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Cu(I)-catalyzed intramolecular cyclizations of substituted 2-iodobenzophenones under thermal and microwave conditions

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ABSTRACT

Novel, easy-to-perform and practical intramolecular Cu(I)-catalyzed cyclizations of substituted 2-iodobenzophenones under thermal and microwave conditions are reported. The isolated cyclized products under microwave conditions are obtained with high yields and with short reaction times offering a valuable and reliable alternative to other protocols for the synthesis of fluorene analogues.

1. Introduction

Fluoren-9-one and its derivatives are currently attracting widespread interest owing to their utilization in several diverse fields. For instance, due to their attractive luminescent properties, fluorenone-based materials are employed as organic and polymer light-emitting diodes, bulk heterojunction solar cells and photochemical sensitizers.[1] In addition, fluoren-9-ones have pharmaceutical applications[2–4] and are key building blocks of many natural products.[5] The synthesis of substituted fluorenones is therefore an important topic for synthetic chemists.

Moreover, there are biologically active fluoren-9-ones, such as dendroflorin, denchrysan A and 1,4,5-trihydroxy-7-methoxyfluoren-9-one, which have been isolated from plants. These fluorene analogues are used as health-foods.[6] The three compounds were evaluated in vitro for their inhibitory effects against the growth of the human lung adenocarcinoma A549 and the human stomach cancer SGC-7901. Additionally, tilorone hydrochloride with a fluorene skeleton has been recognized to be an orally active interferon stimulating agent.[7] It is also used as an antiviral drug for the treatment of a number of viral diseases, diarrhea, herpes and hepatitis.[8] The telomerase enzyme is an essential factor in tumorigenesis.[9] So, there is a great interest in the inhibition of telomerase as a new anticancer strategy.[10] During the last decade hipposudoric and norhipposudoric acids, two natural dyes with a fluorene framework, have been isolated from the red sweat of *Hippopotamus amphibius* by Hashimoto, Nakata et al.[2b–d] It has been demonstrated that hipposudoric acid exhibits antibiotic activity while the two natural dyes may act as sunscreens.

To conclude, fluorenes and related compounds have a broad spectrum biological activities. Various methods have been developed to synthesize these compounds. For example, one approach involves the intramolecular Friedel–Crafts acylation of biaryls.[11] Using an alternative directed metallation methodologies, Snieckus and co-workers have prepared a range of substituted fluoren-9-ones.[12] Langer et al., have recently reported the synthesis of fluoren-9-one using a [3+3] cyclization/Suzuki cross-coupling/Friedel–Crafts acylation route starting from a 1,3-bis-silyl enol ether and a silyloxypentenone.[13]

Over the past years notable progress has been achieved in the field of Cu(I)-catalyzed C-, N-, O- and S-arylations.[14] Depending on the substrate ratio and the reaction conditions, 4*H*-chromenes or naphthalenes were synthesized via Cu(I)-catalyzed domino reactions.[15]

2. Results and discussion

We report a new and simple intramolecular Cu(I)-catalyzed cyclization of substituted 2-iodobenzophenones to methoxy-substituted fluoren-9-ones under both thermal and microwave conditions. The deprotection of the methoxy-substituents was performed using boron tribromide[16] to liberate the hydroxyfluoren-9-one derivative. For this strategy, the substituted 2-aminobenzophenones **1a**–**f** were prepared

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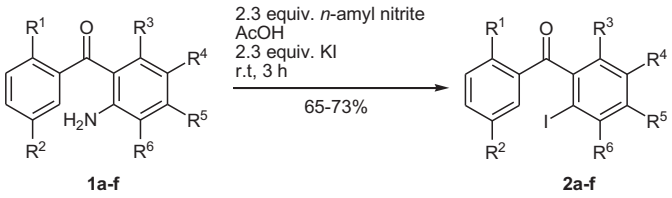
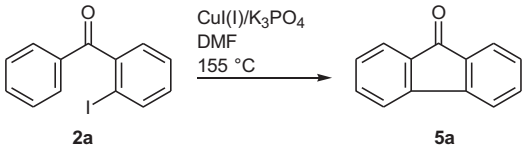
by the reduction of the nitro group of the substituted 2-nitrobenzophenones as starting materials. The reduction process was achieved according to the procedure of Stephenson et al.[17] The substituted 2-iodobenzophenones **2a**–**f** were prepared with yields ranging from 65 to 73% via the protocol of Coffen et al.[18] (Scheme 1).



Scheme 1. Preparation of the starting materials **2a**–**f**.

Unfortunately, we could not prepare (2,5-dimethoxyphenyl)(2′-iodophenyl)methanone (**2c**) by the procedure of Coffen et al.[18] Therefore, **2c** was synthesized by Friedel–Crafts acylation of 1,4-dimethoxybenzene (**3**) with 2-iodobenzoic acid (**4**) with 98% yield according to the method described by Qabaja and Jones.[19,20]

With the substituted 2-iodobenzophenones **2a**–**f** in hand we were ready to investigate their Cu(I)-catalyzed cyclizations. In order to optimize the reaction, the Cu(I)-catalyzed cyclization of the unsubstituted 2-iodobenzophenone (**2a**) was studied under different thermal reaction conditions (Scheme 2).



Scheme 2. Reaction of **2a** with Cu(I) in DMF.

Initially, 2-iodobenzophenone (**2a**) and Cu(I) were reacted under different reaction conditions (Scheme 2, Table 1). We started with the cyclization of **2a**, which was reacted using different amounts of Cu(I). The formation of **5a** was not observed if the reaction time is 20 h using 4.0 mol % Cu(I). If additional Cu(I) was employed, we observed a gradual increasing in the yield of the product and the starting material was consumed only partially (Table 1, entries 2–6). Thus mixtures of the substrate **2a** and fluoren-9-one (**5a**) were isolated after column chromatography. The highest yield of **5a** was observed when **2a** was treated with 15.0–19.0 mol % Cu(I), 3.0 equiv K_3PO_4 and DMF as a solvent for 24 h at 155 °C (Table 1, entries 7–9). The yield of **5a**, however, amounted to only 47%.

Table 1
The influence of the amount of Cu(I) on the conversion of **2a** into **5a** with 3.0 equiv K_3PO_4

Entry	CuI (mol %)	Time (h)	Yield **5a** (%)[a]
1	4.0	20	—
2	6.0	24	15
3	8.0	24	22
4	10.0	24	31
5	12.0	24	36
6	14.0	24	41
7	15.0	24	47
8	16.0	24	47
9	18.0	24	47
10	19.0	24	46

[a] Isolated yields.

After that, we studied the conversion of **2a** into **5a** under different reaction times (Scheme 2, Table 2). We have found that, no reaction on using 6.0 mol % Cu(I) within the first 20 h. If the reaction was performed with 6.0 mol % Cu(I) for 35 h, the yield of **5a** was 37% (Table 2, entry 2). We observed the yield of the product was 55% on using 10.0 mol % Cu(I) for 42 h (Table 2, entry 4). On carrying out the reaction using 12.0 mol % and 14.0 mol % Cu(I) for 48 h, **5a** was isolated in 78% and 85% yield, respectively (Table 2, entries 5, 6). The best yield of **5a** was 89% when the reaction was run for 48 h using 15.0–16.0 mol % Cu(I), (Table 2, entries 7, 8).

Table 2
The influence of the reaction time on the cyclization of **2a** into **5a** with 3.0 equiv K_3PO_4

Entry	CuI (mol %)	Time (h)	Yield (%)[a] **5a**
1	6.0	24	15
2	6.0	35	37
3	8.0	40	49
4	10.0	42	55
5	12.0	48	78
6	14.0	48	85
7	15.0	48	89
8	16.0	48	89

[a] Isolated yields.

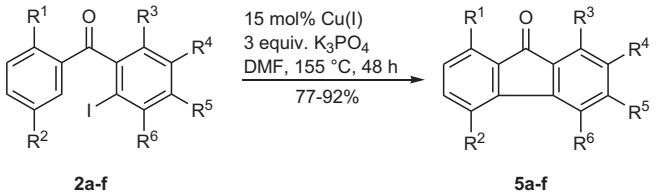
Further experiments revealed that the influence of the amount of the base on the formation of **5a** was studied (Scheme 2, Table 3). With 0.5 equiv K_3PO_4 it was possible to separate the product **5a** with yield 78% (Table 3, entry 1). It was found that the yield slightly differs by increasing the amount of the base (Table 3, entries 1–4). The highest yield (89%) of **5a** was observed when **2a** was treated with 3.0 equiv K_3PO_4 and 15.0 mol % Cu(I) for 48 h.

Table 3
The influence of the amount of K_3PO_4 on the model reaction

Entry	CuI (mol %)	K_3PO_4 (equiv)	Time (h)	Yield (%)[a] **5a**
1	15.0	0.5	48	78
2	15.0	1.0	48	83
3	15.0	2.0	48	85
4	15.0	3.0	48	89
5	15.0	3.5	48	89
6	15.0	4.0	48	89

[a] Isolated yields.

Optimization of the reaction of 2-iodobenzophenone (**2a**) with Cu(I) resulted in a reliable and simple procedure for the synthesis of the methoxy-substituted fluoren-9-ones with high yields and with very easy workup. For evaluation the scope of the cyclization of substituted 2-iodobenzophenones **2a**–**f** a series of methoxy-substituents at different positions of the aromatic ring was tested. The cyclization was carried out with a number of mono-, di- tri- and tetrasubstituted 2-iodobenzophenones using the optimized protocol (Scheme 3, Table 4). The highest yields (92% and 91%) of the trisubstituted **5d** and the tetrasubstituted **5e** were isolated when the reaction was running under thermal conditions for 48 h (Table 4, entries 4, 5). Yields of **5a**–**f** were in the range 77–92%.



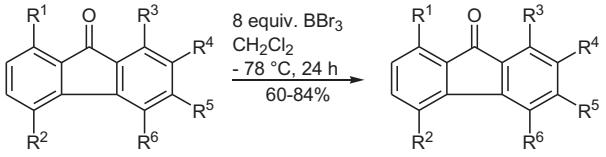
Scheme 3. Reaction of substituted 2-iodobenzophenones **2a**–**f** with Cu(I) in DMF.

Table 4
Cu(I)-catalyzed cyclizations of substituted 2-iodobenzophenones **2a**–**f** under thermal conditions

Entry	2	R^1	R^2	R^3	R^4	R^5	R^6	**5a**–**f** (%)[a]
1	**a**	H	H	H	H	H	H	89
2	**b**	OMe	H	H	H	H	H	77
3	**c**	OMe	OMe	H	H	H	H	87
4	**d**	OMe	H	H	OMe	OMe	H	92
5	**e**	OMe	OMe	H	OMe	OMe	H	91
6	**f**	OMe	OMe	OMe	H	H	OMe	84

[a] Isolated yields.

After the successful Cu(I)-catalyzed cyclizations of the substituted 2-iodobenzophenones **2a**–**f** into the corresponding methoxy-substituted fluoren-9-ones **5a**–**f**, the methoxy groups in the cyclized products **5b**–**f** were transformed into free hydroxyl groups. A standard method for the cleavage of methoxy groups is according to the protocol of Bergeron and Bharti.[16] After purification the hydroxy-sustituted fluoren-9-ones **6b**–**f** were isolated with yields ranging from 60 to 84% (Scheme 4, Table 5, entries 1–5). Both compounds **6e** and **6f** were obtained with 80% and 83%, respectively (Table 5, entries 4, 5), while **6d** was obtained with 84% yield (Table 5, entry 3).



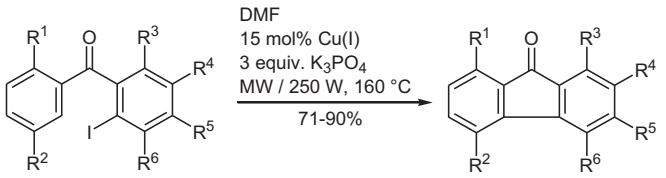
Scheme 4. Deprotection of the compounds **5b**–**f** using BBr_3.[16]

Table 5
Synthesis of hydroxy-substituted fluoren-9-ones **6b**–**f**

Entry	5	R^1	R^2	R^3	R^4	R^5	R^6	**6b**–**f** (%)[a]
1	**b**	OMe	H	H	H	H	H	60
2	**c**	OMe	OMe	H	H	H	H	68
3	**d**	OMe	H	H	OMe	OMe	H	84
4	**e**	OMe	OMe	H	OMe	OMe	H	83
5	**f**	OMe	OMe	OMe	H	H	OMe	80

[a] Isolated yields.

In recent years microwave (MW) irradiation has become a broadly used tool in organic synthesis. Under MW heating, chemical reactions usually proceed faster, with shorter reaction times, in higher yields and can give purer products with fewer side products.[21] As a result of the long reaction times (48 h) under thermal conditions, the cyclizations of **2a**–**f** were repeated under MW conditions (Scheme 5, Table 6). Microwave assisted reactions were run at (250 W, 160 °C). To start with, the unsubstituted 2-iodobenzophenone (**2a**) was reacted with 15.0 mol % Cu(I) and 3.0 equiv K_3PO_4 for 20 and 30 min to afford the cyclized product **5a** with 88 and 83% yields (Table 6, entries 1, 2), respectively. It turned out that indeed the reaction times of the intramolecular cyclization of **2a**–**f** under MW conditions could be shortened. By analysis of the data in (Table 6) we have found that the substituents affect on the yields and the rate of the reactions. For example, the monosubstituted fluoren-9-one **5a** was prepared with 88% through reaction rate of 20 min. On increasing the reaction time to 30 min, the yield slightly decreased to 83% (Table 6, entries 1, 2). On the other hand, the disubstituted fluoren-9-one **5b** could be synthesized in 79% yield with a reaction time of 25 min. But by increasing the reaction time to 30 min the yield increases (84%). Another example, the tetrasubstituted fluoren-9-one **5e** was obtained with 89% and



Scheme 5. Reaction of substituted 2-iodobenzophenones **2a**–**f** with Cu(I) in DMF under microwave conditions.

Table 6
Cu(I)-catalyzed cyclizations of substituted 2-iodobenzophenones **2a**–**f** to substituted fluoren-9-ones **5a**–**f** under microwave conditions

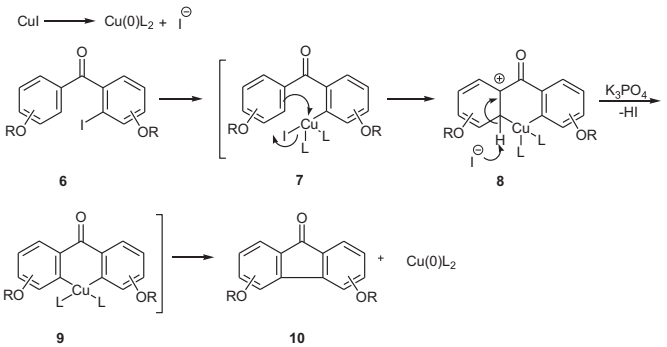
Entry	2	R^1	R^2	R^3	R^4	R^5	R^6	Time (min)	**5a**–**f**	Yield **5a**–**f** (%)[a]
1	**a**	H	H	H	H	H	H	20	**a**	88
2	**a**	H	H	H	H	H	H	30	**a**	83
3	**b**	OMe	H	H	H	H	H	25	**b**	79
4	**b**	OMe	H	H	H	H	H	30	**b**	84
5	**c**	OMe	OMe	H	H	H	H	20	**c**	71
6	**c**	OMe	OMe	H	H	H	H	30	**c**	87
7	**c**	OMe	OMe	H	H	H	H	35	**c**	80
8	**d**	OMe	H	H	OMe	OMe	H	35	**d**	82
9	**d**	OMe	H	H	OMe	OMe	H	40	**d**	85
10	**e**	OMe	OMe	H	OMe	OMe	H	55	**e**	89
11	**e**	OMe	OMe	H	OMe	OMe	H	60	**e**	90
12	**f**	OMe	OMe	OMe	H	H	OMe	55	**f**	75
13	**f**	OMe	OMe	OMe	H	H	OMe	60	**f**	72

[a] Isolated yields.

90% yields within reaction times 55 and 60 min. However, the tetrasubstituted fluoren-9-one **5f** could be obtained with 75% and 72% yields through the same reaction time. The yield decreasing of compound **5f** may due to the crowding effect of the methoxy-substituents. The reaction time required to cyclize **2f** into **5f** could be reduced from 48 h under thermal conditions to 55 min (Table 6, entry 12). The best yield (90%) of **5e** was separated when the reaction was running for 60 min (Table 6, entry 11). All cyclizations proceeded within 20–60 min with formation of methoxy-substituted fluoren-9-ones **5a**–**f** in yields of 71–90%.

Generally, the yields under MW conditions (Table 6) (71–90%) are approximately in the same range in comparison with the conventional thermal conditions (Table 4) (77–92%) but much shorter reaction times.

A proposal for the reaction mechanism of the intramolecular copper-catalyzed cyclization of 2-iodoenzophenones **6** to substituted fluorenones **9** is shown in Scheme 6.[22] It is assumed that the reaction starts with formation of coordinative Cu(0) species. The second step of the sequence is the oxidative addition of the copper complex into the C–I bond of **6** generating the intermediate **7**, which undergoes



Scheme 6. Proposal for the reaction mechanism of substituted 2-iodobenzophenones **6** with K_3PO_4 and Cu(I) in DMF.

Freidel–Crafts type addition to give a cationic intermediate **8**. Subsequently, elimination of HI results in the copper complex **9**. Reductive elimination of **9** gives fluorenones **10** with regeneration of the Cu(0) catalyst.

3. Conclusion

In summary, a valuable and simple intramolecular Cu(I)-catalyzed cyclization of substituted 2-iodobenzophenones to substituted fluoren-9-ones under thermal and microwave conditions is reported. Achievement the reaction under MW conditions showed considerably reduction reaction times as well as very good yields.

4. Experimental section

4.1. General methods

The structures of the compounds described in this paper have been elucidated unambiguously by NMR-spectroscopic methods including HH COSY, HSQC and HMBC experiments. All starting materials were purchased from commercial suppliers (Sigma–Aldrich Chemical Co. and Lancaster Organics) and used without further purification unless otherwise indicated. All reactions were carried out under an argon atmosphere in oven-dried glassware with magnetic stirring. Temperatures are reported as inner temperatures. Solvents used in extraction and purification were distilled prior to use. Thin-layer chromatography (TLC) was performed on Alugram SIL G/UV 254 (Macherey and Nagel). Compounds were visualized with UV light (λ=254 nm) and/or by immersion in an ethanolic vanillin solution followed by heating. Products were purified by flash chromatography on silica gel 60 M, 230–400 mesh (Macherey & Nagel). Melting points were determined on a Büchi melting point apparatus B-545 with open capillary tubes and are uncorrected. IR spectra were measured on a Perkin–Elmer Spectrum One (FT-IR-spectrometer). UV/VIS spectra were recorded with a Varian Cary 50. ^{1}H (^{13}C) NMR spectra were recorded at 300 (75) MHz on a Varian Inova Spectrometer using $CDCl_3$ or DMSO as a solvent. The ^{1}H and ^{13}C chemical shifts were referenced to residual solvent signals at δ_H/C 7.26/77.00 ($CDCl_3$) and at δ_H/C 2.49/39.50 (DMSO) relative to TMS as internal standards. HSQC-, HMBC- and COSY-spectra were recorded on a Varian Inova at 300 MHz. Coupling constants *J* [Hertz] were directly taken from the spectra and are averaged. Low-resolution electron impact mass spectra (MS) and exact mass electron impact mass spectra (HRMS) were obtained at 70 eV on a Finnigan MAT 90 spectrometer. Elemental analyses were carried out at Göttingen University, Germany.

4.2. General procedure for synthesis of methanones 2a–f

n-Amyl nitrite (1.46 mL, 10.7 mmol) was added dropwise to a solution of the (2-aminophenyl)(phenyl)methanones **1a–f** (4.73 mmol) in acetic acid (50 mL) and the resulting reaction mixture was stirred for 1 h at 0 °C. A solution of potassium iodide (1.78 g, 10.7 mmol) in water (10 mL) was added and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was poured into ice-cold water (300 mL), neutralized with 10% NaOH solution (80 mL) and extracted with dichloromethane (4×80 mL). The combined organic layers were washed with water (2×50 mL) and brine (2×50 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2; cyclohexane/EtOAc).

*4.2.1. 2-Iodobenzophenone (**2a**).*[23] According to the general procedure 2-aminobenzophenone (**1a**) (1.50 g, 4.73 mmol) was treated with *n*-amyl nitrite (1.46 mL, 10.7 mmol) and potassium iodide (1.78 g, 10.7 mmol). After column chromatography (SiO_2; cyclohexane/EtOAc=32:1) the title compound **2a** (1.32 g, 73%) was isolated as a pale yellow liquid; R_f (cyclohexane/EtOAc=20:1) 0.40; ν_{max} (ATR) 3065, 2933, 2821, 1652, 1624, 1597, 1473, 789, 773 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.93 (1H, d, ^{3}J 7.8 Hz, 3-H), 7.81 (2H, d, ^{3}J 7.8 Hz, 2′-H and 6′-H), 7.61 (1H, t, ^{3}J 7.8 Hz, 4′-H), 7.48 (1H, d, ^{3}J 7.8 Hz, 3′-H and 5′-H), 7.44 (1H, dd, ^{3}J 7.8 Hz, ^{4}J 1.6, 4-H), 7.30 (1H, dd, ^{3}J 7.8 Hz, ^{4}J 1.6, 6-H), 7.19 (1H, dt, ^{3}J 7.8 Hz, ^{4}J 1.6, 5-H); δ_C (300 MHz, $CDCl_3$) 197.5 (C=O), 144.6 (C-1′), 140.0 (C-3), 136.0 (C-1), 134.0 (C-5), 131.4 (C-4), 130.8 (C-3′ or C-5′), 128.9 (C-2′ or C-6′), 128.8 (C-6), 128.1 (C-4′), 92.5 (C-2).

*4.2.2. (2-Iodophenyl)(2′-methoxyphenyl)methanone (**2b**).* According to the general procedure (2-aminophenyl)(2′-methoxyphenyl) methanone (**1b**) (1.07 g, 4.73 mmol) was treated with *n*-amyl nitrite (1.46 mL, 10.7 mmol) and potassium iodide (1.26 g, 10.7 mmol). After column chromatography (SiO_2; cyclohexane/EtOAc=8:1), the title compound **2b** (1.10 g, 69%) was isolated as pale yellow crystals; mp 120–121 °C; R_f (cyclohexane/EtOAc=4:1) 0.45; ν_{max} (ATR) 3058, 2927, 2830, 1664, 1638, 1595, 1481, 1239 cm^{-1}; λ_{max} (MeCN) (log ε) 333 (3.08), 285 (2.88), 260 (3.43), 237 nm; δ_H (300 MHz, $CDCl_3$) 7.90 (1H, d, ^{3}J 7.9 Hz, 6-H), 7.64 (1H, dd, ^{3}J 7.9 Hz, ^{4}J 1.6 Hz, 3-H), 7.52 (1H, dt, ^{3}J 7.9 Hz, ^{4}J 1.6 Hz, 4-H), 7.37 (1H, t, ^{3}J 7.6 Hz, 5′-H), 7.30 (1H, dd, ^{3}J 7.6 Hz, 6′-H), 7.11 (1H, dt, ^{3}J 7.9 Hz, ^{4}J 1.6 Hz, 5-H), 7.03 (1H, t, ^{3}J 7.6 Hz, 4′-H), 6.94 (1H, d, ^{3}J 7.6 Hz, 3′-H), 3.66 (3H, s, 2′-OCH_3); δ_C (300 MHz, $CDCl_3$) 196.8 (C=O), 159.7 (C-2′), 146.1 (C-1), 140.1 (C-3), 134.7 (C-4), 132.3 (C-6), 131.2 (C-5), 129.2 (C-4′), 127.0 (C-1′), 120.9 (C-6′), 118.3 (C-5′), 112.3 (C-3′), 92.3 (C-2), 56.1 (2′-OCH_3); *m*/*z* (EI, 70 eV) 338 (31, M^+), 196 (M^+-CH_3I) (100), 32 (18%); HRMS (EI, 70 eV): M^+, found 337.9830. $C_{14}H_{11}IO_2$ requires 337.9838.

*4.2.3. (2-Iodo-4,5-dimethoxyphenyl)(2′methoxyphenyl)methanone (**2d**).* According to the general procedure (2-amino-4,5-dimeth oxyphenyl)(2′-methoxyphenyl)methanone (**1d**) (1.36 g, 4.73 mmol) was treated with *n*-amyl nitrite (1.46 mL, 10.7 mmol) and potassium iodide (1.78 g, 10.7 mmol). After column chromatography (SiO_2; cyclohexane/EtOAc=4:1), the title compound **2d** (1.35 g, 72%) was isolated as pale yellow crystals; mp 81–82 °C; R_f (cyclohexane/EtOAc=3:1) 0.35; ν_{max} (ATR) 2967, 2830, 1645, 1584, 1488, 1455, 1296 cm^{-1}; λ_{max} (MeCN) (log ε) 317 (3.53), 239 (4.03), 209 (4.24) nm; δ_H (300 MHz, $CDCl_3$) 7.55–7.47 (2H, m, 5′-H and 6′-H), 7.30 (1H, s, 3-H), 7.02 (1H, t, ^{3}J 7.5 Hz, 4′-H), 6.95 (1H, d, ^{3}J 7.5 Hz, 3′-H), 6.94 (1H, s, 6-H), 3.91 (3H, s, 4-OCH_3), 3.80 (3H, s, 5-OCH_3), 3.72 (3H, s, 2′-OCH_3); δ_C (300 MHz, $CDCl_3$) 196.1 (C=O), 159.3 (C-2′), 151.2 (C-4), 149.0 (C-5), 137.4 (C-1), 134.0 (C-5′), 132.0 (C-6′), 127.5 (C-1′), 122.8 (C-3), 120.9 (C-4′), 113.5 (C-6), 112.1 (C-3′), 82.7 (C-2), 56.5 (4-OCH_3), 56.3 (5-OCH_3), 56.1 (2′-OCH_3); *m*/*z* (EI, 70 eV) 398 (100, M^+), 290 (40), 271 (26), 256 (92), 240 (16), 151 (24), 135 (80%); HRMS (EI, 70 eV): M^+, found 398.0012. $C_{16}H_{15}IO_4$ requires 398.0026.

*4.2.4. (2′,5′-Dimethoxyphenyl)(2-iodo-4,5-dimethoxyphenyl)methanone (**2e**).* According to the general procedure (2-amino-4,5-dimethoxyphenyl)(2′,5′-dimethoxyphenyl)methanone (**1e**) (1.50 g, 4.73 mmol) was treated with *n*-amyl nitrite (1.46 mL, 10.7 mmol) and potassium iodide (1.78 g, 10.7 mmol). After column chromatography (SiO_2; cyclohexane/EtOAc=3:1), the title compound **2e** (1.32 g, 65%) was isolated as pale yellow crystals; mp 107–108 °C; [found: C, 47.75; H, 3.84. $C_{17}H_{17}IO_5$ requires C, 47.66; H, 4.00%]; R_f (cyclohexane/EtOAc=2:1) 0.45; ν_{max} (ATR) 2960, 2820, 1661, 1585, 1493, 1461, 1282 cm^{-1}; λ_{max} (MeCN) (log ε) 327 (3.15), 260 (3.34) nm; δ_H (300 MHz, $CDCl_3$) 7.30 (1H, s, 3-H), 7.12 (1H, d, ^{4}J 3.1 Hz, 6′-H), 7.06 (1H, dd, ^{3}J 8.9 Hz, ^{4}J 3.1 Hz, 4′-H), 6.94 (1H, s, 6-H), 6.88 (1H, d, ^{3}J 8.9 Hz, 3′-H), 3.92 (3H, s, 5-OCH_3), 3.81 (3H, s, 4-OCH_3), 3.80 (3H, s, 5′-OCH_3), 3.64 (3H, s, 2′-OCH_3); δ_C (300 MHz, $CDCl_3$) 195.8

(C=O), 153.9 (C-5′), 153.6 (C-2′), 151.2 (C-5), 149.0 (C-4), 137.4 (C-1), 128.0 (C-1′), 122.8 (C-3), 120.3 (C-4′), 115.8 (C-6′), 113.9 (C-3′), 113.5 (C-6), 82.5 (C-2), 56.9 (2′-OCH_3), 56.5 (5-OCH_3), 56.3 (4-OCH_3), 56.2 (5′-OCH_3); *m*/*z* (EI, 70 eV) 428 (100, M^+), 291 (28), 286 (83), 271 (16), 255 (10), 165 (25), 151 (17%).

*4.2.5. (2,5-Dimethoxyphenyl)(2′-iodo-3′,6′-dimethoxyphenyl)methanone (**2f**).* According to the general procedure (2-amino-3,6-dimethoxyphenyl)(2′,5′-dimethoxyphenyl)methanone (**1f**) (1.50 g, 4.73 mmol) was treated with *n*-amyl nitrite (1.46 mL, 10.7 mmol) and potassium iodide (1.78 g, 10.7 mmol). After column chromatography (SiO_2; cyclohexane/EtOAc=3:1), the title compound **2f** (1.34 g, 66%) was isolated as pale yellow crystals; mp 195–196 °C; [found: C, 48.09; H, 3.90. $C_{17}H_{17}IO_5$ requires C, 47.99; H, 4.00%]; R_f (cyclohexane/EtOAc=1:1) 0.60; ν_{max} (ATR) 2918, 2800, 1649, 1496, 1471, 1416, 1283 cm^{-1}; λ_{max} (MeCN) (log ε) 354 (3.09), 260 (3.34), 226 (3.77) nm; δ_H (300 MHz, $CDCl_3$) 7.44 (1H, d, ^4J 3.2 Hz, 6-H), 7.09 (1H, dd, ^3J 8.9 Hz, ^4J 3.2 Hz, 4-H), 6.89 (1H, d, ^3J 8.9 Hz, 3-H), 6.89 (1H, d, ^3J 8.9 Hz, 5′-H), 6.79 (1H, d, ^3J 8.9 Hz, 4′-H), 3.86 (3H, s, 6′-OCH_3), 3.81 (3H, s, 2-OCH_3), 3.68 (3H, s, 3′-OCH_3), 3.59 (3H, s, 5-OCH_3); δ_C (300 MHz, $CDCl_3$) 194.2 (C=O), 155.1 (C-5), 153.8 (C-2), 152.7 (C-6′), 151.1 (C-3′), 139.7 (C-1′), 126.2 (C-1), 122.1 (C-4), 115.6 (C-6), 114.8 (C-5′), 112.2 (C-3), 110.9 (C-4′), 84.7 (C-2′), 57.4 (6′-OCH_3), 57.1 (3′-OCH_3), 57.0 (5-OCH_3), 56.1 (2-OCH_3); *m*/*z* (EI, 70 eV) 428 (100, M^+), 301 (M^+–I) (13), 209 (35), 165 (45%); HRMS (EI, 70 eV): M^+, found 428.0073. $C_{17}H_{17}IO_5$ requires 428.0075.

*4.2.6. (2,5-Dimethoxyphenyl)(2′-iodophenyl)methanone (**2c**).*[14] 1,4-Dimethoxybenzene (**3**) (0.89 g, 6.41 mmol) was treated with trifluoroacetic acid (10 mL, 13.7 mmol), trifluoroacetic anhydride (5 mL, 5.95 mmol) and 2-iodobenzoic acid (**4**) (1.50 g, 6.41 mmol) and the reaction was refluxed for 12 h. After cooling to room temperature crushed ice (100 g) were added, followed by *tert*-butylmethyl ether (100 mL). After phase separation the organic layer was washed with saturated sodium hydrocarbonate solution (25 mL). The combined organic layers were washed with water (1×50 mL) and brine (2×50 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by recrystallization from cyclohexane to obtain the title compound **2c** (2.32 g, 98%) as colourless crystals; mp 79–80 °C; R_f (cyclohexane/EtOAc=3:1) 0.57; ν_{max} (ATR) 2941, 2840, 1656, 1577, 1491, 1467, 1287 cm^{-1}; λ_{max} (MeCN) (log ε) 348 (3.17), 229 (4.09), 207 (4.16) nm; δ_H (300 MHz, $CDCl_3$) 7.89 (1H, d, ^3J 7.6 Hz, 3′-H), 7.37 (1H, dt, ^3J 7.6 Hz, ^4J 1.8 Hz, 4-H), 7.29 (1H, dd, ^3J 7.6 Hz, ^4J 1.8 Hz, 3-H), 7.24 (1H, d, ^4J 1.8 Hz, 6-H), 7.07–7.13 (2H, m, 4′-H and 5′-H), 6.87 (1H, d, ^3J 7.6 Hz, 6′-H), 3.81 (3H, s, 5-OCH_3), 3.56 (3H, s, 2-OCH_3); δ_C (300 MHz, $CDCl_3$) 196.5 (C=O), 154.2 (C-2), 153.9 (C-5), 146.3 (C-1′), 140.0 (C-3′), 131.2 (C-4′), 129.0 (C-3), 128.0 (C-4), 127.3 (C-1), 121.3 (C-5′), 115.6 (C-6), 114.2 (C-6′), 92.1 (C-2′), 56.8 (2-OCH_3), 56.2 (5-OCH_3), *m*/*z* (EI, 70 eV) 368 (100, M^+), 230 (41), 226 (12), 165 (42), 151 (11%).

4.3. General procedure for the Cu(I)-catalyzed synthesis of the methoxy-substituted fluoren-9-ones under thermal conditions 5a–f

A dry microwave glass vial (10 mL) with magnetic stirrer bar was charged with (2-iodophenyl)(phenyl)methanones **2a–f** (1.00 mmol), CuI (0.03 g, 0.15 mmol) and potassium phosphate (0.64 g, 3.00 mmol) under air. The vial was sealed, evacuated and backfilled with argon three times, then freshly distilled dry DMF (6 mL) were added. The reaction mixture was stirred for 48 h at 155 °C until complete consumption of the substrate (TLC control). After cooling to room temperature the reaction mixture was partitioned between 80 mL dichloromethane and 20 mL saturated brine. The aqueous phase was extracted with dichloromethane (3×50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product obtained was purified by flash column chromatography over silica gel.

*4.3.1. Fluoren-9-one (**5a**).*[7] According to the general procedure 2-iodobenzophenone (**2a**) (0.31 g, 1.00 mmol), CuI (0.03 g, 0.15 mmol) and K_3PO_4 (0.64 g, 3.00 mmol) were reacted in DMF (6 mL) in a sealed vial in an argon atmosphere at 155 °C for 48 h. After column chromatography over silica gel (cyclohexane/EtOAc=3:1), the title compound **5a** (0.16 g, 89%) was isolated as yellow chips; mp 83–84 °C; R_f (cyclohexane/EtOAc=2:1) 0.42; ν_{max} (ATR) 3053, 2944, 2837, 1663, 1591, 1585 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.62 (2H, d, ^3J 7.3 Hz, 1-H, 8-H), 7.47 (2H, d, ^3J 7.3 Hz, 4-H, 5-H), 7.45 (2H, dd, ^3J 7.3 Hz, ^4J 1.6 Hz, 3-H, 6-H), 7.23 (2H, dd, ^3J 7.3 Hz, ^4J 1.6 Hz, 2-H, 7-H); δ_C (300 MHz, $CDCl_3$) 194.2 (C=O), 144.7 (C-4a, C-4b), 134.9 (C-3, C-6), 134.4 (C-8a, C-9a), 129.3 (C-1, C-8), 124.6 (C-4, C-5), 120.6 (C-2, C-7).

*4.3.2. 1-Methoxyfluoren-9-one (**5b**).*[24] According to the general procedure (2-iodophenyl)(2′-methoxyphenyl)methanone (**2b**) (0.34 g, 1.00 mmol), CuI (0.03 g, 0.15 mmol) and K_3PO_4 (0.64 g, 3.00 mmol) were reacted in DMF (6 mL) in a sealed vial in an argon atmosphere at 155 °C for 48 h. After column chromatography over silica gel (cyclohexane/CH_2Cl_2=1:1), the title compound **5b** (0.16 g, 77%) was isolated as pale yellow crystals; mp 133–134 °C; R_f (cyclohexane/EtOAc=8:1) 0.33; ν_{max} (ATR) 2947, 1660, 1597, 1580, 1486, 1293 cm^{-1}; λ_{max} (MeCN) (log ε) 249 (3.89), 203 (4.15) nm; δ_H (300 MHz, $CDCl_3$) 7.85 (1H, d, ^3J 7.8 Hz, 8-H), 7.58 (1H, dd, ^3J 7.8 Hz, ^4J 1.3 Hz, 3-H), 7.44–7.53 (2H, m, 5-H and 6-H), 7.40 (1H, dd, ^3J 7.8 Hz, ^4J 1.3 Hz, 7-H), 7.09 (1H, t, ^3J 7.8 Hz, 4-H), 7.03 (1H, dd, ^3J 8.5 Hz, ^4J 1.3 Hz, 2-H), 3.76 (3H, s, 1-OCH_3); δ_C (300 MHz, $CDCl_3$) 196.7 (C=O), 157.6 (C-1), 138.1 (C-4a), 133.2 (C-4b), 132.1 (C-3), 130.1 (C-8), 130.1 (C-7), 129.8 (C-8a), 129.1 (C-9a), 128.5 (C-5), 120.8 (C-2), 111.7 (C-4), 55.9 (1-OCH_3), *m*/*z* (EI, 70 eV) 212 (87, M^{2+}), 201 (M^+–CH_2=CH_2) 195 (66), 194 (33), 136 (15), 135 (M^{2+}-C_6H_5) (100), 105 (73), 77 (90%).

*4.3.3. 1,4-Dimethoxyfluoren-9-one (**5c**).*[19,20] According to the general procedure (2,5-dimethoxyphenyl)(2′-iodophenyl)methanone (**2c**) (0.37 g, 1.00 mmol), CuI (0.03 g, 0.15 mmol) and K_3PO_4 (0.64 g, 3.00 mmol) were reacted in DMF (6 mL) in a sealed vial in an argon atmosphere at 155 °C for 48 h. After column chromatography over silica gel (cyclohexane/EtOAc=3:1), the title compound **5c** (0.21 g, 87%) was isolated as orange crystals crystals; mp 170–171 °C; R_f (cyclohexane/EtOAc=1:1) 0.26; ν_{max} (ATR) 2930, 1698, 1584, 1499, 1453, 1263 cm^{-1}; λ_{max} (MeCN) (log ε) 433 (2.95), 373 (2.96), 250 (4.15), 244 (4.03) nm; δ_H (300 MHz, $CDCl_3$) 7.83 (1H, d, ^3J 7.8 Hz, 5-H), 7.62 (1H, d, ^3J 7.8 Hz, 8-H), 7.42 (1H, dd, ^3J 7.8 Hz, ^4J 1.2 Hz, 6-H), 7.21 (1H, dd, ^3J 7.8 Hz, ^4J 1.2 Hz, 7-H), 7.02 (1H, d, ^3J 9.0 Hz, 3-H), 6.78 (1H, d, ^3J 9.0 Hz, 2-H), 3.96 (6H, s, 1-OCH_3 and 4-OCH_3); δ_C (300 MHz, $CDCl_3$) 192.4 (C=O), 152.8 (C-4), 149.9 (C-1), 142.8 (C-4b), 136.8 (C-4a), 134.4 (C-8a), 134.2 (C-6), 132.6 (C-9a), 128.5 (C-7), 124.6 (C-5), 124.0 (C-8), 120.6 (C-3), 114.4 (C-2), 56.5 (4-OCH_3), 56.3 (1-OCH_3); *m*/*z* (EI, 70 eV) 240 (60, M^+), 211 (M^+–CHO) (85), 197 (37), 169 (30),139 (17%); HRMS (EI, 70 eV): M^+, found 240.0803. $C_{15}H_{12}O_3$ requires 240.0783.

*4.3.4. 1,6,7-Trimethoxyfluoren-9-one (**5d**).* According to the general procedure (2-iodo-4,5-dimethoxyphenyl)(2′-methoxyphenyl)methanone (**2d**) (0.40 g, 1.00 mmol), CuI (0.03 g, 0.15 mmol) and K_3PO_4 (0.64 g, 3.00 mmol) were reacted in DMF (6 mL) in a sealed vial in an argon atmosphere at 155 °C for 48 h. After column chromatography over silica gel (cyclohexane/EtOAc=2:1), the title compound **5d** (0.25 g, 92%) was isolated as dark orange crystals; mp 178–179 °C; [found: C, 71.36; H, 5.44. $C_{16}H_{14}O_4$ requires C, 71.09; H, 5.22%]; R_f (cyclohexane/EtOAc=2:1) 0.49; ν_{max} (ATR)

2825, 1694, 1589, 1499, 1406, 1264 cm^{-1}; λ_{max} (MeCN) (log ε) 365 (3.50), 316 (3.76), 304 (3.77), 281 (4.20), 260 (4.20), 213 (4.18) nm; δ_H (300 MHz, $CDCl_3$) 7.35 (1H, dd, ^3J 7.6 Hz, ^3J 7.6 Hz, 3-H), 7.16 (1H, s, 8-H), 6.96 (1H, s, 5-H), 6.95 (1H, d, ^3J 7.6 Hz, 4-H), 6.75 (1H, d, ^3J 7.6 Hz, 2-H), 3.98 (3H, s, 6-OCH_3), 3.95 (3H, s, 7-OCH_3), 3.91 (3H, s, 1-OCH_3); δ_C (300 MHz, $CDCl_3$) 191.7 (C=O), 158.1 (C-1), 154.2 (C-6), 150.2 (C-7), 146.4 (C-4a), 138.1 (C-4b), 136.6 (C-3), 127.5 (C-8a), 120.4 (C-9a), 112.9 (C-2), 112.3 (C-4), 107.1 (C-8), 103.7 (C-5), 56.6 (6-OCH_3), 56.5 (7-OCH_3), 56.2 (1-OCH_3); *m/z* (EI, 70 eV) 270 (100, M^+), 255 (16), 239 (M^+-OCH_3) (36), 227 (12), 212 (14%); HRMS (EI, 70 eV): M^+, found 270.2917. $C_{16}H_{14}O_4$ requires 270.2908.

*4.3.5. 1,4,6,7-Tetramethoxyfluoren-9-one (**5e**).* According to the general procedure (2′,5′-dimethoxyphenyl)(2-iodo-4,5-dimethoxyphenyl)methanone (**2e**) (0.43 g, 1.00 mmol), CuI (0.03 g, 0.15 mmol) and K_3PO_4 (0.64 g, 3.00 mmol) were reacted in DMF (6 mL) in a sealed vial in an argon atmosphere at 155 °C for 48 h. After column chromatography over silica gel (cyclohexane/EtOAc=1:1), the title compound **5e** (0.27 g, 91%) was isolated as yellow orange crystals; mp 135–136 °C; [found: C, 67.86; H, 5.08. $C_{17}H_{16}O_5$ requires C, 67.98; H, 5.27%]; R_f (cyclohexane/EtOAc=1:2) 0.42; ν_{max} (ATR) 2947, 2825, 1694, 1583, 1488, 1475, 1255 cm^{-1}; λ_{max} (MeCN) (log ε) 487 (2.96), 325 (2.84), 312 (2.89), 279 (3.73), 264 (3.80) nm; δ_H (300 MHz, $CDCl_3$) 7.36 (1H, s, 5-H), 7.16 (1H, s, 8-H), 6.96 (1H, d, ^3J 9.1 Hz, 3-H), 6.71 (1H, d, ^3J 9.1 Hz, 2-H), 3.98 (3H, s, 6-OCH_3), 3.91 (9H, s, 1-OCH_3, 4-OCH_3 and 7-OCH_3); δ_C (300 MHz, $CDCl_3$) 191.7 (C=O), 153.9 (C-6), 152.4 (C-4), 149.3 (C-1), 149.0 (C-7), 134.7 (C-8a), 132.0 (C-9a), 127.0 (C-4b), 121.6 (C-4a), 120.4 (C-3), 114.0 (C-2), 107.8 (C-5), 107.1 (C-8), 56.50 (6-OCH_3), 56.46 (1-OCH_3 and 7-OCH_3), 56.3 (4-OCH_3); *m/z* (EI, 70 eV) 300 (100, M^+), 269 (M^+–OCH_3) (35), 242 (14), 150 (7%); HRMS (EI, 70 eV): M^+, found 300.0960. $C_{17}H_{16}O_5$ requires 300.0996.

*4.3.6. 1,4,5,8-Tetramethoxyfluoren-9-one (**5f**).* According to the general procedure (2,5-dimethoxyphenyl)(2′-iodo-3′,6′-dimethoxyphenyl)methanone (**2f**) (0.43 g, 1.00 mmol), CuI (0.03 g, 0.15 mmol) and K_3PO_4 (0.64 g, 3.00 mmol) were reacted in DMF (6 mL) in a sealed vial in an argon atmosphere at 155 °C for 48 h. After column chromatography over silica gel (cyclohexane/EtOAc=1:1), the *title compound* **5f** (0.25 g, 84%) was isolated as yellow orange crystals; mp 134–135 °C; R_f (CH_2Cl_2/EtOAc=1:1) 0.29; ν_{max} (ATR) 2939, 2836, 1692, 1587, 1577, 1493, 1265 cm^{-1}; λ_{max} (MeCN) (log ε) 443 (3.83), 360 (3.53), 245 (3.82), 214 (3.80) nm; δ_H (300 MHz, $CDCl_3$) 7.10 (2H, d, ^3J 8.9 Hz, 3-H and 6-H), 6.86 (2H, d, ^3J 8.9 Hz, 2-H and 7-H), 3.96 (6H, s, 4-OCH_3 and 5-OCH_3), 3.91 (6H, s, 1-OCH_3 and 8-OCH_3); δ_C (300 MHz, $CDCl_3$) 189.9 (C=O), 153.7 (C-4 and C-5), 149.3 (C-1 and C-8), 131.8 (C-4a and C-4b), 124.0 (C-3 and C-6′), 122.0 (C-8a and C-9a), 115.3 (C-2 and C-7), 58.8 (4-OCH_3 and 5-OCH_3), 56.8 (1-OCH_3 and 8-OCH_3); *m/z* (EI, 70 eV) 300 (60, M^+), 285 (M^+–CH_3) (100), 242 (16), 227 (10), 71 (20%); HRMS (EI, 70 eV): M^+, found 300.0996. $C_{17}H_{16}O_5$ requires 300.0993.

4.4. General procedure for the deprotection of the methoxy-substituted fluoren-9-ones 5b–f

Boron tribromide 1 M in DCM (1.33 mL, 1.33 mmol) was added dropwise to a solution of the methoxy-substituted fluoren-9-ones **5b–f** (0.67 mmol) in CH_2Cl_2 (15 mL) at −78 °C. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. After quenching with water at 0 °C the precipitate was filtered. The filtrate was extracted with *tert*-butylmethyl ether (4×50 mL). The combined organic layers were washed with water (1×50 mL) and brine (2×50 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography over silica gel (cyclohexane/EtOAc).

*4.4.1. 1-Hydroxyfluoren-9-one (**6b**).*[24] According to the general procedure 1-methoxyfluoren-9-one (**5b**) (0.14 g, 0.67 mmol) was treated with boron tribromide 1 M in DCM (1.33 mL, 1.33 mmol). After column chromatography over silica gel (cyclohexane/DCM=4:3), the title compound **6b** (0.097 g, 60%) was isolated as orange crystals; mp 110–111 °C; R_f (cyclohexane/DCM=1:1) 0.39; ν_{max} (ATR) 3358, 1684, 1595, 1468, 1437, 1283 cm^{-1}; λ_{max} (MeCN) (log ε) 352 (3.04), 250 (4.12), 205 (3.81) nm; δ_H (300 MHz, $CDCl_3$) 8.44 (1H, br s, 1-OH), 7.63 (1H, d, ^3J 7.1 Hz, 8-H), 7.49 (1 H, overlapped, ^3J 7.1 Hz, 5-H), 7.48 (1 H, overlapped, ^3J 7.1 Hz, 6-H), 7.36 (1H, dd, ^3J 8.0 Hz, ^3J 8.0 Hz, 3-H), 7.30 (1H, dt, ^3J 7.1 Hz, ^4J 1.9 Hz, 7-H), 7.03 (1H, d, ^3J 7.2 Hz, 2-H), 6.76 (1H, d, ^3J 8.0 Hz, 4-H); δ_H (300 MHz, $CDCl_3$, H/D-exchange) 7.63 (1H, d, ^3J 7.1 Hz, 8-H), 7.49 (1H, overlapped, ^3J 7.1 Hz, 5-H), 7.48 (1H, overlapped, ^3J 7.1 Hz, 6-H), 7.36 (1H, dd, ^3J 8.0 Hz, ^3J 8.0 Hz, 3-H), 7.30 (1H, dt, ^3J 7.1 Hz, ^4J 1.9 Hz, 7-H), 7.03 (1H, d, ^3J 7.2 Hz, 2-H), 6.76 (1H, d, ^3J 8.0 Hz, 4-H); δ_C (300 MHz, $CDCl_3$) 196.4 (C=O), 157.4 (C-1), 144.2 (C-8a), 143.9 (C-4a), 137.5 (C-3), 134.7 (C-6), 134.3 (C-4b), 129.1 (C-7), 124.1 (C-8), 121.1 (C-5), 118.2 (C-4), 117.5 (C-9a), 112.9 (C-2); *m/z* (EI, 70 eV) 196 (40, M^+), 168 (M^+–CO) (26), 139 (17), 44 (10), 32 (24), 28 (M^+–$C_{12}H_8O$) (100%).

*4.4.2. 1,4-Dihydroxyfluoren-9-one (**6c**).*[16] According to the general procedure 1,4-dimethoxyfluoren-9-one (**5c**) (0.16 g, 0.67 mmol) was treated with boron tribromide 1 M in DCM (1.33 mL, 1.33 mmol). After column chromatography over silica gel (cyclohexane/EtOAc=2:1) the title compound **6c** (0.97 g, 68%) was isolated as dark red crystals; mp 268–269 °C; R_f (cyclohexane/EtOAc=2:1) 0.29; IR (ATR) 3300–3000, 1673, 1595, 1485, 1282 cm^{-1}; λ_{max} (MeCN) (log ε) 442 (2.99), 368 (2.96), 250 (3.19) nm; δ_H (300 MHz, $CDCl_3$) 9.83 (1H, s, 4-OH), 9.79 (1H, s, 1-OH), 7.82 (1H, d, ^3J 7.7 Hz, 5-H), 7.50–7.55 (2H, m, 7-H and 8-H), 7.28 (1H, dd, ^3J 7.3 Hz, ^3J 7.7 Hz, 6-H), 6.95 (1H, d, ^3J 8.9 Hz, 3-H), 6.68 (1H, d, ^3J 8.9 Hz, 2-H); δ_H (300 MHz, $CDCl_3$, H/D-exchange) 7.82 (1H, d, ^3J 7.7 Hz, 5-H), 7.50–7.55 (2H, m, 7-H and 8-H), 7.28 (1H, dd, ^3J 7.3 Hz, ^3J 7.7 Hz, 6-H), 6.95 (1H, d, ^3J 8.9 Hz, 3-H), 6.68 (1H, d, ^3J 8.9 Hz, 2-H); δ_C (300 MHz, $CDCl_3$) 192.4 (C=O), 150.7 (C-1), 147.0 (C-4), 143.5 (C-8a), 135.0 (C-8), 134.2 (C-4b), 128.4 (C-6), 127.4 (C-4a), 127.2 (C-3), 124.4 (C-5), 123.7 (C-7), 121.1 (C-2), 118.6 (C-9a); *m/z* (EI, 70 eV) 212 (100, M^+), 184 (13), 183 (7), 128 (11), 59 (10%); HRMS (EI, 70 eV): M^+, found 212.0464. $C_{13}H_8O_3$ requires 212.0467.

*4.4.3. 1,6,7-Trihydroxyfluoren-9-one (**6d**).* According to the general procedure 1,6,7-trimethoxyfluoren-9-one (**5d**) (0.18 g, 0.67 mmol) was treated with boron tribromide 1 M in DCM (1.33 mL, 1.33 mmol). After column chromatography over silica gel (cyclohexane/EtOAc=1:1), the title compound **6d** (0.13 g, 84%) was isolated as dark red crystals; mp 282–283 °C; R_f (cyclohexane/EtOAc=1:1) 0.30; ν_{max} (ATR) 3446, 3251, 1665, 1600, 1595, 1469, 1274 cm^{-1}; λ_{max} (MeCN) (log ε) 364 (2.56), 316 (2.50), 304 (2.48), 271 (2.43), 211 (2.32) nm; δ_H (300 MHz, $CDCl_3$) 10.05–9.71 (3H, br, 1-OH, 6-OH and 7-OH), 7.26 (1H, t, ^3J 7.8 Hz, 3-H), 7.03 (1H, s, 5-H), 6.94 (1H, d, ^3J 7.8 Hz, 4-H), 6.90 (1H, s, 8-H), 6.65 (1H, d, ^3J 7.8 Hz, 2-H); δ_H (300 MHz, $CDCl_3$, H/D-exchange) 7.26 (1H, t, ^3J 7.8 Hz, 3-H), 7.03 (1H, s, 5-H), 6.94 (1H, d, ^3J 7.8 Hz, 4-H), 6.90 (1H, s, 8-H), 6.65 (1H, d, ^3J 7.8 Hz, 2-H); δ_C (300 MHz, $CDCl_3$) 191.8 (C=O), 156.4 (C-1), 152.0 (C-6), 146.8 (C-7), 145.9 (C-4a), 137.1 (C-4b), 136.8 (C-3), 126.5 (C-8a), 118.7 (C-9a), 118.5 (C-2), 111.7 (C-4), 111.3 (C-8), 109.1 (C-5); *m/z* (EI, 70 eV) 228 (100, M^+), 200 (M^+–CO) (40), 171 (8), 154 (7), 126 (9), 100 (11%); HRMS (EI, 70 eV): M^+, found 228.0420. $C_{13}H_8O_4$ requires 228.0420.

*4.4.4. 1,4,6,7-Tetrahydroxyfluoren-9-one (**6e**).* According to the general procedure 1,4,6,7-tetramethoxyfluoren-9-one (**5e**) (200 mg, 0.67 mmol) was treated with boron tribromide 1 M in DCM (1.33 mL, 1.33 mmol). After column chromatography over

silica gel (cyclohexane/EtOAc=2:3), the title compound **6e** (0.14 g, 83%) was isolated as dark red crystals; mp 270–271 °C; R_f (cyclohexane/EtOAc=2:3) 0.25; ν_{max} (ATR) 3350–2900, 1648, 1600, 1579, 1480, 1277 cm^{-1}; λ_{max} (MeCN) (log ε) 474 (3.22), 364 (2.95), 243 (3.98), 217 (3.72) nm; δ_H (300 MHz, $CDCl_3$) 9.88 (1H, s, 6-OH), 9.53 (1H, s, 4-OH), 9.33 (1H, s, 1-OH), 9.28 (1H, s, 7-OH), 7.23 (1H, s, 5-H), 6.88 (1H, s, 8-H), 6.84 (1H, d, ^3J 8.8 Hz, 3-H), 6.51 (1H, d, ^3J 8.8 Hz, 2-H); δ_H (300 MHz, $CDCl_3$, H/D-exchange) 7.23 (1H, s, 5-H), 6.88 (1H, s, 8-H), 6.84 (1H, d, ^3J 8.8 Hz, 3-H), 6.51 (1H, d, ^3J 8.8 Hz, 2-H); δ_C (300 MHz, $CDCl_3$) 192.3 (C=O), 151.8 (C-7), 149.9 (C-1), 145.6 (C-4), 145.5 (C-6), 137.1 (C-4b), 127.5 (C-4a), 126.5 (C-3), 125.9 (C-8a), 119.7 (C-2), 119.2 (C-9a), 112.2 (C-5), 111.44 (C-8); *m/z* (EI, 70 eV) 244 (100, M^+), 216 (9), 170 (6), 99 (5%); HRMS (EI, 70 eV): M^+, found 244.0357. $C_{13}H_8O_5$ requires 244.0339.

*4.4.5. 1,4,5,8-Tetrahydroxyfluoren-9-one (**6f**).* According to the general procedure 1,4,5,8-tetramethoxyfluoren-9-one (**5f**) (200 mg, 0.67 mmol) was treated with boron tribromide (1.33 mL, 1.33 mmol). After column chromatography over silica gel (cyclohexane/EtOAc=1:3) the title compound **6f** (0.14 g, 80%) was isolated as dark red crystals; mp 238–239 °C; R_f (cyclohexane/EtOAc=2:3) 0.62; ν_{max} (ATR) 3300–2980, 1659, 1601, 1492, 1449, 1259 cm^{-1}; λ_{max} (MeCN) (log ε) 474 (3.22), 364 (2.95), 243 (3.98), 217 (3.72) nm; δ_H (300 MHz, $CDCl_3$) 10.69 (2H, s, 1-OH and 8-OH), 9.62 (2H, s, 4-OH and 5-OH), 6.89 (2H, d, ^3J 8.9 Hz, 3-H and 6-H), 6.68 (2H, d, ^3J 8.9 Hz, 2-H and 7-H); δ_H (300 MHz, $CDCl_3$, H/D-exchange) 6.89 (2H, d, ^3J 8.9 Hz, 3-H and 6-H), 6.68 (2H, d, ^3J 8.9 Hz, 2-H and 7-H); δ_C (300 MHz, $CDCl_3$) 191.2 (C=O), 151.3 (C-1 and C-8), 143.8 (C-4 and C-5), 126.3 (C-3 and C-6), 126.0 (C-4a and C-4b), 120.6 (C-2 and C-7), 118.2 (C-8a and C-9a); *m/z* (EI, 70 eV) 244 (100, M^+), 222 (75), 177 (18), 150 (15), 28 (M^+-$C_{12}H_8O_4$) (100%); HRMS (EI, 70 eV): M^+, found 244.0331. $C_{13}H_8O_5$ requires 244.0339.

4.5. General procedure for the Cu(I)-catalyzed synthesis of the methoxy-substituted fluoren-9-ones under microwave conditions 5a–f

A dry microwave glass vial (10 mL) with magnetic stirrer bar was charged with (2-iodophenyl)(phenyl)methanones **2a–f** (1.00 mmol), CuI (0.30 g, 0.15 mmol) and potassium phosphate (0.64 g, 3.00 mmol) under air. The vial was sealed, evacuated and backfilled with argon three times, then freshly distilled dry DMF (6 mL) were added. The sealed vial was irradiated with microwaves (Discover™ by CEM, 2450 MHz, 250 W, 160 °C) for 20–60 min. After cooling to room temperature the reaction mixture was partitioned between 60 mL EtOAc and 30 mL brine. The aqueous phase was extracted with EtOAc (3×50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude products isolated was purified by flash column chromatography over silica gel. The yields of the products are given in Table 6.

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