

column chromatography (SiO_2; cyclohexane/ethyl acetate; **5a**, **5e**, **5f**) or by recrystallization (**5g**). For systematic numbering of the carbon atoms see Scheme 3.

2,3-Dimethoxy-5,6,7,8-tetrahydrobenzo[3,4]cycloocta[1,2-*f*][1,3]-benzodioxole (5e): Colorless oil (0.60 g, 38%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.45 (t, $^3J_{H,H}$ = 9 Hz, 2 H, 8-*H*), 1.99−2.18 (m, 4 H, 6-, 7-*H*), 2.57−2.67 (m, 2 H, 5-*H*), 3.87, 3.92 (s, 6 H, OCH_3), 5.94, 5.95 (s, 2 H, CH_2), 6.71, 6.72, 6.73, 6.74 (s, 4 H, $H_{arom.}$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 29.2, 29.3 (C-5, C-8), 32.4, 32.4 (C-6, C-7), 55.9, 56.0 (OCH_3), 100.8 (O-CH_2-O), 109.0, 109.1 (C-1, C-12), 112.2, 112.5 (C-4, C-9), 132.5, 135.5 (C-12a, C-12b), 135.0, 136.3 (C-4a, C-8a), 145.3, 146.7, 147.0, 148.5 (C-2, C-3, C-9, C-10) ppm. MS (EI, 70 eV): *m*/*z* (%) = 312.2 (100) $[M]^+$. HRMS: *m*/*z* calcd. for $C_{21}H_{26}O_5$ 312.1362; found 312.1343.

2,3,9,10-Tetramethoxy-5,6,7,8-tetrahydrodibenzo[*a*,*c*]cyclooctene (5f): Colorless crystals (0.67 g, 41%). M.p. 133−134 °C (from MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.47 (t, $^3J_{H,H}$ = 9 Hz, 2 H, 5-, 8-*H*), 1.84 (t, $^3J_{H,H}$ = 12 Hz, 1 H, 6-*H*), 1.99−2.14 (m, 3 H, 6-, 7-*H*), 2.63 (dd, $^3J_{H,H}$ = 8, $^3J_{H,H}$ = 13 Hz, 1 H, 5-*H*), 3.08 (dd, $^3J_{H,H}$ = 8, $^3J_{H,H}$ = 13 Hz, 1 H, 8-*H*), 3.87, 3.89, 3.91, 3.92 (s, 12 H, OCH_3), 6.74, 6.76 (s, 2 H, 1-, 4-*H*), 6.83, 6.97 (d, $^3J_{H,H}$ = 9 Hz, 2 H, 11-, 12-*H*) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 25.8 (C-8), 28.5 (C-5), 29.4 (C-6), 32.6 (C-7), 55.7, 55.9, 56.0 (C-2-, C-3-, C-10-OCH_3), 60.4 (C-9-OCH_3), 109.5 (C-11), 112.2, 112.4 (C-1, C-4), 124.0 (C-12), 132.4 (C-8a), 134.4 (C-12a), 135.2 (C-12b), 137.0 (C-4a), 146.4, 146.6 (C-2, C-3), 148.4 (C-10), 151.9 (C-9) ppm. ^{1}D NOE (360 MHz, $CDCl_3$): Irradiation at δ = 1.47 (5-H) ppm, NOE signal at δ = 1.99−2.14 (6-H), 6.76 (4-H) ppm; irradiation at δ = 1.47 (8-H) ppm, NOE signal at δ = 3.89 (C-9-OCH_3) ppm; irradiation at δ = 1.84 (6-H) ppm, NOE signal at δ = 3.08 (8-H) ppm; irradiation at δ = 1.99−2.14 (6-H) ppm, NOE signal at δ = 1.47 (5-H), 2.63 (5-H) ppm; irradiation at δ = 1.99−2.14 (7-H) ppm, NOE signal at δ = 3.89 (C-9-OCH_3) ppm; irradiation at δ = 3.08 (8-H) ppm, NOE signal at δ = 1.84 (6-H), 3.89 (C-9-OCH_3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 328.2 (100) $[M]^+$. $C_{20}H_{24}O_4$ (328.2): calcd. C 73.15, H 7.37; found C 72.78, H 7.41.

2,3,9,10,11-Pentamethoxy-5,6,7,8-tetrahydrodibenzo[*a*,*c*]cyclooctene (5g): Colorless crystals (1.11 g, 62%). M.p. 156−157 °C (from MeOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.37−1.53 (m, 2 H, 5-, 8-*H*), 1.77 (dd, $^3J_{H,H}$ = 11, $^3J_{H,H}$ = 13 Hz, 1 H, 6-*H*), 1.97−2.04 (m, 2 H, 6-, 7-*H*), 2.15 (dd, $^3J_{H,H}$ = 11, $^3J_{H,H}$ = 13 Hz, 1 H, 7-*H*), 2.64 (dd, $^3J_{H,H}$ = 8, $^3J_{H,H}$ = 13 Hz, 1 H, 5-*H*), 2.98 (dd, $^3J_{H,H}$ = 8, $^3J_{H,H}$ = 13 Hz, 1 H, 8-*H*), 3.87, 3.89 (s, 6 H, C-2-, C-3-OCH_3), 3.92, 3.93, 3.94 (s, 9 H, C-9-, C-10-, C-11-OCH_3), 6.58 (s, 1 H, 12-*H*), 6.75, 6.76 (s, 2 H, 1-, 4-*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 25.4 (C-8), 28.4 (C-5), 29.2 (C-6), 32.5 (C-7), 55.9, 56.0 (C-2-, C-3-OCH_3), 60.6, 60.7, 60.8 (C-9-, C-10-, C-11-OCH_3), 107.9 (C-12), 112.0, 112.1 (C-1, C-4), 129.0 (C-8a), 132.4 (C-12b), 135.1, 136.0 (C-4a, C-12a), 141.4 (C-10), 146.5, 148.6 (C-2, C-3), 150.8 (C-11), 151.1 (C-9) ppm. MS (EI, 70 eV): *m*/*z* (%) = 358.2 (100) $[M]^+$, 343.2 (14) $[M - CH_3]^+$. $C_{21}H_{26}O_5$ (358.2): calcd. C 70.37, H 7.31; found C 69.98, H 7.31.

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[23] X-ray crystal structure analysis of **5g**: Empirical formula $C_{21}H_{26}O_5$, M = 358.42, colorless crystal 0.20 × 0.20 × 0.15 mm, a = 17.975(1), b = 6.902(1), c = 30.994(1) Å, β = 103.04(1)°, V = 3746.1(6) Å^3, $\rho_{calcd.}$ = 1.271 g cm^{-3}, μ = 0.90 cm^{-1}, empirical absorption correction (0.982 ≤ T ≤ 0.987), Z = 8, monoclinic, space group $C2/c$ (no. 15), λ = 0.7103 Å, T = 198 K, ω and scans, 14391 reflections collected (±h, ±k, ±l), [(sinθ)/λ] = 0.66 Å^{-1}, 4458 independent (R_{int} = 0.054) and 2627 observed reflections [$I \geq 2\sigma(I)$], 240 refined parameters, R = 0.051, $wR2$ = 0.102, max. residual electron density 0.23 (−0.2) e·Å^{-3}, hydrogen atoms calculated and refined as riding atoms. X-ray crystal structure analysis of **5f**: Empirical formula $C_{20}H_{24}O_4$, M = 328.39, colorless crystal 0.30 × 0.25 × 0.10 mm, a = 8.986(1), b = 9.183(1), c = 10.853(1) Å, α = 79.12(1), β = 74.66(1), γ = 84.62(1)°, V = 847.2(2) Å^3, $\rho_{calcd.}$ = 1.287 g cm^{-3}, μ = 0.89 cm^{-1}, empirical absorption correction (0.974 ≤ T ≤ 0.991), Z = 2, triclinic, space group $P\bar{1}$ (no. 2), λ = 0.71073 Å, T = 198 K, ω and scans, 9075 reflections collected (±h, ±k, ±l), [(sinθ)/λ] = 0.66 Å^{-1}, 3993 independent (R_{int} = 0.041) and 2926 observed reflections [$I \geq 2\sigma(I)$], 221 refined parameters, R = 0.047, wR_2 = 0.113, max. residual electron density 0.23 (−0.28) e·Å^{-3}, hydrogen atoms calculated and refined as riding atoms. Data sets were collected using a Nonius KappaCCD diffractometer, equipped with a Nonius FR591 rotating anode generator. Programs used: data collection COLLECT (Nonius B. V., **1998**), data reduction Denzo-SMN (see: Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, *276*, 307−326), absorption correction SORTAV (R. H. Bless-

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