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Synthesis and Photophysical Properties of Alkynylated Pyrimidines by Site-Selective Sonogashira Reactions of 2,4,5,6-Tetrachloropyrimidine; First Synthesis of Tetraalkynyl-pyrimidines

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A variety of novel alkynyl-substituted pyrimidines were prepared by the first site-selective Sonogashira cross-coupling reactions of 2,4,5,6-tetrachloropyrimidine. The products, di-, tri-, and tetraalkynyl-pyrimidines, exhibit fluorescence in the range of 395–470 nm. The synthesis of tetraalkynyl-pyrimidines has not been previously reported, nor has the synthesis of chlorinated di- and trialkynylated pyrimidines.

Introduction

The chemistry of pyrimidine and its derivatives has been intensively studied because of the pharmacological and physical properties of these important heterocycles. Pyrimidine derivatives, including uracil, thymine, cytosine, adenine, and guanine, are fundamental building blocks of deoxyribonucleic acids (DNA) and ribonucleic acids (RNA). Vitamin B_1 (thiamine) is a well-known example of a naturally occurring pyrimidine that is encountered in our daily lives. Synthetic pyrimidine derivatives are used in the pharmaceutical industry as potent drugs. For example, pyrimethamine is used as an antimalarial and antiprotozoal drug that is used in combination with sulfadiazine.[1] Pyrimidines also play a role as analgesic, antihypertensive, antipyretic, antiinflammatory, antineoplastic, antibacterial, antiprotozoal, antifungal, antiviral, and antifolate drugs and as pesticides, herbicides, and plant growth regulators.[2] In recent studies it was shown that bicyclic pyrimidine nucleosides are potent and selective inhibitors of Varicella Zoster Virus (VZV) replication.[3] Tao Wang and co-workers reported that pyrimidine derivatives were identified as potent inhibitors of TrK kinase. The latter plays a critical role in cell signaling and cancer related processes.[4] Pyrimidines are also of considerable importance in the field of material sciences. For example, they have been reported[5] to be efficient organic light emitting devices (OLED), which play an important role in biological and material sciences.[6,7]

Monohalogenated pyrimidines have been used as building blocks in Negishi and Suzuki coupling reactions.[8] The synthesis of dialkynyl- and trialkynyl-pyrimidines by Sonogashira reactions of 2,4,6-trichloropyrimidine has been previously reported.[9] Recently, we have reported the first Suzuki–Miyaura cross-coupling reactions of 2,4,5,6-tetrachloropyrimidine.[10] Herein, we report a series of reactions that constitute, to the best of our knowledge, the first Sonogashira reactions of 2,4,5,6-tetachloropyrimidine. All products, 4,6-dialkynyl-2,5-dichloropyrimidines, 2,4,6-trialkynyl-5-chloropyrimidines, and tetraalkynylpyrimidines, exhibit a fluorescence in the range of 395–470 nm. From a preparative viewpoint, it is worth noting that the synthesis of tetraalkynylpyrimidines has, to the best of our knowledge, not been previously reported. This type of molecule not only attracts attention because of its fluorescence properties, but also because of its beautiful symmetrical structure. It is also worth noting that chlorinated di- and trialkynylated pyrimidines, related to those described herein, have not previously been reported in the literature.

Results and Discussion

Synthesis

The Sonogashira reaction of commercially available 2,4,5,6-tetrachloropyrimidine (**1**) with a range of substituted arylacetylenes **2a**–**d** (2.4 equiv.) afforded the 4,6-bis-(arylethynyl)-2,5-dichloropyrimidines **3a**–**d** in 73–91% yield (Scheme 1, Table 1). The reaction conditions were carefully optimized. The employment of either $[Pd(PPh_3)_4]$ (5 mol-%) or $[Pd(OAc)_2]$ (5 mol-%) in the presence of PCy_3 (10 mol-%) both allowed product **3b** to be prepared in moderate yield. The use of $[Pd(PPh_3)_2Cl_2]$ (10 mol-%) allowed the yield to be improved to 76%. Initially, the reactions were carried out in a range of organic solvents, but the reactions generally proceeded sluggishly. However, the reactions

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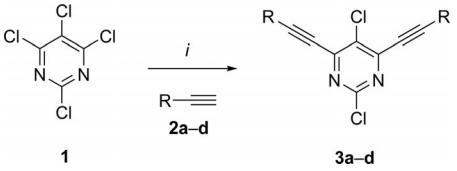
proceeded in good yields when diisopropylamine (DIPA) was used (both as the solvent and base). To avoid multiple coupling, the reactions were performed at 55 °C for a relatively short period of time (2 h).



Scheme 1. Synthesis of **3a**–**d**. Reagents and conditions: **1** (1.0 equiv.), **2a**–**d** (2.4 equiv.), CuI (5 mol-%), $[Pd(PPh_3)_2Cl_2]$ (10 mol-%), DIPA, 55 °C, 2 h.

Table 1. Synthesis of **3a**–**d**.

2,**3**	R	% Yield for **3**[a]
a	4-*t*BuC_6H_4	76
b	Ph	73
c	3-(MeO)C_6H_4	81
d	6-(MeO)$C_{10}H_6$	91

[a] Yield of isolated product.

The structure of product **3c** was independently confirmed by a crystal structure X-ray analysis (Figure 1).[11] The pyridine moiety and the two aryl groups were found to be in plane, which might be due to electronic interactions of the aryl groups or due to crystal packing effects.

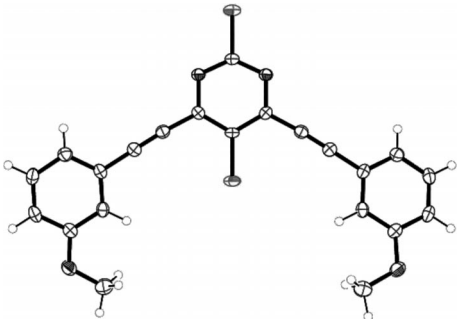
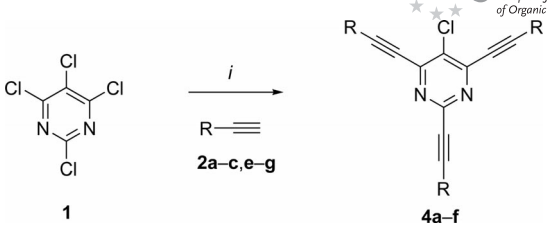


Figure 1. X-ray crystal structure of **3c**.[11]

The Sonogashira reaction of **1** with different substituted acetylenes (3.6 equiv.) afforded the 2,4,6-tri(alkynyl)-5-chloropyrimidines **4a**–**f** in 68–84% yield (Scheme 2 and Table 2). The reactions were carried out following the protocol discussed above for the synthesis of **3a**–**d**. A slight increase in the temperature proved to be important (70 °C, 2 h).

The synthesis of hitherto unknown 2,4,5,6-tetraalkynylpyrimidines was next studied. The application of the reaction conditions, as discussed above, for the synthesis of products **3** and **4**, proved to be unsatisfactory in terms of yields (formation of complex mixtures). Unsuccessful attempts were made to improve the yields by addition of various solvents (*N*,*N*-dimethylformamide (DMF), toluene, xylene) using DIPA or triethylamine as the base. After extensive optimization, it was found that products **5a**–**c** could be obtained in good yields when dioxane was used in the



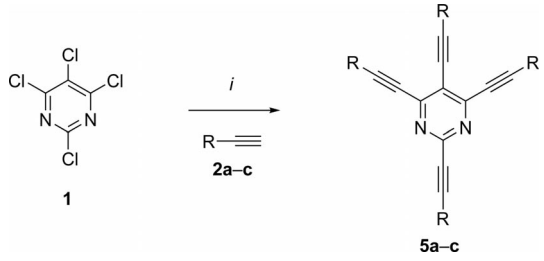
Scheme 2. Synthesis of **4a**–**f**. Reagents and conditions: **1** (1.0 equiv.), **2a**–**c** or **2e**–**g** (3.6 equiv.), CuI (5 mol-%), $[Pd(PPh_3)_2Cl_2]$ (10 mol-%), DIPA, 70 °C, 2 h.

Table 2. Synthesis of **4a**–**f**.

2	**4**	R	% Yield for **4**[a]
a	**a**	4-*t*BuC_6H_4	80
b	**b**	Ph	71
c	**c**	3-(MeO)C_6H_4	77
e	**d**	4-MeC_6H_4	84
f	**e**	*n*Pent	68
g	**f**	*n*Pr	69

[a] Yield of isolated product.

presence of DIPA (Scheme 3 and Table 3). The temperature was increased to 85 °C and the reaction time was considerably extended to 16 h.



Scheme 3. Synthesis of **5a**–**c**. Reagents and conditions: **1** (1.0 equiv.), 2 (6.0 equiv.), CuI (5 mol-%), $[Pd(PPh_3)_2Cl_2]$ (10 mol-%), DIPA (3 mL), dioxane (7 mL), 85 °C, 16 h.

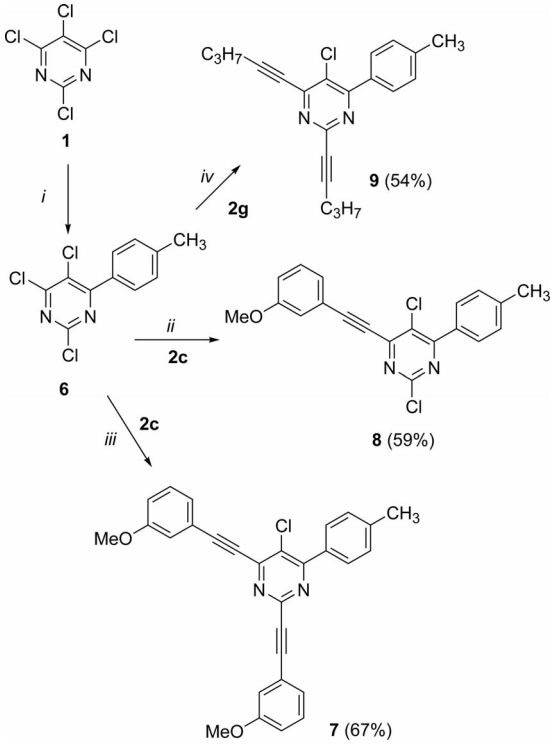
Table 3. Synthesis of **5a**–**c**.

2,**5**	R	% Yield for **5**[a]
a	4-*t*BuC_6H_4	76
b	Ph	73
c	3-(MeO)C_6H_4	79

[a] Yield of isolated product.

The Suzuki–Miyaura reaction of 2,4,5,6-tetrachloropyrimidine with (4-methylphenyl)boronic acid (1.0 equiv.), in the presence of 5 mol-% $[Pd(PPh_3)_2Cl_2]$ (60 °C, 2 h), afforded product **6** in 76% yield. The Sonogashira reaction of **6** with 3-ethynylanisole (**2c**; 1 equiv.) yielded **8** in 59% yield. The reaction of **6** with 2 equiv. of **2c** afforded product **7** in 67% yield. Likewise, product **9** was prepared from 1-pentyne (**2g**) in 54% yield (Scheme 4). During the optimization of the reaction conditions, the temperature was found to play an important role. The mono Sonogashira reaction of **1** and **6** was best carried out at 55 °C, whereas the twofold Sonogashira reactions of **6** had to be carried out at 70 °C. Compounds **7**–**9** are conceptually related to recently reported combined Suzuki/Sonogashira products derived

from pyridine.[12] The structure of product **7** was independently confirmed by a crystal structure analysis (Figure 2),[11] which shows that the aryl groups are slightly twisted out of plane.



Scheme 4. Synthesis of products **6**–**9**. Reagents and conditions: (i) **1** (1.0 equiv.), 4-methylphenylboronic acid (1.0 equiv.), $[Pd(PPh_3)_2Cl_2]$ (5 mol-%), K_2CO_3 (2 M, 1 mL), dioxane, 60 °C, 2 h; (ii) **2c** (1.0 equiv.), CuI (5 mol-%), $[Pd(PPh_3)_2Cl_2]$ (10 mol-%), DIPA (5 mL), 55 °C, 2 h; (iii) **2c** (2.0 equiv.), CuI (5 mol-%), $[Pd(PPh_3)_2Cl_2]$ (10 mol-%), DIPA (5 mL), 70 °C, 3 h; (iv) **2g** (2.0 equiv.), CuI (5 mol-%), $[Pd(PPh_3)_2Cl_2]$ (10 mol-%), DIPA, 70 °C, 3 h.

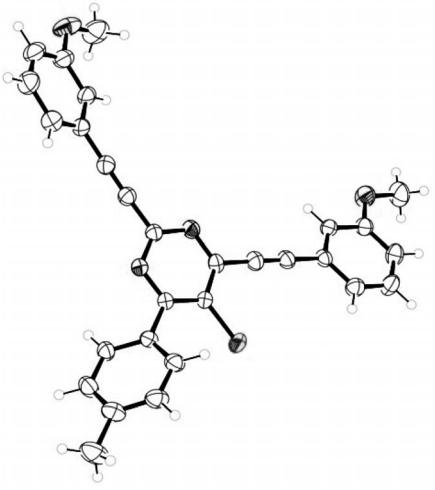


Figure 2. X-ray crystal structure of **7**.[11]

Absorption and Fluorescence

The UV/Vis and fluorescence spectroscopic data of various pyrimidine derivatives, measured in chloroform at 25 °C, are summarized in Table 4 (for the spectra, see the Supporting Information). All the compounds contain a pyrimidine core; their absorption wavelengths (λ_{abs}) are in the UV region (297–371 nm) and their emission wavelengths (λ_{em}) (fluorescence) are in the UV or blue region (395–470 nm). Pyrimidines containing methoxy-substituted aryl groups exhibit absorption and emission bands in the range of λ_{abs} = 301–367 nm and λ_{em} = 426–470 nm, respectively. For *tert*-butyl derivatives, the absorption and emission wavelengths are in the range of λ_{abs} = 325–371 nm and λ_{em} = 426–440 nm.

Table 4. Absorption and emission spectroscopic data of alkynylated pyrimidines.

Product	λ_{abs} [nm]	lg ε	λ_{em} [nm]	Stokes shift [nm]
3a	371	3.86	426	55
3b	354	3.35	395	41
3c	367	3.74	470	103
	λ_{abs} [nm]	lg ε	λ_{em} [nm]	
4b	312	4.25	406	94
4c	301	3.73	426	125
5a	325	4.01	440	115
5b	316	4.32	426	110
5c	302	4.11	438	136
7	297	4.19	405	108

The symmetrical Sonogashira products **3a** and **3b** exhibit absorption bands $\lambda_{abs,max}$ = 371 and 354 nm and emission bands at $\lambda_{em,max}$ = 426 and 395 nm, respectively, with Stokes shifts of 55 and 41 nm. Compound **3c** showed absorption at $\lambda_{abs,max}$ = 376 nm and emission at $\lambda_{em,max}$ = 470 nm with a larger Stokes shift (103 nm). In fact, larger Stokes shifts generally correspond with better fluorescence properties. Thus, the electron-donating 3-methoxyphenyl group of **3c** seems to be advantageous. In the case of unsymmetrical Sonogashira products, compound **4c** (containing a 3-methoxyphenyl group) showed a large Stokes shift (125 nm), whereas **4b** showed a smaller, but still acceptable, Stokes shift (94 nm). The same phenomenon was observed for tetrakis(arylethynyl)pyrimidines **5a**–**c**. Whereas compound **5c** showed a large Stokes shift (136 nm), **5a** and **5b** exhibited relatively small shifts. The mixed Suzuki/Sonogashira product **7** also showed a large Stokes shift (108 nm).

Conclusions

We have reported the synthesis of di-, tri-, and tetraalkynylpyrimidines by the first Sonogashira reactions of 2,4,5,6-tetrachloropyrimidine. The synthesis of tetraalkynylpyrimidines has been reported for the first time. All products are blue fluorescence dyes. Promising fluorescence properties, with regard to the Stokes shift, were observed for di-, tri-, and tetraalkynylated pyrimidines containing a *m*-methoxyphenyl substituent. This can be explained by push–pull substitution. In fact, inspection of the X-ray crystal structures shows that the central pyrimidine core and the aryl groups are only slightly twisted out of plane, which

allows almost ideal electronic interaction between the aromatic moieties through the alkynyl bridge. The tetralkynylated pyrididines are also interesting in their own right because this type of alkynylated molecule has not been previously reported. Preliminary results suggest that different alkynyl substituents can be introduced in a sequential manner. The application of a one-pot approach proved to be less efficient in terms of yield.

Experimental Section

General Procedure for Sonogashira Cross-Coupling Reactions: A suspension of 2,4,5,6-tetrachloropyrimidine, $[Pd(PPh_3)_2Cl_2]$ (10 mol-%), and CuI (5 mol-%) in diisopropylamine was degassed three times in a pressure tube. The acetylene derivative (1.2 equiv. per chlorine atom) was then added by using a syringe. The mixture was heated at the indicated temperature (60–80 °C) for 4–10 h then filtered and the residue was washed with CH_2Cl_2. The filtrate was washed with a saturated solution of ammonium chloride (2×25 mL), water (2×25 mL), and dried with anhydrous Na_2SO_4. The solvent was removed in vacuo and the product was purified by column chromatography on silica gel.

General Procedure for Suzuki Cross-Coupling Reactions: The reaction was carried out in a pressure tube. To a dioxane suspension (3–5 mL) of 2,4,5,6-tetrachloropyrimidine, $[Pd(PPh_3)_2Cl_2]$ (3–5 mol-%), and arylboronic acid was added an aqueous solution of K_2CO_3 (2 M, 1–2 mL). The mixture was heated at the indicated temperature (60–100 °C) for the indicated period of time (2–8 h), then diluted with water and extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were dried with Na_2SO_4, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (silica gel; ethyl acetate/heptanes).

4,6-Bis[(4-*tert*-butylphenyl)ethynyl]-2,5-dichloropyrimidine (3a): Starting with **1** (217 mg, 1 mmol), [4-(*tert*-butyl)phenyl]acetylene (**2a**; 0.4 mL, 2.4 mmol), CuI (5 mol-%), $[Pd(PPh_3)_2Cl_2]$ (10 mol-%), and diisopropylamine (5 mL), **3a** was isolated as a yellowish, highly viscous oil (350 mg, 76%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.24 (s, 18 H, $6 \times CH_3$), 7.34 (d, J = 8.5 Hz, 4 H), 7.52 (d, J = 8.5 Hz, 2 H), 7.54 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.0 (CH_3), 35.1, 84.0, 102.6, 117.4 (C), 125.7, 125.8, 132.5, 132.7 (CH), 133.1, 151.3, 154.6, 158.0 (C) ppm. IR (KBr): $\tilde{\nu}$ = 2960 (w), 2208 (s), 1516 (s), 1362 (m), 1259 (s), 1106 (m), 1016 (m), 922 (m), 832 (s), 774 (w) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 460 (33) $[M]^+$, 445 (100), 417 (7), 364 (3), 305 (7), 273 (5), 245 (6), 215 (45), 202 (33). HRMS (EI, 70 eV): calcd. for $C_{28}H_{26}Cl_2N_2$ $[M^+]$ 460.14685; found 460.14730.

2,5-Dichloro-4,6-bis(phenylethynyl)pyrimidine (3b): Starting with **1** (217 mg, 1 mmol), phenylacetylene (**2b**; 0.2 mL, 2.4 mmol), CuI (5 mol-%), $[Pd(PPh_3)_2Cl_2]$ (10 mol-%), and diisopropylamine (5 mL), **3b** was isolated as a light-brown solid (254 mg; 73%); m.p. 197–199 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.41 (m, 6 H), 7.59–7.62 (m, 4 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 84.1, 102.0, 120.4 (C), 128.6, 130.8, 132.8 (CH), 137.1, 151.2, 158.0 (C) ppm. IR (KBr): $\tilde{\nu}$ = 2961 (w), 2209 (s), 1517 (s), 1471 (m), 1261 (s), 1025 (m), 927 (m), 770 (m), 751 (s), 679 (s) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 348 (100) $[M]^+$, 331 (1), 315 (2), 276 (4), 251 (8), 226 (3), 186 (2), 160 (20). HRMS (EI, 70 eV): calcd. for $C_{20}H_{10}Cl_2N_2$ $[M^+]$ 348.02156; found 348.02110.

2,5-Dichloro-4,6-bis(3-methoxyphenyl)ethynylpyrimidine (3c): Starting with **1** (217 mg, 1 mmol), 3-ethynylanisole (**2c**; 0.3 mL, 2.4 mmol), CuI (5 mol-%), $[Pd(PPh_3)_2Cl_2]$ (10 mol-%), and diisopropylamine (5 mL), **3c** was isolated as brown solid (331 mg, 81%), m.p. 177–179 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.76 (s, 6 H, $2 \times OCH_3$), 6.93–6.97 (m, 2 H), 7.09–7.10 (m, 2 H), 7.17–7.25 (m, 4 H) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 55.4 (CH_3), 83.8, 101.9 (C), 117.2, 117.6 (CH), 121.3 (C), 125.4, 129.8 (CH), 132.1, 151.2, 158.0, 159.4 (C) ppm. IR (KBr): $\tilde{\nu}$ = 2974 (w), 2207 (m), 1596 (m), 1518 (m), 1268 (s), 1151 (m), 1035 (m), 955 (w), 850 (m), 772 (s), 673 (s), 541 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 408 (87) $[M^+]$, 379 (4), 356 (2), 331 (5), 281 (23), 253 (17), 207 (100), 170 (5), 147 (8). HRMS (EI, 70 eV): calcd. for $C_{22}H_{14}Cl_2N_2O_2$ $[M^+]$ 408.04370; found 408.04320.

2,5-Dichloro-4,6-bis[(6-methoxynaphthalen-2-yl)ethynyl]pyrimidine (3d): Starting with **1** (217 mg, 1 mmol), 2-ethynyl-6-methoxynaphthalene (**2d**; 436 mg, 2.4 mmol), CuI (5 mol-%), $[Pd(PPh_3)_2Cl_2]$ (10 mol-%), and diisopropylamine (5 mL), **3d** was isolated as a light-yellow solid (463 mg, 91%); m.p. 206–208 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.87 (s, 6 H, $2 \times OCH_3$), 7.07 (s, 2 H), 7.13 (d, J = 8.9 Hz, 2 H), 7.54 (d, J = 8.5 Hz, 2 H), 7.67 (d, J = 8.5 Hz, 2 H), 7.69 (d, J = 8.9 Hz, 2 H), 8.07 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 84.2, 104.2 (C), 106.0 (CH), 114.7 (C), 120.1, 127.3 (CH), 128.1 (C), 128.8 (CH), 129.5 (C), 130.0, 134.1 (CH), 135.7, 152.0, 157.0, 159.6 (C) ppm. IR (KBr): $\tilde{\nu}$ = 2934 (w), 2199 (s), 1626 (m), 1515 (m), 1476 (s), 1394 (w), 1266 (s), 1225 (m), 1192 (m), 1176 (m), 1032 (m), 969 (m), 849 (m), 798 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 508 (100) $[M]^+$, 493 (3), 465 (22), 422 (12), 362 (3), 325 (6), 281 (4), 254 (10), 211 (21). HRMS (EI, 70 eV): calcd. for $C_{30}H_{18}Cl_2N_2O_2$ $[M^+]$ 508.07428; found 508.07450.

2,4,6-Tris[(4-*tert*-butylphenyl)ethynyl]-5-chloropyrimidine (4a): Starting with **1** (217 mg, 1 mmol), 4-(*tert*-butyl)phenylacetylene (**2a**; 0.6 mL, 3.6 mmol), CuI (5 mol-%), $[Pd(PPh_3)_2Cl_2]$ (10 mol-%), and diisopropylamine (5 mL), **4a** was isolated as a deep-yellow solid (468 mg; 80%); m.p. 227–229 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.24 (s, 9 H, $3 \times CH_3$), 1.29 (s, 18 H, $6 \times CH_3$), 6.99 (d, J = 8.3 Hz, 3 H), 7.29 (d, J = 8.5 Hz, 3 H), 7.33 (d, J = 8.4 Hz, 3 H), 7.45 (d, J = 8.5 Hz, 3 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 31.1, 31.4 (CH_3), 34.7, 34.9, 84.9, 93.2, 97.4, 118.6, 124.8 (C), 125.4, 125.5, 127.4, 132.1 (CH), 134.0, 146.9, 151.6, 153.1, 156.0 (C) ppm. IR (KBr): $\tilde{\nu}$ = 2959 (m), 1504 (s), 1432 (s), 1356 (m), 1292 (m), 1263 (s), 1133 (s), 1036 (s), 931 (m), 816 (s), 767 (m), 735 (w) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 582 (70) $[M]^+$, 567 (16), 552 (38), 537 (46), 518 (100), 482 (3), 462 (2), 447 (2), 410 (12), 382 (02), 344 (31). HRMS (EI, 70 eV): calcd. for $C_{40}H_{39}ClN_2$ $[M^+]$ 582.28004; found 582.28020.

5-Chloro-2,4,6-tris(phenylethynyl)pyrimidine (4b): Starting with **1** (217 mg, 1 mmol), phenylacetylene (**2b**; 0.4 mL, 3.6 mmol), CuI (5 mol-%), $[Pd(PPh_3)_2Cl_2]$ (10 mol-%), and diisopropylamine (5 mL), **4b** was isolated as light-brown solid (294 mg, 71%); m.p. 220–222 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.40 (m, 10 H), 7.58–7.63 (m, 5 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 84.4, 87.1, 89.2, 100.5, 120.8, 121.1 (C), 128.4, 128.6, 129.9, 130.5 (CH), 132.0 (C), 132.7 (CH), 149.8, 150.4 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3054 (w), 2215 (s), 1512 (s), 1490 (m), 1363 (s), 1229 (m), 1177 (m), 1025 (m), 970 (m), 918 (w), 842 (w), 751 (s), 686 (s) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 414 (89) $[M]^+$, 377 (60), 346 (20), 315 (12), 250 (27), 238 (23), 189 (33). HRMS (EI, 70 eV): calcd. for $C_{28}H_{15}ClN_2$ $[M^+]$ 414.09215; found 414.09240.

5-Chloro-2,4,6-tris[(3-methoxyphenyl)ethynyl]pyrimidine (4c): Starting with **1** (217 mg, 1 mmol), 3-ethynyl anisole (**2c**; 0.45 mL, 3.6 mmol), CuI (5 mol-%), $[Pd(PPh_3)_2Cl_2]$ (10 mol-%), and diisopropylamine (5 mL), **4c** was isolated as a deep-brown solid

(388 mg, 77%); m.p. 163–165 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.74 (s, 3 H, OCH_3), 3.76 (s, 6 H, 2 × OCH_3), 6.87–6.96 (m, 3 H), 7.11–7.13 (m, 3 H), 7.18–7.25 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.3, 55.4 (OCH_3), 84.2, 86.8, 89.2, 100.4 (C), 117.0, 117.1, 117.2, 117.4 (CH), 121.7, 122.0 (C), 125.3, 129.5, 129.7 (CH), 132.0, 149.8, 150.4, 159.3, 159.4 (C) ppm. IR (KBr): $\tilde{\nu}$ = 2940 (w), 2214 (s), 1573 (m), 1513 (s), 1483 (m), 1368 (m), 1261 (s), 1162 (m), 1039 (s), 848 (m), 769 (s), 677 (s) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 504 (100) [M]$^+$, 473 (3), 431 (2), 389 (4), 355 (12), 312 (22), 252 (31), 190 (31). HRMS (EI, 70 eV): calcd. for $C_{31}H_{21}ClN_2O_3$ [M$^+$] 504.12392; found 504.12410.

5-Chloro-2,4,6-tris(*p*-tolylethynyl)pyrimidine (4d): Starting with **1** (217 mg, 1 mmol), *p*-tolylacetylene (**2e**; 0.4 mL, 3.6 mmol), CuI (5 mol-%), [Pd(PPh_3)$_2$$Cl_2$] (10 mol-%), and diisopropylamine (5 mL), **4d** was isolated as a yellow solid (383 mg, 84%); m.p. 102–104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3 H, CH_3), 2.32 (s, 6 H, 2 × CH_3), 7.09–7.15 (m, 8 H), 7.50 (d, *J* = 8.1 Hz, 4 H) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 21.6, 21.7 (CH_3), 84.2, 86.8, 89.5, 100.9, 117.5, 118.1 (C), 129.2, 129.3, 132.6 (CH), 140.3, 141.1, 149.8, 150.5 (C) ppm. IR (KBr): $\tilde{\nu}$ = 2918 (w), 2208 (s), 1682 (w), 1510 (s), 1479 (s), 1361 (m), 1226 (w), 1176 (m), 1019 (m), 969 (m), 907 (m), 810 (s), 727 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 456 (100) [M$^+$], 422 (4), 280 (7), 264 (5), 230 (11), 174 (36), 139 (54). HRMS (EI, 70 eV): calcd. for $C_{31}H_{21}ClN_2$ [M$^+$] 456.13971; found 456.13930.

5-Chloro-2,4,6-tri(hept-1-ynyl)pyrimidine (4e): Starting with **1** (217 mg, 1 mmol), 1-heptyne (**2e**; 0.5 mL, 3.6 mmol), CuI (5 mol-%), [Pd(PPh_3)$_2$$Cl_2$] (10 mol-%), and diisopropylamine (5 mL), **4e** was isolated as a yellowish, highly viscous oil (270 mg, 68%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.1 Hz, 6 H, CH_3), 1.07 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.21–1.43 (m, 12 H), 1.53–1.64 (m, 6 H), 2.33 (t, *J* = 7.1 Hz, 2 H), 2.41 (t, *J* = 7.2 Hz, 4 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 12.9, 13.9 (CH_3), 19.7, 22.1, 27.7, 28.2, 29.5, 30.9, 40.8, 41.7 (CH_2), 80.2, 91.2, 99.0, 131.5, 149.6, 150.2 (C) ppm. IR (KBr): $\tilde{\nu}$ = 2930 (m), 2232 (w), 1604 (s), 1455 (m), 1165 (m), 1079 (m), 783 (m), 760 (w) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 396 (90) [M]$^+$, 382 (60), 368 (41), 344 (100), 330 (40), 316 (7), 301 (4), 287 (6), 231 (4), 209 (4). HRMS (EI, 70 eV): calcd. for $C_{25}H_{33}ClN_2$ [M$^+$] 396.23160; found 396.23176.

5-Chloro-2,4,6-tri(pent-1-ynyl)pyrimidine (4f): Starting with **1** (217 mg, 1 mmol), 1-pentyne (**2f**; 0.3 mL, 3.6 mmol), CuI (5 mol-%), [Pd(PPh_3)$_2$$Cl_2$] (10 mol-%), and diisopropylamine (5 mL), **4f** was isolated as a brownish, highly viscous oil (216 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.3 Hz, 6 H, CH_3), 0.99 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.53–1.64 (m, 6 H), 2.32 (t, *J* = 7.1 Hz, 2 H), 2.42 (t, *J* = 7.0 Hz, 4 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 13.5, 13.6 (CH_3), 21.4, 21.7, 29.6, 30.1 (CH_2), 79.1, 91.4, 103.1, 131.5, 149.7, 150.1 (C) ppm. IR (KBr): $\tilde{\nu}$ = 2926 (m), 2228 (m), 1727 (w), 1515 (s), 1489 (s), 1359 (s), 1172 (m), 1080 (w), 962 (m), 790 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 312 (100) [M]$^+$, 297 (21), 282 (40), 267 (13), 254 (15), 225 (23), 211 (33), 183 (43). HRMS (EI, 70 eV): calcd. for $C_{19}H_{21}ClN_2$ [M$^+$] 312.14321; found 312.14336.

2,4,5,6-Tetrakis[(4-*tert*-butylphenyl)ethynyl]pyrimidine (5a): Starting with **1** (217 mg, 1 mmol), 4-(*tert*-butyl)phenylacetylene (**2a**; 1.0 mL, 6.0 mmol), CuI (5 mol-%), [Pd(PPh_3)$_2$$Cl_2$] (10 mol-%), dioxane (7 mL), and diisopropylamine (3 mL), **5a** was isolated as a deep-brown solid (535 mg; 76%); m.p. 110–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (s, 9 H, CH_3), 1.26 (s, 18 H, CH_3), 1.28 (s, 9 H, CH_3), 7.31–7.37 (m, 8 H), 7.49–7.56 (m, 8 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.0, 30.1 (CH_3), 33.9, 34.0, 82.2, 85.0, 86.7, 89.2, 98.2, 102.4, 117.3 (C), 124.4, 124.6, 130.5, 131.4, 131.6 (CH), 149.2, 151.2, 151.9, 152.3, 152.8 (C) ppm. IR (KBr): $\tilde{\nu}$ = 2959 (w), 2209 (w), 1483 (m), 1398 (m), 1264 (m), 1106 (m), 1016 (m), 831 (s), 634 (w), 560 (s) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 704 (100) [M]$^+$, 644 (9), 471 (2), 337 (12), 281 (2), 207 (4), 173 (39). HRMS (EI, 70 eV): calcd. for $C_{52}H_{52}N_2$ [M$^+$] 704.41250; found 704.41482.

2,4,5,6-Tetrakis(phenylethynyl)pyrimidine (5b): Starting with **1** (217 mg, 1 mmol), phenylacetylene (**2b**; 0.62 mL, 6.0 mmol), CuI (5 mol-%), [Pd(PPh_3)$_2$$Cl_2$] (10 mol-%), dioxane (7 mL), and diisopropylamine (3 mL), **5b** was isolated as a light-brown solid (349 mg; 73%); m.p. 188–190 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.77–6.86 (m, 12 H), 7.02–7.11 (m, 8 H) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 83.5, 86.2, 87.9, 90.0, 98.9, 103.4, 121.2, 121.3, 122.3 (C), 128.4, 128.6, 128.7, 129.5, 129.8, 130.3, 131.7, 132.6, 132.7 (CH), 150.3, 152.3 (C) ppm. IR (KBr): $\tilde{\nu}$ = 2918 (w), 2213 (m), 1479 (s), 1398 (s), 1211 (w), 1067 (w), 970 (w), 797 (m), 767 (m), 748 (s), 680 (s) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 480 (92) [M$^+$], 375 (40), 330 (20), 305 (10), 260 (18), 218 (23). HRMS (EI, 70 eV): calcd. for $C_{36}H_{20}N_2$ [M$^+$] 480.16292; found 480.16260.

2,4,5,6-Tetrakis[(3-methoxyphenyl)ethynyl]pyrimidine (5c): Starting with **1** (217 mg, 1 mmol), 3-ethynylanisole (**3c**; 0.76 mL, 6.0 mmol), CuI (5 mol-%), [Pd(PPh_3)$_2$$Cl_2$] (10 mol-%), dioxane (7 mL), and diisopropylamine (3 mL), **5c** was isolated as a deep-brown solid (474 mg, 79%); m.p. 152–154 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.72 (s, 6 H, 2 × OCH_3), 3.74 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 6.81–6.85 (m, 2 H), 6.93–6.97 (m, 4 H), 7.00–7.03 (m, 2 H), 7.12–7.23 (m, 8 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.2, 55.3, 55.4 (OCH_3), 83.5, 84.2, 86.8, 89.2, 100.4, 102.7 (C), 115.4, 116.9, 117.0, 117.1, 117.2, 117.3 (CH), 121.7, 122.0, 123.1 (C), 124.6, 125.3, 129.4, 129.5, 129.7 (CH), 149.8, 150.4, 159.2, 159.3, 159.4 (C) ppm. IR (KBr): $\tilde{\nu}$ = 2939 (w), 2213 (s), 1574 (m), 1513 (s), 1483 (m), 1367 (m), 1315 (m), 1261 (s), 1161 (m), 1039 (s), 848 (m), 769 (s), 677 (s) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 600 (80) [M]$^+$, 569 (60), 538 (34), 507 (100), 470 (51), 440 (12), 410 (17), 380 (32), 304 (56), 280 (40), 204 (12). HRMS (EI, 70 eV): calcd. for $C_{40}H_{28}N_2O_4$ [M$^+$] 600.20221; found 600.20246.

5-Chloro-2,4-bis[(3-methoxyphenyl)ethynyl]-6-(*p*-tolyl)pyrimidine (7): Starting with **6** (100 mg, 0.36 mmol), 3-ethynylanisole (**2c**; 0.1 mL, 0.72 mmol), CuI (5 mol-%), [Pd(PPh_3)$_2$$Cl_2$] (10 mol-%), and diisopropylamine (5 mL), **7** was isolated as a crystalline brown solid (114 mg, 67%); m.p. 167–169 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.34 (s, 3 H, CH_3), 3.72 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 6.85–6.93 (m, 2 H), 7.10–7.12 (m, 2 H), 7.19–7.25 (m, 6 H), 7.69 (d, *J* = 8.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 55.3 (OCH_3), 55.4 (OCH_3), 84.7, 87.3, 88.6, 99.3 (C), 116.8, 117.0, 117.1, 117.2 (CH), 121.9, 122.2 (C), 125.2 (CH), 128.5 (C), 129.0, 129.3, 129.5, 129.6, 129.7 (CH), 132.7, 141.0, 150.2, 150.6, 159.3, 159.4, 164.1 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3008 (w), 2214 (m), 1573 (w), 1525 (m), 1486 (s), 1357 (s), 1287 (m), 1255 (s), 1180 (m), 1043 (m), 859 (m), 774 (s), 683 (s) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 464 (100) [M$^+$], 424 (61), 389 (09), 272 (02), 232 (27), 190 (10), 150 (06). HRMS (EI, 70 eV): calcd. for $C_{29}H_{21}O_2N_2Cl$ [M$^+$] 464.12926; found 464.12920.

2,5-Dichloro-4-[(3-methoxyphenyl)ethynyl]-6-(*p*-tolyl)pyrimidine (8): Starting with **6** (100 mg, 0.36 mmol), 3-ethynylanisole (**2c**; 0.05 mL, 0.36 mmol), CuI (5 mol-%), [Pd(PPh_3)$_2$$Cl_2$] (10 mol-%), and diisopropylamine (5 mL), **8** was isolated as a crystalline light-brown solid (79 mg, 59%); m.p. 110–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3 H, CH_3), 3.75 (s, 3 H, OCH_3), 6.91–6.95 (m, 1 H), 7.09–7.10 (m, 1 H), 7.17–7.25 (m, 4 H), 7.72 (d, *J* = 8.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 55.4 (OCH_3), 84.4, 100.7 (C), 117.2, 117.4 (CH), 121.6 (C), 125.3 (CH), 128.5 (C), 129.1, 129.6, 129.7 (CH), 131.9, 141.6, 152.2, 158.1,

159.4, 165.8 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3013 (w), 2935 (w), 2213 (w), 1578 (m), 1481 (m), 1255 (s), 1151 (s), 1035 (s), 914 (m), 838 (m), 775 (s), 676 (s) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 368 (100) $[M]^+$, 333 (10), 325 (2), 303 (2), 290 (12), 227 (20), 184 (26), 140 (40). HRMS (EI, 70 eV): calcd. for $C_{20}H_{14}ON_2Cl_2$ $[M^+]$ 368.04777; found 368.04752.

5-Chloro-2,4-di(pent-1-ynyl)-6-(*p*-tolyl)pyrimidine (9): Starting with **6** (100 mg, 0.36 mmol), 1-pentyne (**2f**; 0.07 mL, 0.72 mmol), CuI (5 mol-%), $[Pd(PPh_3)_2Cl_2]$ (10 mol-%), and diisopropylamine (5 mL), **9** was isolated as a light-yellow semi-solid (66 mg, 54%). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.4 Hz, 3 H, CH_3), 0.98 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.53–1.64 (m, 4 H), 2.31 (s, 3 H, CH_3), 2.34 (t, *J* = 7.1 Hz, 2 H), 2.42 (t, *J* = 7.0 Hz, 2 H), 7.19 (d, *J* = 8.1 Hz, 2 H), 7.62 (d, *J* = 8.3 Hz, 2 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 13.5, 13.7 (CH_3), 21.3 (CH_2), 21.4 (CH_3), 21.5, 21.7 (CH_2), 80.0, 90.7, 102.3 (C), 128.8, 129.5 (CH), 129.9, 132.8, 133.5, 150.2, 150.8, 163.7 (C) ppm. IR (KBr): $\tilde{\nu}$ = 2961 (w), 2232 (m), 1611 (w), 1529 (m), 1492 (s), 1355 (s), 1179 (m), 1149 (m), 1035 (m), 821 (m), 795 (m), 756 (w) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 336 (20) $[M]^+$, 321 (4), 308 (100), 292 (3), 279 (3), 256 (1), 229 (20), 243 (10), 208 (15), 178 (21). HRMS (EI, 70 eV): calcd. for $C_{21}H_{21}ClN_2$ $[M^+]$ 336.13915; found 336.13930.

Supporting Information (see footnote on the first page of this article): Copies of absorption and emission spectra.

[1] a) M. Palucki, *Palladium in Heterocyclic Chemistry*, vol. 26, Elsevier, **2007**, p. 475; b) C. Sirichaiwat, C. Intaraudom, S. Kamchonwongpaisan, J. Vanichtanankul, Y. Thebtaranonth, Y. Yuthavong, *J. Med. Chem.* **2004**, *47*, 345; c) N. J. White, *Br. Med. Bull.* **1998**, *54*, 703; d) J. H. McKie, K. T. Douglas, C. Chan, S. A. Roser, R. Yates, M. Read, J. E. Hyde, M. J. Dascombe, Y. Yuthavong, W. Sirawaraporn, *J. Med. Chem.* **1998**, *41*, 1367.

[2] a) K. S. Jain, T. S. Chitre, P. B. Miniyar, M. K. Kathiravan, V. S. Bendre, V. S. Veer, S. R. Shahane, S. J. Shishoo, *Curr. Sci.* **2006**, *90*, 793; b) N. A. Hassan, *Molecules* **2000**, *5*, 826; c) M. Perrisin, M. Favre, L. D. Cuong, F. Huguet, C. Gaultier, J. Narcisse, *Eur. J. Med. Chem.* **1988**, *23*, 543; d) A. Cannito, M. Perrisin, C. Lnu-Due, F. Huguet, C. Gaultier, J. Narcisse, *Eur. J. Med. Chem.* **1990**, *25*, 635; e) P. A. S. Smith, R. O. Kan, *J. Org. Chem.* **1964**, *29*, 2261; f) S. Nega, J. Aionso, A. Diazj, F. Junquere, *J. Heterocycl. Chem.* **1990**, *27*, 269; g) C. J. Shishoo, K. S. Jain, *J. Heterocycl. Chem.* **1992**, *29*, 883.

[3] a) J. Balzarini, C. McGuigan, *J. Antimicrob. Chemother.* **2002**, *50*, 5; b) C. McGuigan, C. J. Yarnold, G. Jones, S. Velazquez, H. Barucki, A. Brancale, G. Andrei, R. Snoeck, E. D. Clercq, J. Balzarini, *J. Med. Chem.* **1999**, *42*, 4479; c) C. McGuigan, H. Barucki, S. Blewett, A. Carangio, J. T. Erichsen, G. Andrei, R. Snoeck, E. D. Clercq, J. Balzarini, *J. Med. Chem.* **2000**, *43*, 4993.

[4] T. Wang, M. L. Lamb, D. A. Scott, H. Wang, M. H. Block, P. D. Lyne, J. W. Lee, A. M. Davies, H. J. Zhang, Y. Zhu, F. Gu, Y. Han, B. Wang, P. J. Mohr, R. J. Kaus, J. A. Josey, E. Hoffman, K. Thress, T. MacIntyre, H. Wang, C. A. Omer, D. Yu, *J. Med. Chem.* **2008**, *51*, 4672.

[5] G. Hughes, Ch. Wang, A. S. Batsanov, S. Fern, M. R. Frank, I. F. Bryce, A. P. Perepichka, A. P. Monkman, B. P. Lyons, *Org. Biomol. Chem.* **2003**, *1*, 3069.

[6] a) G. W. Gray, M. Hird, K. J. Toyne, *Mol. Cryst. Liq. Cryst.* **1991**, *195*, 221; b) F. Lincker, P. Bourgun, P. Masson, P. Dider, L. Guidoni, J. Y. Bigot, J. F. Nicoud, B. Donnio, D. Guillon, *Org. Lett.* **2005**, *7*, 1505; c) A. Kraft, A. C. Grimsdale, A. B. Holmes, *Angew. Chem. Int. Ed.* **1998**, *37*, 402; d) S. C. Lo, P. L. Burn, *Chem. Rev.* **2007**, *107*, 1097; e) D. Fichou, *J. Mater. Chem.* **2000**, *10*, 571; f) M. Funahashi, F. Zhang, N. Tamaoki, *Adv. Mater.* **2007**, *19*, 353; g) G. Yu, J. Gao, J. C. Hummelen, F. Wudl, A. J. Heeger, *Science* **1995**, *270*, 1789; h) W. Denk, J. H. Strickler, W. W. Webb, *Science* **1990**, *248*, 73.

[7] a) K. Itami, D. Yamazaki, J.-I. Yoshida, *J. Am. Chem. Soc.* **2004**, *126*, 15396; b) Y.-C. Lin, C. K. Lai, Y. C. Chang, K. T. Liu, *Liq. Cryst.* **2002**, *29*, 237.

[8] a) Y. Yang, A. R. Martin, *Heterocycles* **1992**, *34*, 1395; b) S. Gronowitz, A.-B. Hoenfeldt, V. Kristjannson, T. Musil, *Chem. Scripta* **1986**, *26*, 305; c) D. Peters, A.-B. Hoenfelt, S. Gronowitz, *J. Heterocycl. Chem.* **1990**, *27*, 2165.

[9] a) S. Acelle, Y. Ramondenc, G. Dupas, N. Ple, *Tetrahedron* **2008**, *64*, 2783; b) G. A. Molander, B. W. Katona, F. Machrouhi, *J. Org. Chem.* **2002**, *67*, 8416; c) R. D. Chambers, C. W. Hall, J. Hutchinson, R. W. Millar, *J. Chem. Soc. Perkin Trans. 1* **1998**, 1705; d) S. Achelle, Y. Ramondenc, G. Dupas, N. Plé, *Eur. J. Org. Chem.* **2008**, 3129.

[10] M. Hussain, N. T. Hung, R. A. Khera, I. Malik, D. S. Zinad, P. Langer, *Adv. Synth. Catal.* **2010**, *352*, 1429.

[11] CCDC-814657 (for **3c**) and -805299 (for **7**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[12] L. M. Daykin, J. S. Siddle, A. L. Ankers, A. S. Batsanov, M. R. Bryce, *Tetrahedron* **2010**, *66*, 668.

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