A Palladium-Catalyzed Ullmann–Ziegler Cross-Coupling for Sterically Hindered Biaryls

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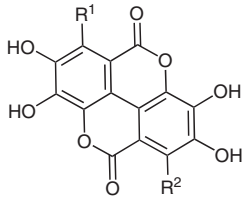
Abstract: We present a facile and versatile biaryl cross-coupling procedure based on a modified Ullmann coupling that may be applied to a wide range of substrates. This even allows the coupling of sterically hindered substrates under mild reaction conditions.

Key words: biaryls, catalysis, copper, cross-coupling, palladium

The synthesis of functionalized biaryl compounds has received much interest due to the importance of the biaryl moiety in natural products[1] and functional molecules.[2] Many examples of this scaffold are present in pharmaceutically active compounds[3] such as antibiotic,[4] antihypertensive,[5] anti-inflammatory,[6] antimalarial,[7] and anticancer[8] agents, and they play an equally important role in the synthesis of new organic materials such as organic semiconductors,[9] OLEDs,[10] and liquid crystals.[2a]

Among this multitude of compounds, ellagic acid (**1**), and its higher hydroxylated homologues flavellagic acid (**2**) and coruleoellagic acid (**3**) (Figure 1) triggered our interest, as they possess an interesting range of pharmaceutical properties,[11] for example, against malaria[12] and cancer.[13] For the synthesis of these compounds, an aryl–aryl coupling is often the key-step.

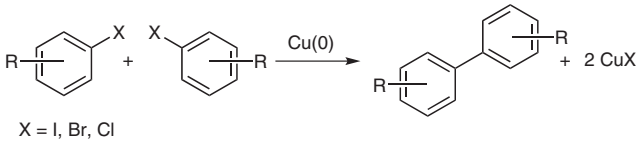


ellagic acid (**1**): $R^1 = R^2 = H$
flavellagic acid (**2**): $R^1 = H$, $R^2 = OH$
coruleoellagic acid (**3**): $R^1 = R^2 = OH$

Figure 1 Ellagic acid (**1**), flavellagic acid (**2**), and coruleoellagic acid (**3**)

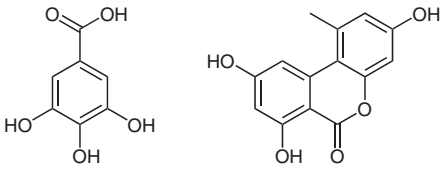
It is therefore hardly surprising that the development of efficient protocols for the synthesis of biaryl compounds has received a great deal of interest, leading to a vast variety of procedures amongst which transition-metal-catalyzed reactions are the most common ones.[14–16]

One of the first reactions to form an aryl–aryl bond was the reductive copper-mediated coupling reaction between two aryl halides in the presence of copper powder first described in 1901 by Ullmann[17] (Scheme 1). Unfortunately, this procedure leads in most cases to symmetrical biaryl products and often requires harsh reaction conditions. Subsequently improved protocols have been developed. Ziegler[18] and co-workers described a modification of the Ullmann biaryl synthesis allowing the cross-coupling of aryl halides at ambient temperature.[19] It relies on the preformation of an aryl–copper species by lithiation and transmetalation, but has certain requirements regarding the substitution pattern of the aromatic substrates, for example, a coordinating substituent (nitrogen or sulfur) ortho to the halide.



Scheme 1 Classical Ullmann synthesis of symmetrical biaryls

We wish to report herein our efforts in developing an improved variant of the Ullmann–Ziegler cross-coupling reaction. We particularly focused our attention on biaryls derived from gallic acid (**4**) derivatives as these compounds are useful precursors for the synthesis of ellagic acid derivatives and other compounds based on the 6*H*-benzo[*c*]chromen-6-one scaffold, for example, alternariol (**5**) (Figure 2).



4 **5**

Figure 2 Gallic acid (**4**) and alternariol (**5**)

Similar to the method described by Ziegler, 3,4,5-trimethoxybenzoic acid diethylamide (**6a**) was treated with *s*-BuLi/TMEDA at –78 °C to effect ortho-lithiation [directed ortho-metalation (DoM)], followed by transmetalation with a copper(I) salt to give intermediate **7a**. To the thus obtained organocopper solution was added $Pd(PPh_3)_4$

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as catalyst and iodobenzene, which after heating under reflux for 12 hours gave the desired cross-coupling product **8** in good yield (Table 1, entries 1, 2) with only minor amounts of homocoupling or dehalogenation products. For the reaction, $CuBr{\cdot}SMe_2$ and CuI proved to be equally suitable, while the Liebeskind reagent [copper(I) thiophene 2-carboxylate][20] led to slightly inferior results. We were also able to show that the lithiation additive TMEDA seems to play an important role for the outcome of the reaction by affecting the solubilization of the arylcopper intermediate. Upon addition of the copper(I) salt, an insoluble precipitate formed when no TMEDA was added. No cross-coupling was observed in these cases.

As an alternative to conventional heating, the reaction was also carried out in a microwave reactor that proved to give comparable yields, but speeded up the coupling significantly (30 min compared to 12 h, Table 1, entries 2 vs. 4).

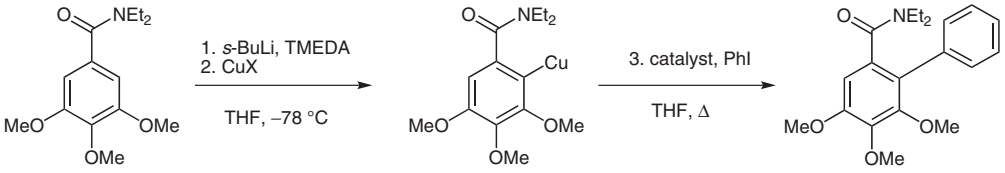
Several established palladium catalysts were tested, which all gave satisfactory to good yields (58–81%), except $PdCl_2$ which gave only 20% of the desired product. Also nickel catalysts may be employed as shown for the catalyst system $NiCl_2(PPh)_2/PPh_3$ (Table 1, entry 10). To verify the necessity of a catalyst, in contrast to the Ziegler method, control experiments were conducted: In all cases where the catalyst was omitted, no cross-coupling product could be detected, only small quantities of homocoupling products were found (Table 1, entries 11, 12).

To determine the scope of the reaction protocol regarding the range of substrates, several DoM precursors, as well as aryl halides were employed. Aryl bromides gave comparable results (Table 2, entries 1, 5, 6, 7) to iodides while aryl chlorides (entry 2) were unsuitable. Even sterically demanding coupling partners with ortho substituents (entry 3), or with a naphthalene body (entry 5), or heteroaromatics (entry 6) gave satisfactory results.

On the other hand, the arylcopper compound seemed to require an amide (entries 1–8) or a carbamate (entry 11) in the ortho-position to the coupling site to achieve satisfactory yields. This is probably due to the coordinating effect of these functional groups to copper, thereby stabilizing the organocopper intermediate. Substitution of the amide or carbamate for oxygen-containing donors like ethers (entries 9, 10) led to reduced yields.

To achieve the efficient coupling of such organocopper compounds the solvent was changed from THF to a THF–pyridine mixture, with pyridine being able to provide further stabilization for the arylcopper intermediate and the aryllithium to copper ratio was increased to 2:1. By doing so, we were able to couple the aryl copper derived from resorcinol dimethyl ether (**7c**) for which two examples are shown (Table 2, entries 9, 10).

Table 1 Optimization of Reaction Conditions

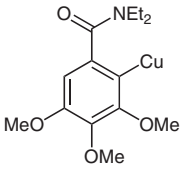
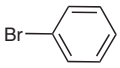
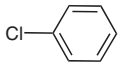
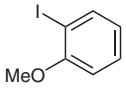
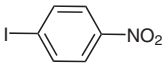
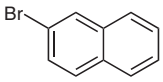
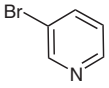
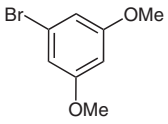
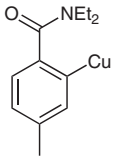
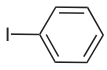
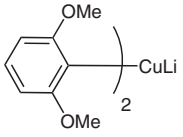
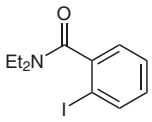
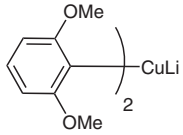
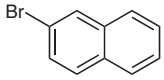
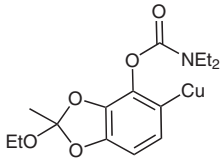
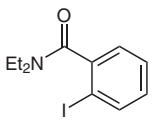


6a **7a** **8a**

Entry	CuX	Catalyst	Conditions	Yield (%)
1	$CuBr{\cdot}SMe_2$	7.5 mol% $Pd(PPh_3)_4$	80 °C, 12 h	79
2	CuI	7.5 mol% $Pd(PPh_3)_4$	80 °C, 12 h	78
3[a]	CuI	7.5 mol% $Pd(PPh_3)_4$	80 °C, 12 h	–
4	CuI	7.5 mol% $Pd(PPh_3)_4$	MW,[b] 110 °C, 30 min	81
5	CuTC[c]	7.5 mol% $Pd(PPh_3)_4$	MW,[b] 110 °C, 30 min	60
6	$CuBr{\cdot}SMe_2$	7.5 mol% $PdCl_2$(dppe)	80 °C, 12 h	78
7	CuI	7.5 mol% $PdCl_2$	80 °C, 12 h	20
8	CuI	7.5 mol% $Pd(PCy_3)_2$	MW,[b] 110 °C, 30 min	66
9	CuI	3 mol% PEPPSI-IPr	MW,[b] 110 °C, 30 min	58
10	CuI	5 mol% $NiCl_2(PPh_3)_2$/10 mol% Ph_3P	MW,[b] 110 °C, 30 min	62
11	CuI	no catalyst	80 °C, 12 h	–
12	CuI + $P(OEt)_3$ (1 equiv)	no catalyst	80 °C, 12 h	–

[a] *t*-BuLi, no TMEDA.
[b] P_{max} = 200 W.
[c] Copper(I) thiophene-2-carboxylate.

Table 2 Screening of Substrates

Entry	Ar^1–Cu, Method[a]	Ar^2–X	Product Ar^1–Ar^2	Yield (%)
1	 **7a**, A		**8a**	76
2	**7a**, A		–	–
3	**7a**, A		**8b**	76
4	**7a**, A		**8c**	79
5	**7a**, A		**8d**	63
6	**7a**, A		**8e**	84
7	**7a**, A		**8f**	65
8	 **7b**, A		**8g**	53
9	 **7c**, B		**8h**	66
10	 **7c**, B		**8i**	44
11	 **7d**, C		**8j**	79

[a] Method A: THF, 60 °C, 12 h; method B: THF–py or DME–py, 60 °C, 12 h; method C: THF, MW, 110 °C, P_{max} = 200 W, 30 min.

In conclusion, the procedure described above is a useful supplement to the Ullmann–Ziegler cross-coupling as it expands the range of substrates to those without a nitrogen containing ortho substituent on both substrates. Our protocol allows a facile cross-coupling even of sterically hindered arenes employing easily available reagents.

All reactions were carried out under inert atmosphere, unless otherwise mentioned, following standard syringe septa techniques. Solvents were purified by distillation and dried, if necessary, prior to use. Reactions conducted by heating with microwaves were carried out in a CEM Discover apparatus (CEM Corp.). Products were purified by flash chromatography on silica gel 60 (Merck). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II 200 spectrometer (^{1}H at 200 MHz; ^{13}C at 50 MHz), Bruker Avance II 400 spectrometer (^{1}H at 400 MHz; ^{13}C at 100 MHz) and Bruker Avance III 600 spectrometer (^{1}H at 600 MHz; ^{13}C at 150 MHz) in $CDCl_3$ using TMS as internal standard. IR spectra were recorded on a Bruker IFS 25 spectrometer. EI-MS were obtained using a Finnigan MAT 95 mass spectrometer, ESI-MS were obtained using a Bruker Daltonics MicroTOF spectrometer. Melting points were measured on a Krüss Optronics melting point apparatus and are uncorrected.

3,4,5-Trimethoxybenzoic Acid Diethylamide (6a)

To a solution of 3,4,5-trimethoxybenzoic acid (6.0 g, 28.3 mmol) in anhyd CH_2Cl_2 (50 mL) was added $SOCl_2$ (13.9 g, 115 mmol, 8.5 mL) and the resulting mixture was heated overnight at 45 °C. After cooling to r.t., the solvent and excess $SOCl_2$ were removed under reduced pressure. The obtained residue was dissolved in anhyd THF (50 mL) and cooled to 0 °C. Et_2NH (12.4 g, 170 mmol, 17.5 mL) was added slowly by syringe and the reaction mixture was stirred for 1 h at r.t., after which the mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL) and dried ($MgSO_4$). After removal of the solvents in vacuo, the product was purified by flash chromatography on silica gel [pentane–MTBE (1:1) to MTBE] to yield **6a** (6.1 g, 81%) as colorless oil, which solidified upon standing; mp 52 °C.

IR (KBr): 2972, 2936, 1629, 1582, 1507, 1473, 1410, 1332, 1276, 1235, 1126, 1003, 855, 824, 764 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (br s, 6 H), 3.37 (br d, 4 H), 3.80 (s, 3 H), 3.82 (s, 6 H), 6.54 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.9, 14.3, 39.4, 43.4, 56.2, 60.9, 103.6, 132.6, 138.7, 153.2, 171.0.

MS (ESI+): *m*/*z* (%) = 290.1 (75, $[M + Na]^+$), 557.3 (100, $[2 M + Na]^+$), 824.4 (50, $[3 M + Na]^+$).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{21}NO_4$ + Na: 290.1368; found: 290.1369.

Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.60; H, 7.89; N, 5.23.

Ullmann Cross-Coupling Reactions

General Procedure A

In an oven-dried Schlenk flask, the respective amide and TMEDA (1.1 equiv) were dissolved in anhyd THF (10 mL) and cooled to –78 °C. *s*-BuLi (1.3 M solution in cyclohexane, 1.1 equiv) was added slowly and the resulting mixture was stirred 30 min. CuBr·SMe_2 or CuI (1.1 equiv) was added as solid, the cooling bath was removed, and the reaction was allowed to stir for 15 minutes. $Pd(PPh_3)_4$ (7.5 mol%) was added, followed by the aryl halide. The reaction was heated for 12 h at 60 °C and was subsequently quenched by the addition of sat. aq NH_4Cl (10 mL). The layers were separated and the aqueous layer was extracted with MTBE (3 × 15 mL). The combined organic layers were washed first with a 30% aq solution of ammonia (15 mL) and then with brine (15 mL). After drying ($MgSO_4$), the solvent was removed in vacuo and the product was

isolated from the residue by flash chromatography on silica gel (pentane–MTBE).

General Procedure B

In an oven-dried Schlenk flask the 1,3-dimethoxybenzene and TMEDA (2.2 equiv) were dissolved in anhyd DME (3 mL) and cooled to –78 °C. *n*-BuLi (1.6 M solution in hexanes, 2.2 equiv) was added slowly and the resulting mixture was stirred 90 min. $CuBr{\cdot}SMe_2$ (1 equiv) was added as solid, the cooling bath was removed and the reaction was allowed to stir for 30 min. $Pd(PPh_3)_4$ (7.5 mol%) was added, followed by a solution of aryl halide (1 equiv) in anhyd pyridine (3 mL). The reaction was heated for 12 h at 60 °C in a sealed vessel and was subsequently quenched by the addition of sat. aq NH_4Cl (10 mL). The layers were separated and the aqueous layer was extracted with MTBE (3 × 15 mL). The combined organic layers were washed first with a 30% aq solution of ammonia (15 mL) and then with brine (15 mL). After drying ($MgSO_4$), the solvent was removed in vacuo and the product was isolated from the residue by flash chromatography (pentane–MTBE) (Table 2).

***N*,*N*-Diethyl-4,5,6-trimethoxy[1,1′-biphenyl]-2-carboxamide (8a)**

Prepared according to general procedure A using amide **6a** (250 mg, 0.94 mmol) and iodobenzene (380 mg, 1.87 mmol, 0.21 mL) yielding **8a** (255 mg, 79%) after flash chromatography on silica gel [pentane–MTBE (1:2) to MTBE] as a white solid; mp 111 °C.

IR (film): 2971, 2934, 1631, 1594, 1471, 1429, 1396, 1333, 1275, 1155, 1127, 1096, 1007, 752, 701 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.70 (t, *J* = 7.1 Hz, 3 H), 0.83 (t, *J* = 7.1 Hz, 3 H), 2.62 (m, 1 H), 2.82 (m, 1 H), 3.06 (m, 1 H), 3.57 (s, 3 H), 3.74 (m, 1 H), 3.90 (s, 3 H), 3.93 (s, 3 H), 6.69 (s, 1 H), 7.24–7.46 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8, 13.7, 38.0, 42.2, 56.2, 61.1, 61.2, 105.6, 125.6, 127.3, 127.9, 130.2, 132.9, 135.2, 142.7, 151.3, 153.2, 169.8.

MS (EI, 70 eV): *m*/*z* (%) = 256 (86), 271 (100, $[M - NEt_2]^+$), 343 (69, $[M]^+$).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{25}NO_4$: 343.1784; found: 343.1791.

Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.83; H, 7.30; N, 3.98.

***N*,*N*-Diethyl-2′,4,5,6-tetramethoxy[1,1′-biphenyl]-2-carboxamide (8b)**

Prepared according to general procedure A using amide **6a** (250 mg, 0.94 mmol) and 2-iodoanisole (219 mg, 0.94 mmol) yielding **8b** (266 mg, 76%) after flash chromatography on silica gel (pentane–MTBE, 1:4) as a white solid; mp 97 °C.

IR (film): 2971, 2937, 1632, 1595, 1463, 1430, 1397, 1334, 1242, 1154, 1115, 1089, 1006, 802, 755 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.61 (t, *J* = 7.1 Hz, 3 H), 0.88 (t, *J* = 7.1 Hz, 3 H), 2.93–2.48 (m, 2 H), 3.37–3.13 (m, 2 H), 3.69 (s, 3 H), 3.75 (s, 3 H), 3.89 (s, 6 H), 6.67 (s, 1 H), 6.99–6.82 (m, 2 H), 7.31–7.21 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.7, 13.9, 37.7, 41.6, 55.1, 56.0, 60.8, 104.7, 109.8, 120.4, 122.1, 124.4, 128.9, 132.2, 133.1, 141.8, 152.0, 153.2, 156.9, 169.6.

MS (EI, 70 eV): *m*/*z* (%) = 73 (100), 195 (43, $[M - NEt_2 - PhOMe]^+$), 286 (22), 301 (77, $[M - NEt_2]^+$), 342 (21, $[M - OMe]^+$), 373 (28, $[M]^+$).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{27}NO_5$: 373.1889; found: 373.1887.

***N*,*N*-Diethyl-4,5,6-trimethoxy-4′-nitro[1,1′-biphenyl]-2-carboxamide (8c)**

Prepared according to general procedure A using amide **6a** (260 mg, 0.97 mmol) and 4-iodonitrobenzene (242 mg, 0.97 mmol) yielding **8c** (298 mg, 79%) after flash chromatography on silica gel [pentane–MTBE (1:2) to MTBE] as yellow solid; mp 161 °C.

IR (film): 2975, 2936, 1628, 1595, 1513, 1464, 1390, 1342, 1332, 1280, 1192, 1152, 1131, 1092, 1040, 1000, 840, 800, 752, 715 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.75 (t, *J* = 7.1 Hz, 3 H), 0.85 (t, *J* = 7.1 Hz, 3 H), 2.69 (br s, 1 H), 2.90 (br s, 1 H), 3.01 (br s, 1 H), 3.55–3.75 (m, 4 H), 3.90 (s, 3 H), 3.92 (s, 3 H), 6.68 (s, 1 H), 7.57 (d, *J* = 8.9 Hz, 2 H), 8.19 (d, *J* = 8.9 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.0, 13.8, 38.4, 42.5, 56.3, 61.2, 61.3, 105.8, 123.0, 123.2, 131.3, 132.7, 142.4, 142.8, 147.0, 151.2, 154.2, 169.1.

MS (EI, 70 eV): *m*/*z* (%) = 255 (28), 270 (63), 316 (100, $[M - NEt_2]^+$), 373 (24, $[M - CH_3]^+$), 388 (66, $[M]^+$).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{24}N_2O_6$: 388.1634; found: 343.1632.

Anal. Calcd for $C_{20}H_{24}N_2O_6$: C, 61.84; H, 6.23; N, 7.21. Found: C, 62.05; H, 6.19; N, 7.32.

***N*,*N*-Diethyl-3,4,5-trimethoxy-2-(naphthalen-2-yl)benzamide (8d)**

Prepared according to general procedure A using amide **6a** (275 mg, 1.02 mmol) and 2-bromonaphthalene (213 mg, 1.03 mmol, 0.13 mL) yielding **8d** (254 mg, 63%) after flash chromatography on silica gel (pentane–MTBE, 1:3) as a pale yellow solid; mp 114 °C.

IR (film): 2972, 2935, 1621, 1463, 1429, 1399, 1332, 1270, 1153, 1121, 1091, 1010, 924, 731 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.51 (t, *J* = 7.0 Hz, 3 H), 0.79 (t, *J* = 7.0 Hz, 3 H), 2.51–2.64 (m, 1 H), 2.69–2.82 (m, 1 H), 3.04–3.16 (m, 1 H), 3.55 (s, 3 H), 3.60–3.72 (m, 1 H), 3.92 (s, 3 H), 3.96 (s, 3 H), 6.74 (s, 1 H), 7.43–7.50 (m, 2 H), 7.54 (d, *J* = 8.4 Hz, 1 H), 7.80–7.86 (m, 3 H), 7.88 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8, 13.7, 38.2, 42.4, 56.2, 61.1, 61.2, 105.8, 125.4, 125.9, 126.0, 127.2, 127.6, 128.3, 128.5, 129.1, 132.5, 132.8, 133.1 (2 ×), 142.8, 151.5, 153.3, 169.8.

MS (EI, 70 eV): *m*/*z* (%) = 256 (24), 271 (30), 291 (20), 306 (44), 322 (89, $[M - NEt_2]^+$), 343 (20), 393 (74, $[M]^+$).

HRMS (EI): *m*/*z* calcd for $C_{24}H_{27}NO_4$: 393.1940; found: 343.1946.

Anal. Calcd for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.25; H, 6.96; N, 3.32.

***N*,*N*-Diethyl-3,4,5-trimethoxy-2-(pyrid-3-yl)benzamide (8e)**

Prepared according to general procedure A using amide **6a** (250 mg, 0.94 mmol) and 3-bromopyridine (148 mg, 0.94 mmol) yielding **8e** (272 mg, 84%) after flash chromatography on Al_2O_3 (pentane–MTBE, 1:3) as a pale yellow solid; mp 85 °C.

IR (film): 2972, 2936, 1630, 1471, 1430, 1395, 1335, 1281, 1220, 1155, 1128, 1096, 1036, 1002, 793, 716 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.68 (t, *J* = 7.1 Hz, 3 H), 0.80 (t, *J* = 7.1 Hz, 3 H), 2.70–2.56 (m, 1 H), 2.87–2.71 (m, 1 H), 3.06–2.91 (m, 1 H), 3.55 (s, 3 H), 3.71–3.60 (m, 1 H), 3.84 (s, 3 H), 3.86 (s, 3 H), 6.64 (s, 1 H), 7.71–7.65 (m, 1 H), 8.48 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.53 (d, *J* = 1.5 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.0, 13.7, 38.2, 42.3, 56.2, 61.1, 61.2, 105.7, 121.8, 122.9, 131.2, 133.1, 137.7, 142.7, 148.3, 150.7, 151.3, 153.8, 169.2.

MS (ESI+): *m*/*z* (%) = 345.2 (100, $[M + Na]^+$).

HRMS (ESI+): *m*/*z* calcd for $C_{19}H_{25}N_2O_4$: 345.1814; found: 345.1823.

***N*,*N*-Diethyl-3′,4,5,5′,6-pentamethoxy[1,1′-biphenyl]-2-carboxamide (8f)**

Prepared according to general procedure A using amide **6a** (250 mg, 0.94 mmol) and 3,5-dimethoxybromobenzene (202 mg, 0.94 mmol) yielding **8f** (242 mg, 65%) after flash chromatography on silica gel [pentane–MTBE (1:1) to MTBE] as a colorless oil.

IR (film): 2971, 2937, 1627, 1593, 1460, 1426, 1394, 1329, 1272, 1240, 1204, 1153, 1125, 1100, 1064, 1019, 846, 814, 795 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.76 (t, *J* = 7.5 Hz, 3 H), 0.85 (t, *J* = 7.5 Hz, 3 H), 2.68 (m, 1 H), 2.84 (m, 1 H), 3.07 (m, 1 H), 3.62 (s, 3 H), 3.77 (s, 6 H), 3.82–3.87 (m, 1 H), 3.88 (s, 3 H), 3.90 (s, 3 H), 6.41 (t, *J* = 2.3 Hz, 1 H), 6.55 (d, *J* = 2.3 Hz, 2 H), 6.66 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.7, 13.7, 38.0, 42.4, 55.3, 56.1, 61.0, 61.1, 99.8, 105.5, 108.1, 125.3, 132.7, 136.9, 142.6, 151.2, 153.1, 160.1, 169.7.

MS (ESI+): *m*/*z* (%) = 404.2 (100, $[M + H]^+$), 426.2 (60, $[M + Na]^+$).

HRMS (ESI+): *m*/*z* calcd for $C_{22}H_{30}NO_6$ + Na: 404.2073; found: 404.2069.

Anal. Calcd for $C_{22}H_{29}NO_6$: C, 65.49; H, 7.24; N, 3.47. Found: C, 65.47; H, 7.43; N, 3.42.

***N*,*N*-Diethyl-4-methyl[1,1′-biphenyl]-2-carboxamide (8g)**

Prepared according to general procedure A using amide **6b** (191 mg, 1 mmol) and iodobenzene (204 mg, 0.97 mmol, 0.12 mL) yielding **8g** (141 mg, 53%) after flash chromatography on silica gel (pentane–MTBE, 1:1) as a colorless oil.

IR (film): 2973, 2934, 1627, 1458, 1428, 1380, 1315, 1289, 1221, 1093, 840, 822, 779, 766, 735, 701 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.72 (t, *J* = 7.2 Hz, 3 H), 0.88 (t, *J* = 7.2 Hz, 3 H), 2.40 (s, 3 H), 2.56–2.71 (m, 1 H), 2.88–3.05 (m, 2 H), 3.66–3.84 (m, 1 H), 7.17–7.22 (m, 2 H), 7.23–7.28 (m, 1 H), 7.30–7.39 (m, 3 H), 7.47 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9, 13.3, 21.2, 38.2, 42.2, 126.9, 127.3, 128.7, 128.7, 130.0, 133.5, 138.2, 138.6, 139.9, 170.7.

MS (EI, 70 eV): *m*/*z* (%) = 152 ($C_{12}H_{10}^+$, 18), 165 (17), 195 (100, $[M – NEt_2]^+$), 266 (40, $[M]^+$).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{21}NO$: 267.1623; found: 267.1610.

***N*,*N*-Diethyl-2′,6′-dimethoxy[1,1′-biphenyl]-2-carboxamide (8h)**

Prepared according to general procedure B using 1,3-dimethoxybenzene (257 mg, 0.93 mmol, 0.24 mL) and *N*,*N*-diethyl-2-iodobenzamide (282 mg, 0.93 mmol) yielding **8h** (191 mg, 66%) after flash chromatography on silica gel (pentane–MTBE, 1:1 to 1:2) as a colorless oil.

IR (film): 2969, 2934, 1633, 1592, 1471, 1430, 1287, 1246, 1110, 1040, 1003, 785, 760, 742 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$, 248 K): δ = 0.75 (t, *J* = 7.0 Hz, 3 H), 0.98 (t, *J* = 7.0 Hz, 3 H), 2.73–2.83 (m, 2 H), 3.36–3.44 (m, 1 H), 3.70 (s, 3 H), 3.75 (s, 3 H), 3.79–3.90 (m, 1 H), 6.57 (d, *J* = 8.4 Hz, 1 H), 6.63 (d, *J* = 8.4 Hz, 1 H), 7.25–7.33 (m, 2 H), 7.36–7.48 (m, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$, 248 K): δ = 11.8, 13.9, 37.5, 41.7, 55.2, 55.7, 102.5, 103.6, 116.3, 125.8, 127.0, 128.3, 129.1, 131.4, 131.9, 137.3, 156.7, 158.0, 170.0.

MS (ESI+): *m*/*z* (%) = 314.2 (100, $[M + H]^+$), 336.2 (50, $[M + Na]^+$), 649.3 (50, $[2 M + Na]^+$).

HRMS (ESI+): *m*/*z* calcd for $C_{19}H_{24}NO_3$: 314.1756; found: 314.1763.

2-(2,6-Dimethoxyphenyl)naphthalene (8i)

Prepared according to general procedure B using 1,3-dimethoxybenzene (257 mg, 1.86 mmol, 0.24 mL) and 2-bromonaphthalene (193 mg, 0.93 mmol) yielding **8i** (108 mg, 44%) after flash chromatography on silica gel (pentane–MTBE, 3:1 to 1:1) as a colorless oil.

IR (film): 3053, 3003, 2937, 2835, 1602, 1587, 1471, 1430, 1246, 1109, 1037, 1025, 858, 819, 783, 749, 728 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.63 (s, 6 H), 6.58 (d, *J* = 8.4 Hz, 2 H), 7.21 (t, *J* = 8.4 Hz, 1 H), 7.34–7.39 (m, 3 H), 7.74–7.78 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.9, 104.2, 119.4, 125.5, 126.9, 127.6, 128.1, 128.8, 129.3, 129.7, 131.7, 132.4, 133.3, 157.8.

MS (ESI+): *m*/*z* (%) = 265.1 (100, $[M + H]$).

HRMS (ESI+): *m*/*z* calcd for $C_{18}H_{17}NO_2$: 265.1229; found: 265.1227.

5-[2-(Diethylcarbamoyl)phenyl]-2-ethoxy-2-methylbenzo[*d*][1,3]dioxol-4-yl Diethylcarbamate (8j)

In an oven-dried flask, 2-ethoxy-5-iodo-2-methylbenzo[*d*][1,3]dioxol-4-yl diethylcarbamate (250 mg, 0.59 mmol) was dissolved in anhyd THF (10 mL) and cooled to –78 °C. *t*-BuLi (1.5 M solution in pentane, 2.3 equiv) was added slowly and the resulting mixture was stirred 45 min. Copper(I) thiophene-2-carboxylate was added as solid, the cooling bath was removed, and the reaction mixture was allowed to stir for 15 min. $Pd(PPh_3)_4$ (7.5 mol%) was added, followed by the aryl halide. The reaction mixture was transferred to a sealed glass vial and heated in a microwave reactor (110 °C, P_{max} = 220 W, 30 min). The reaction was subsequently quenched by the addition of sat. aq NH_4Cl (10 mL). The layers were separated and the aqueous layer was extracted with MTBE (3 × 15 mL). The combined organic layers were washed first with a 30% aq solution of ammonia (15 mL) and then with brine (15 mL). After drying ($MgSO_4$), the solvent was removed in vacuo. The product was isolated from the residue by flash chromatography on silica gel (pentane–MTBE, 5:1 to 1:2) as a pale yellow oil (220 mg, 79%).

IR (film): 2976, 2934, 1727, 1632, 1484, 1421,1383, 1269, 1252, 1193, 1152, 1097, 1068, 1051, 1021, 919, 872, 833, 803, 785, 754 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.70–0.81 (br m, 3 H), 0.82–0.94 (br m, 6 H), 1.06–1.18 (br m, 3 H), 1.84 (s, 3 H), 2.67–3.17 (br m, 4 H), 3.22–4.00 (br m, 6 H), 6.67 (d, *J* = 8.1 Hz, 1 H), 6.90 (d, *J* = 8.5 Hz, 1 H), 7.29–7.40 (m, 4 H).

^{13}C NMR (150 MHz, $CDCl_3$, 248 K): δ = 11.4, 11.7, 13.4, 13.5, 13.6, 14.5, 14.6, 24.6, 24.7, 37.3, 37.7, 41.6, 41.9, 42.1, 42.3, 42.7, 57.6, 58.0, 104.5, 123.2, 126.2, 127.8, 128.0, 128.0, 128.4, 128.5, 129.9, 130.3, 133.1, 136.8, 136.9, 138.6, 147.1, 147.2, 152.5, 169.8.

MS (EI, 70 eV): *m*/*z* (%) = 72 (43), 100 (100), 105 (44), 176 (21), 310 (15), 470 (2, M^+).

HRMS (EI): *m*/*z* calcd for $C_{26}H_{34}N_2O_6$: 470.2412; found: 470.2400.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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