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Synthesis of 4,5-diarylquinazolines: a system with cofacial aromatic rings. Diazines. Part 39

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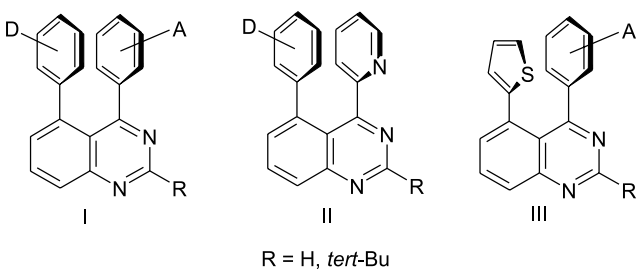
Abstract—Using metallation reactions and Pd-catalyzed coupling, we report here two synthetic routes leading to eight new 4,5-di(hetero)-arylquinazolines. Non-linear activity has been highlighted for some of these compounds with stacked aromatic rings.

Stacked or cofacial aromatic or heteroaromatic rings appear in a number of natural products, the most important being nucleic acids where the rings are offset to each other.[1] Furthermore, several studies dealing with 1,8-diaryl[2–10] and 1,8-dihetarylnaphthalenes,[11–13] where the aromatic rings are π-stacked, have been developed. In such naphthalenes, the two aromatic rings are held cofacial but are splayed out from each other and are able to rotate about the bonds attaching them to the rigid naphthalene frame. Crystal structures show that the aryl rings in such naphthalenes are not parallel to each other but are tilted away in order to increase separation and thereby minimize electrostatic repulsion.

Among the 1,8-di(hetero)arylnaphthalenes previously described in the literature, some of them have highlighted interesting non-linear optic (NLO) activities.[14] These results urged us to synthesize aza-analogues of such structures which could present potential applications in NLOs.

In the context of our studies on the synthesis of benzodiazines using metallation and cross-coupling reactions, we report here the synthesis of various di(hetero)aryl-quinazolines I–III (Scheme 1).



Scheme 1.

In these structures, one aryl substituent is rendered electron-rich by an electron-donor (D) or an heteroarene while the other has reduced density as a result of an electron-withdrawing group (A) or heteroarene, it could also be noticed that position of aryl or hereroarene at the C_4 and C_5 positions avoid a direct conjugation between the donor (D) and acceptor (A). So compounds of this type offer potential non-covalent interactions between the opposite faces of the D/A π-electron systems.[15] To improve this through-space effect which is defined as Coulombic (electrostatic) interactions, we have synthesized compounds with The (A) π-electron system on the pyrimidine moiety which is a π-deficient ring and the (D) π-electron system on the benzene ring.

Using cross-coupling reactions and metallations, we report here two synthetic routes for compounds of type I–III (Scheme 1), the first one involves cyclization of substituted benzene derivatives to obtain 4(3*H*)-quinazolinone derivatives, whereas the second one uses in a first step metallation reaction of 4(3*H*)-quinazolinone to functionalize the benzene moiety.

In the first synthetic route, the starting material was the methyl 2-amino-6-methoxybenzoate **1** prepared according to the procedure previously described in the literature.[16] Reaction of **1** with formamidine acetate at 180 °C led to 5-methoxy-4-(3*H*)-quinazolinone **2** which has been converted with a mixture of phosphorus pentachloride and phosphorus oxychloride to 4-chloro-5-methoxy-4-(3*H*)-quinazolinone **3**. This last compound underwent cross-coupling reactions under Suzuki or Stille conditions allowing formation of the first aryl–aryl bond at the C_4 position (Scheme 2).

Keywords: Metallation; Cross-coupling reactions; 4,5-Di(hetero)-arylquinazolines; Non-linear optics.
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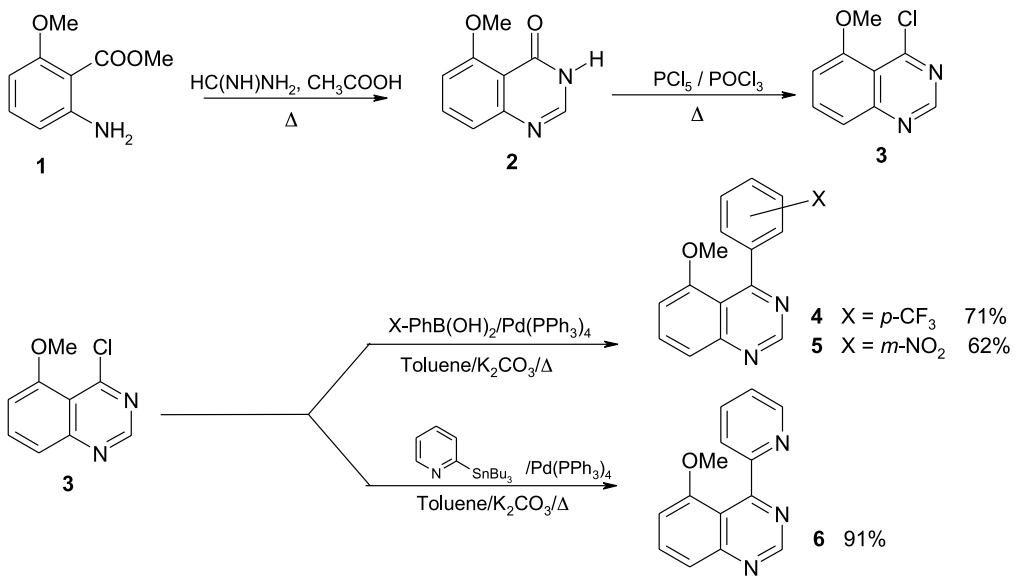


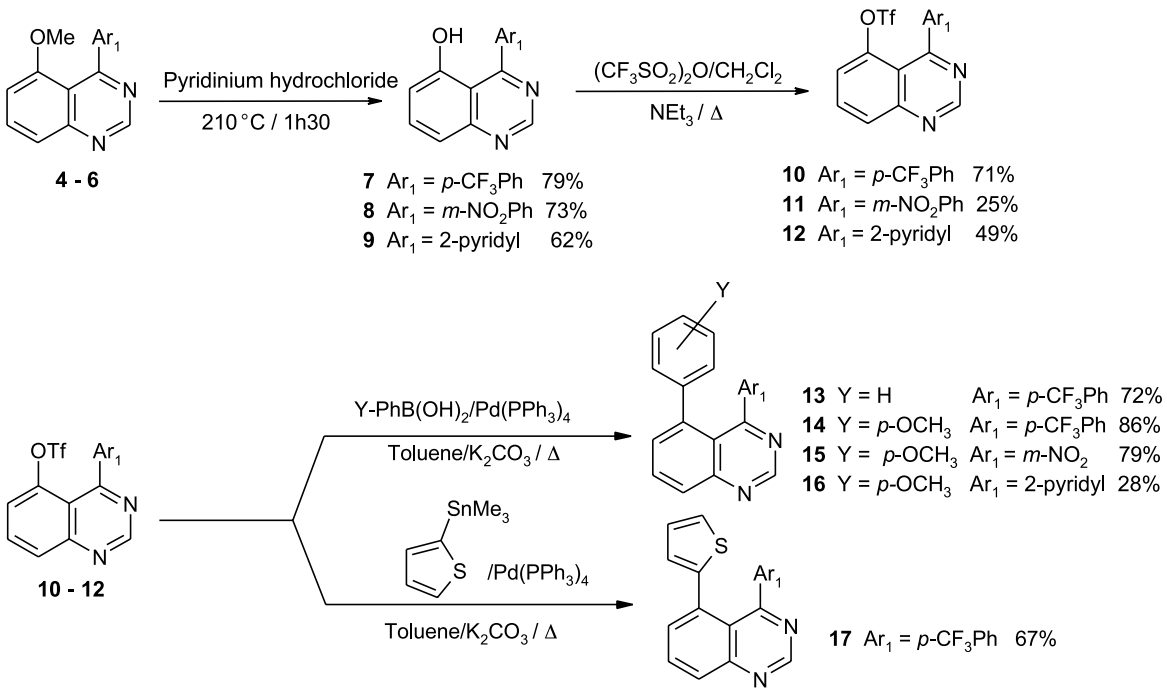
Scheme 2.

In a second time, cleavage of the methoxy group has been achieved with pyridinium hydrochloride under reflux leading to corresponding hydroxy compounds **7**–**9** which were reacted with trifluoromethanesulfonic anhydride to obtain triflate derivatives **10**–**12**. A subsequent cross-coupling reaction with various arylboronic acids was used to obtain the unsymmetrical diarylquinazolines **13**–**17** (Scheme 3).

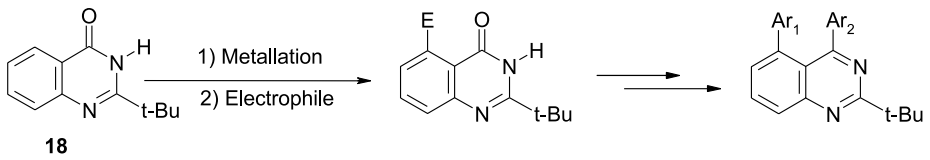
In the second synthetic route, the starting material was 2-*tert*-butyl-4(3*H*)-quinazolinone **18**. In a first step, lithiation and functionalization of the benzene moiety of **18** have been performed regioselectively at the C_5 position, then further cross-coupling reactions allowed us to access to new 4,5-di(hetero)arylquinazolines (Scheme 4).

In a previous paper,[18] we have mentioned the metallation of substituted 4-(3*H*)-quinazolones with 1 equiv. of *n*-BuLi at −78 °C, followed by reaction of LTMP in excess (4 equiv.). Under these conditions, lithiation was observed at the C_8 position, *péri* to the ring nitrogen atom N_1. We have reinvestigated the conditions of metallation with compound **18**,[21] which presents a *tert*-butyl group on the C_2 position. This group avoids a nucleophilic attack of the metallating agent at this position[19–20] and prevents deprotonation on the carbon C_α of the lateral chain.[22–24] It could be noticed that with such a product, alkyllithiums could be used as metallating agent.

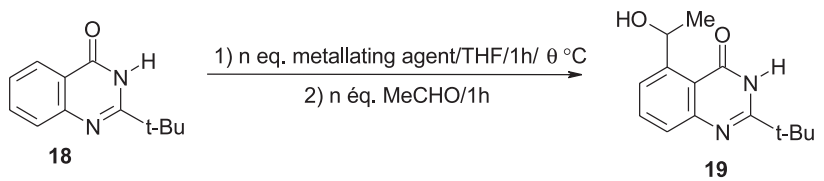
Treatment of **18** with n equivalents of LTMP (*n*=4 to 8) at 0 °C for 1 h and acetaldehyde as electrophile did not allow



Scheme 3.



Scheme 4.



Scheme 5.

Table 1. Metallation of compound **18**

Entry	Metallating agent	nequiv.	Temperature (°C)	Time, *t* (h)	Starting material (%)	
					18	**19**
1	*n*-BuLi	3	−78	1	64	36
2	*n*-BuLi	3	0	1	60	40
3	*n*-BuLi	4	0	1	28	72
4	(*n*-BuLi/TMEDA)	4	−20	2	22	78
5	(*s*-BuLi/TMEDA)	4	−78	1	62	38
6	(*s*-BuLi/TMEDA)	4	−20	1	6	94

any reaction and starting material has been recovered. So, use of alkyllithiums was performed under various conditions with acetaldehyde as electrophile, leading to compound **19** (Scheme 5, Table 1).

The results given in Table 1 revealed that the best results were obtained with 4 equiv. of *s*-BuLi and TMEDA at −20 °C for 1 h (entry 6), under these conditions, **19** was obtained in good yield (94%) beside small amounts of starting material.

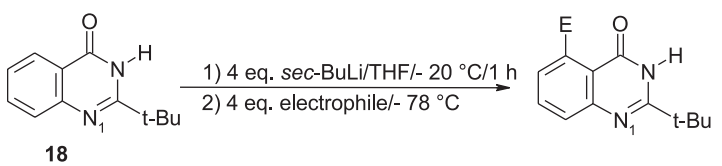
Structure of compound **19** was established unambigously by NMR experiments highlighting a regioselective metallation at the C_5 position. These conditions were used with other electrophiles (Scheme 6).

Starting from compound **24**, cross-coupling reactions were performed under Suzuki conditions leading to 2-*tert*-butyl-5-aryl-4-(3*H*)-quinazolones **25**–**27**. These 4-oxo derivatives were converted with phosphorus oxychloride to their 4-chloro derivatives **28**–**29**. In a last step compounds **28** and **29** reacted with arylboronic acids to give the expected compounds **30**–**31**. Compound **28** was also reacted with 2-tributylstannylpyridine following Stille cross-coupling conditions and afforded **32** (Scheme 7).

The X-ray structure analysis of **14** (Fig. 1) shows that both phenyl rings subtend angles of 62 and 68° with the plane of quinazoline. Similarly high torsion angles are observed in other diarylnaphthalenes[14,17] and lead to face–face arrangement of such π-electron systems. The very close approach of the two phenyl rings is noteworthy: the value of 297.1 pm observed for C_9–C_{15} is slightly smaller than in the other 1,8-diphenylnaphthalenes and markedly smaller than the van der Waals distance for parallel aromatic systems (about 345 pm).[17b]

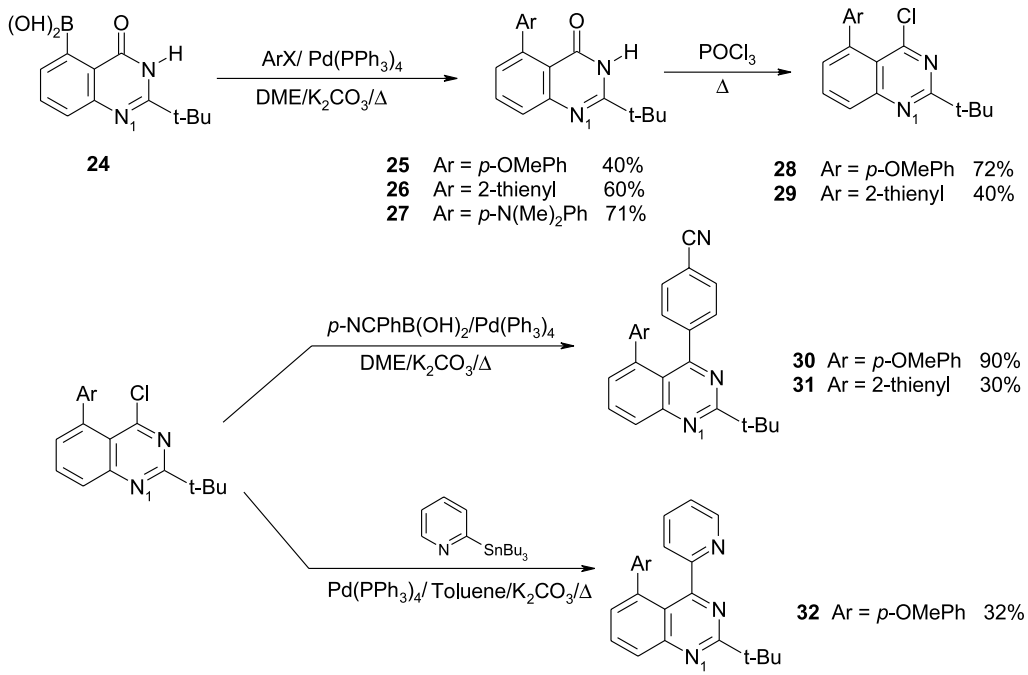
As it has been previously mentioned in the literature,[14] through-space interaction and lack of D/A conjugation with possible D–A/D–A stacking, tend to favor the formation of acentric structures. Thus **14** crystallizes in the non-centrosymmetric space group $P2_1$, which renders such a structure candidate to non-linear activity for a frequency-doubling function.

The NLO measurements of the $\mu\beta$ values of compounds **15**



19 E = MeCH(OH) 94% **22** E = Bu_3Sn 50%
20 E = PhCH(OH) 92% **23** E = I 37%
21 E = PhS 17% **24** E = $B(OH)_2$ 68%

Scheme 6.



Scheme 7.

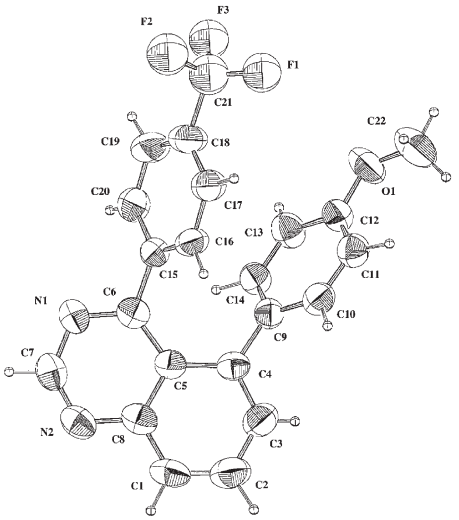


Figure 1. Crystal structure of **14**. Selected distances (ppm): C4–C6 256.5; C9–C15 297.1; N2–C1 241.9; C18–C12 435.6. Planar angles (°): C4–C5–C6: 126.4. Interplanar angles (°) C5–C6/C15–C20: 61.7; C4–C5/C9–C14: 68.0.

and **17** have been performed by means of the EFISH method (Table 2). The values μ_{calc} are the computed ground-state dipole moments calculated by AM1.

The high β values of these compounds **15**, **17**, compared to paranitroanilin (PNA) (17×10^{-30} esu)[14a] indicate that 4,5-diarylquinazolines may have appreciable non-linear optical properties. Further and complete measurements will be performed with the other compounds.

Table 2. μ_{calcd} (D): computed ground state dipole moments, experimental $\mu\beta$ values determined by EFISH measurements and evaluated first-order hyperpolarizability β of compounds **15**, **17**

Compound	μ_{calcd} (D)	$\mu\beta\times10^{-48}$ esu	$\beta\times10^{-30}$ esu
15	6.62	22.4	547
17	3.42	11.6	169

1. Conclusion

We have synthesized eight new 4,5-di(hetero)aryl quinazolines using cross-coupling reactions. The regioselective functionalization of the C_5 position of the 2-*tert*-butyl-4(*3H*)-quinazolinone **18** allowed us to develop a second synthetic route to access to compounds **29**–**31**. The non-linear optical properties of two compounds of these series have been measured and interesting and promising results have been observed. Synthesis of other new 4,5-di(hetero)-aryl quinazolines and measurement of their first-order hyperpolarizability β are in progress.

2. Experimental

Melting points were determined on a Kofler hot-stage. The ^{1}H, ^{13}C and ^{19}F spectra were recorded on a Bruker AC 300 (300 MHz ^{1}H, 75 MHz ^{13}C, 282 MHz ^{19}F) instrument. Microanalyses were performed on a Carlo Erba CHNOS 1160 apparatus. The IR spectra were obtained as potassium bromide pellets with a Perkin–Elmer Paragon 500 spectrophotometer.

All reagents were of commercial quality and were purchased from Acros, Aldrich Chemical Co. or Avocado. The Pd(0)-catalyst $Pd(PPh_3)_4$ was prepared according to the literature.[25] 4-Trifluoromethyl-, 4-methoxyphenyl-, 4-*N*,*N*-dimethylaminophenyl- and 4-cyanophenylboronic acids were synthesized by halogen–metal exchange followed by reaction with trimethylborate or triisopropylborate from the commercially available 1-bromo-4-trifluoromethylbenzene,

4-bromoanisole, 4-bromo-*N*,*N*-dimethylaniline or 4-bromobenzonitrile.

2.1. Procedure A for direct lithiation by lithium alkylamide (LTMP)

A solution of *n*-butyllithium (1.6 or 2.5 M in hexane) was added to cold (−50 °C), stirred and anhydrous tetrahydrofuran (15 mL) under an atmosphere of dry nitrogen. Then 2,2,6,6-tetramethylpiperidine (TMPH) was added. The mixture was warmed to 0 °C. After 20 min, the temperature was lowered to −78 °C and the substrate dissolved in 5 mL of THF was added. After a time t_1 at temperature T_1, iodine was introduced and stirring was continued for a time t_2 at T_2. Hydrolysis was then carried out using a mixture of ethanol and water (5/5). At room temperature, the solution was decolorized with sodium thiosulphate. After concentration, the residue was extracted with dichloromethane or ethyl acetate (3×15 mL). The combined organic extracts were dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel.

2.2. Procedure B for direct lithiation by *sec*-butyllithium/tetramethylethylenediamine (*sec*-butyllithium/TMEDA

A solution of *sec*-butyllithium (1.3 M in hexane) was added to cold stirred and anhydrous tetrahydrofuran (20 mL) under an atmosphere of dry nitrogen. Then tetramethylethylenediamine (TMEDA) was added. The mixture was cooled to −78 °C and added to a solution of 2-*tert*-butylquinazolin-4(*3H*)-one **18** in THF. After a time t_1 at temperature T_1, the electrophile was introduced and the mixture was keeped at T_2 for a time t_2. Hydrolysis was then carried out using a solution of ethanol and water (5/5) at −78 °C. At room temperature, water (10 mL) was added to the mixture and THF was removed under reduced pressure. The aqueous layer was extracted with dichloromethane or ethyl acetate (3×20 mL), the combined organic extracts were then dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel.

2.3. Procedure C for cross-coupling of arylboronic acids with heteroaryl halide under Suzuki conditions

A mixture of the heteroaryl halide (2 mmol), the arylboronic acid (1.3 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), aqueous 2 M potassium carbonate (2 equiv.) and DME (12 mL) and H_2O (3 mL) or ethanol (1 mL) in degassed toluene (15 mL) was heated under reflux and under nitrogen for 15–48 h. The reaction mixture was cooled, diluted with 15 mL of water and dichloromethane (1/1) and the organic layers separated. The aqueous layer was extracted with dichloromethane (3×15 mL), the combined organic extracts were dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel.

2.4. Procedure D for cross-coupling of heteroaryl halides with tributylstannylheteroarene under Stille conditions

A solution of tributylstannylheteroarene, arylhalide (0.8 equiv.) and $Pd(PPh_3)_4$ (0.05 equiv.) in degassed toluene (15 mL) was heated under reflux under nitrogen atmosphere for a time *t*. After cooling, a mixture of water (10 mL) and dichloromethane (10 mL) was added. The organic phase was extracted with dichloromethane (3×20 mL). The combined organic extracts were then dried over magnesium sulphate and evaporated. The crude product was purified by column chromatography on silica gel.

2.4.1. 4-Chloro-5-methoxyquinazoline (3). Reaction of **2** (1.5 g, 8.5 mmol) with phosphorus pentachloride (1.5 equiv.) in $POCl_3$ (30 mL) under reflux for 15 h, followed by removal of excess of $POCl_3$ under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL), then poured on ice and neutralized by an aqueous Na_2CO_3 solution. The aqueous phase was extracted with dichloromethane (3×20 mL), the combined organic extracts were then dried over magnesium sulfate and evaporated. The crude product purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 2/8) gave after purification 1.1 g (66%) of **3** as a white solid, mp 113–114 °C; ^{1}H NMR ($CDCl_3$): δ 8.84 (s, 1H, H_2); 7.73 (dd, J=8.3, 7.9 Hz, 1H, H_7); 7.52 (d, J=8.3 Hz, 1H, H_{Ph}); 7.08 (d, J=7.9 Hz, 1H, H_{Ph}); 3.94 (s, 3H, OCH_3). Anal. calcd for $C_9H_7ClN_2O$ (194.62): C, 55.54; N, 14.39; H, 3.63. Found: C, 55.53; N, 14.40; H, 3.89.

2.4.2. 5-Methoxy-4-(4′-trifluoromethylphenyl)quinazoline (4). Cross-coupling reaction of 4-trifluoromethylphenylboronic acid (1.3 equiv.) with **3** (390 mg, 2 mmol) according to the general procedure C (t=40 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate 5/5) 445 mg (71%) of **4** as a pale yellow solid, mp 94–95 °C; ^{1}H NMR ($CDCl_3$): δ 9.32 (s, 1H, H_2); 7.88–7.61 (m, 5H, $5H_{ar}$); 6.95 (d, J=7.7 Hz, 2H, $2H_{PhCF3}$); 3.64 (s, 3H, OCH_3); ^{19}F NMR ($CDCl_3$): −62.8; IR: ν 1614, 1573, 1331, 1122, 1067, 831 cm^{-1}. Anal. calcd for $C_{16}H_{11}F_3N_2O$ (304.27): C, 63.16; N, 9.21; H, 3.63. Found: C, 62.81; N, 9.52; H, 3.99.

2.4.3. 5-Methoxy-4-(3′-nitrophenyl)quinazoline (5). Cross-coupling reaction of 3-nitrophenylboronic acid (1.3 equiv.) with **3** (390 mg, 2 mmol) according to the general procedure C (t=62 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate 5/5) 348 mg (62%) of **5** as a white solid, mp 172–173 °C; ^{1}H NMR ($CDCl_3$): δ 9.32 (s, 1H, H_2); 8.40 (s, 1H, H_{PhNO2}); 8.34 (d, J=8.2 Hz, 1H, H_{Ph}); 7.89 (m, 2H, $2H_{Ph}$); 7.77–7.64 (m, 2H, $2H_{Ph}$); 6.97 (d, J=7.7 Hz, 1H, H_{ar}); 3.65 (s, 3H, OCH_3); IR: ν 1571, 1525, 1350, 691 cm^{-1}. Anal. calcd for $C_{15}H_{11}N_3O_3$ (281.27): C, 64.05; N, 14.94; H, 3.94. Found: C, 63.74; N, 14.86; H, 4.32.

2.4.4. 5-Methoxy-4-(2′-pyridyl)quinazoline (6). Cross-coupling reaction of (2-pyridyl)-tributylstannane (1.3 equiv.) with **3** (390 mg, 2 mmol) according to the general procedure D (t=50 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate 2/1) 431 mg (91%) of **6** as a pale yellow solid, mp 115–116 °C; ^{1}H NMR ($CDCl_3$): δ 9.24 (s, 1H, H_2); 8.61 (dd, J=4.9, 0.75 Hz, 1H, $H_{6'}$); 7.75 (m, 2H, $H_{7/4'}$); 7.62 (d, J=8.3 Hz, 1H, H_8); 7.45 (m, 1H, $H_{3'}$); 7.29 (m, 1H, $H_{5'}$); 6.82 (d, J=7.9 Hz, 1H, H_6); 3.49 (s, 3H, OCH_3)); ^{13}C NMR ($CDCl_3$): δ 165.5, 159.4, 156.2, 154.4 (C_2), 152.7, 148.6

(CH), 136.0 (CH), 134.8 (CH), 123.1 (CH), 122.8 (CH), 120.9 (CH), 115.6, 107.3 (CH), 55.9 (OCH_3). Anal. calcd for $C_{14}H_{11}N_3O$ (237.26): C, 70.87; N, 17.71; H, 4.67. Found: C, 71.32; N, 18.12; H, 4.56.

2.4.5. 5-Hydroxy-4-(4′-trifluoromethylphenyl)quinazoline (7). A mixture of **4** (625 mg, 2.1 mmol) and pyridinium chloride (5 g) was heated to 210 °C for 1 h 30 min. After cooling, the mixture was poured onto ice and neutralized with a 10% ammoniac solution. The aqueous layer was extracted with ethyl acetate (5×20 mL), the combined organic extracts were dried over magnesium sulfate and evaporated. The crude product was washed with dichloromethane and **7** (488 mg, 79%) was obtained as a brown solid, mp 230–231 °C; ^{1}H NMR (d_6-DMSO): δ 10.83 (1H, OH); 9.22 (s, 1H, H_2); 7.75 (m, 5H, $4H_{PhCF3}$ and H_7); 7.52 (d, J=8.3 Hz, 1H, H_{ar}); 7.03 (d, J=7.7 Hz, 1H, H_{ar}); IR: ν 3052, 1572, 1498, 1329, 1169, 1068, 850, 828 cm^{-1}. Anal. calcd for $C_{15}H_9F_3N_2O$ (290.24): C, 62.07; N, 9.65; H, 3.13. Found: C, 62.10; N, 9.84; H, 3.44.

2.4.6. 5-Hydroxy-4-(3′-nitrophenyl)quinazoline (8). A mixture of **5** (400 mg, 1.4 mmol) and pyridinium chloride (5 g) was heated to 210 °C for 1 h 30 min. After cooling, the mixture was poured onto ice and neutralized with a 10% ammoniac solution. The aqueous layer was extracted with ethyl acetate (3×20 mL), the combined organic extracts were dried over magnesium sulfate and evaporated. The crude product was washed with dichloromethane and **8** (277 mg, 73%) was obtained as a brown solid, mp >260 °C; ^{1}H NMR (d_6-DMSO): δ 9.23 (s, 1H, H_2); 8.34 (m, 2H, $2H_{PhNO2}$); 8.02 (m, 1H, H_{PhNO2}); 7.85 (dd, J=8.4, 8 Hz, 1H, $1H_{PhNO2}$); 7.74 (dd, J=8, 7.6 Hz, 1H, H_7); 7.54 (d, J=8 Hz, 1H, H_{ar}); 7.02 (d, J=7.6 Hz, 1H, H_{ar}); IR: ν 3070, 1526, 1502, 1347, 830, 692 cm^{-1}. Anal. calcd for $C_{14}H_9N_3O_3$ (267.24): C, 62.92; N, 15.72; H, 3.39. Found: C, 63.16; N, 15.77; H, 3.65.

2.4.7. 5-Hydroxy-4-(2′-pyridyl)quinazoline (9). A mixture of **6** (200 mg, 0.84 mmol) and pyridinium chloride (5 g) was heated to 210 °C for 1 h 30 min. After cooling, the mixture was poured onto with ice and neutralized with a 10% ammoniac solution. The aqueous layer was extracted with ethyl acetate (3×50 mL), the combined organic extracts were dried over magnesium sulfate and evaporated. Purification by column chromatography (neutral alumina, eluent: petroleum ether/ethyl acetate (5/5)) afforded 116 mg (62%) of **77** as an orange solid, mp 120–121 °C; ^{1}H NMR ($CDCl_3$): δ 15.57 (1H, OH); 9.20 (s, 1H, H_2); 8.83 (dd, J=8.3, 0.75 Hz, 1H, $H_{3'}$); 8.61 (dd, J=4.9, 0.75 Hz, 1H, $H_{6'}$); 8.03 (m, 1H, $H_{4'}$); 7.76 (dd, J=8.3, 7.9 Hz, 1H, H_7); 7.55–7.51 (m, 2H, $H_{5'/8}$); 7.10 (dd, J=7.9, 1.1 Hz, 1H, H_6) ^{13}C NMR ($CDCl_3$): δ 160.3, 155.1, 154.9, 153.0, 152.0 (C_2), 144.4 ($C_{3'}$), 138.9 ($C_{5'}$), 134.7 (C_7), 126.5 ($C_{6'}$), 125.1 (CH), 118.6 (CH), 115.3 (C_{4a}), 114.3 (CH); IR: ν 3059, 1564, 1522, 1480, 1418, 1352, 1274, 831, 796 cm^{-1}. HRMS(IC) calculated for $C_{13}H_{10}N_3O$: 224.0824. Found: 224.0829.

2.4.8. 4-(4′-Trifluoromethylphenyl)-5-trifluoromethylsulfonyloxyquinazoline (10). A mixture of **7** (460 mg, 1.59 mmol), triethylamine (0.67 mL, 3 equiv.) and trifluromethanesulfonic anhydride (0.53 mL, 2 equiv.) dissolved in 12 mL of anhydrous dichloromethane was heated under reflux for 15 h. After cooling and hydrolysis with 10 mL of water and neutralization with saturated aqueous sodium carbonate solution, the mixture was extracted with dichloromethane (3×15 mL). The combined organic extracts were dried over magnesium sulfate and evaporated. Purification by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate (5/5)) afforded 476 mg (71%) of **10** as a brown solid, mp 98–99 °C; ^{1}H NMR ($CDCl_3$): δ 9.45 (s, 1H, H_2); 8.26 (d, J=8.4 Hz, 1H, H_8); 8.01 (dd, J=8.4, 7.7 Hz, 1H, H_{ar}); 7.89 (m, 4H, $4H_{PhCF3}$); 7.62 (d, J=7.7 Hz, 1H, H_{ar}); ^{19}F NMR ($CDCl_3$): δ −63.2, −73.1; IR: ν 1543, 1402, 1332, 1220, 1131, 1064, 838, 822 cm^{-1}. Anal. calcd for $C_{16}H_8F_6N_2SO_3$ (422.31): C, 45.51; N, 6.63; H, 1.91; S, 7.59. Found: C, 45.32; N, 6.39; H, 2.03; S, 7.56.

2.4.9. 4-(3′-Nitrophenyl)-5-trifluoromethylsulfonyloxyquinazoline (11). A mixture of **8** (270 mg, 1.01 mmol), triethylamine (0.43 mL, 3 equiv.) and trifluromethanesulfonic anhydride (0.34 mL, 2 equiv.) dissolved in 10 mL of anhydrous dichloromethane was heated under reflux for 15 h. After cooling and hydrolysis with 10 mL of water and neutralization with saturated aqueous sodium carbonate solution, the mixture was extracted with dichloromethane (3×15 mL). The combined organic extracts were dried over magnesium sulfate and evaporated. Purification by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate (5/5)) afforded 110 mg (25%) of **11** as an orange oil; ^{1}H NMR ($CDCl_3$): δ 9.46 (s, 1H, H_2); 8.50–8.40 (m, 2H, $2H_{PhNO2}$); 8.28 (d, J=8.5 Hz, 1H, $1H_{ar}$); 8.04 (m, 2H, $H_{7/PhNO2}$); 7.74 (t, J=8 Hz, 1H, $1H_{PhNO2}$); 7.64 (d, J=7.8 Hz, 1H, H_{ar}); ^{19}F NMR ($CDCl_3$): δ −73.0; IR: ν 3418, 1623, 1532, 1428, 1350, 1217, 1136 cm^{-1}. Anal. calcd for $C_{15}H_8N_3SO_5$ (399.31): C, 45.12; N, 10.52; H, 2.02; S, 8.01. Found: C, 45.38; N, 10.25; H, 2.38; S, 7.97.

2.4.10. 4-(2′-Pyridyl)-5-trifluoromethylsulfonyloxyquinazoline (12). A mixture of **9** (120 mg, 0.54 mmol), triethylamine (0.22 mL, 3 equiv.) and trifluromethanesulfonic anhydride (0.19 mL, 1 equiv.) dissolved in 10 mL of anhydrous dichloromethane was heated under reflux for 15 h. After cooling and hydrolysis with 10 mL of water and neutralization with saturated aqueous sodium carbonate solution, the mixture was extracted with dichloromethane (3×15 mL). The combined organic extracts were dried over magnesium sulfate and evaporated. Purification by column chromatography (neutral alumina, eluent: ethyl acetate) afforded 95 mg (49%) of **12** as a brown solid, mp 74–75 °C; ^{1}H NMR ($CDCl_3$): δ 9.38 (s, 1H, H_2)); 8.66 (dd, J=4.9, 1.1 Hz, 1H, $H_{6'}$); 8.14 (dd, J=8.7, 1.1 Hz, 1H, H_{ar}); 7.97–7.86 (m, 3H, $H_{3',4',7}$); 7.54 (d, J=7.9 Hz, 1H, H_{ar}); 7.41 (m, 1H, $H_{5'}$); ^{19}F NMR ($CDCl_3$): δ −73.2; ^{13}C NMR ($CDCl_3$): δ 164.7, 156.9, 154.8 (CH), 153.1, 149.5 (CH), 144.2, 137.5 (CH), 133.6 (CH), 130.3 (CH), 125.1 (2×CH), 121.5 (CH), 117.5, 30.1 (CF_3). HRMS(IC) calculated for $C_{14}H_8F_3N_3O_3S$: 356.0317. Found: 356.0319.

2.4.11. 5-Phenyl-4-(4′-trifluoromethylphenyl)quinazoline (13). Cross-coupling reaction of phenylboronic acid (1.3 equiv.) with **10** (200 mg, 0.47 mmol) according to the general procedure C (t=38 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate 5/5) 120 mg (72%) of **13** as a white solid, mp 133–134 °C; ^{1}H NMR ($CDCl_3$): δ 9.41 (s, 1H, H_2); 8.20

(dd, J=8.4, 1.2 Hz, 1H, H_8); 8.00 (dd, J=8.4, 7.2 Hz, 1H, H_7); 7.67 (dd, J=7.2, 1.2 Hz, 1H, H_6); 7.28 (m, 4H, $H_{2'/3'/5'/6'}$); 7.01 (m, 5H, $5H_{Ph}$); ^{19}F NMR ($CDCl_3$): δ −63.4; IR: ν 1537, 1324, 1108, 1065, 836, 762, 699 cm^{-1}. Anal. calcd for $C_{21}H_{13}F_3N_2$ (350.34): C, 72.00; N, 8.00; H, 3.74. Found: C, 72.30; N, 7.73; H, 3.82.

2.4.12. 5-(4″-Methoxyphenyl)-4-(4′-trifluoromethylphenyl)quinazoline (14). Cross-coupling reaction of 4-methoxyphenylboronic acid (1.3 equiv.) with **10** (200 mg, 0.47 mmol) according to the general procedure C (t=38 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate 5/5) 155 mg (86%) of **14** as a pale yellow solid, mp 45–46 °C; ^{1}H NMR ($CDCl_3$): δ 9.40 (s, 1H, H_2); 8.18 (dd, J=8.4, 1.2 Hz, 1H, H_8); 7.99 (dd, J=8.4, 7.2 Hz, 1H, H_7); 7.66 (dd, J=7.2, 1.2 Hz, 1H, H_6); 7.32 (m, 4H, $H_{2'/3'/5'/6'}$); 6.90 (d, J=6.7 Hz, 2H, $2H_{PhOCH3}$); 6.54 (d, J=6.7 Hz, 2H, $2H_{PhOCH3}$); ^{19}F NMR ($CDCl_3$): δ −63.3; IR: ν 1611, 1514, 1324, 1164, 1066, 831 cm^{-1}. Anal. calcd for $C_{22}H_{15}F_3N_2O$ (380.37): C, 69.47; N, 7.36; H, 3.97. Found: C, 69.35; N, 7.17; H, 3.58.

2.4.13. 5-(4″-Methoxyphenyl)-4-(3′-nitrophenyl)quinazoline (15). Cross-coupling reaction of 4-methoxyphenylboronic acid (1.3 equiv.) with **11** (100 mg, 0.25 mmol) according to the general procedure C (t=86 h) gave after purification by column chromatography (silica gel, eluent: ethyl acetate) 70 mg (79%) of **15** as a pale yellow solid, mp 136–137 °C; ^{1}H NMR ($CDCl_3$): δ 9.42 (s, 1H, H_2); 8.20 (d, J=7.9 Hz, 1H, H_{ar}); 8.03 (m, 2H, $2H_{ar}$); 7.68 (d, J=7.3 Hz, 1H, H_{ar}); 7.36 (t, J=7.9 Hz, 1H, H_{ar}); 6.94 (d, J=8.5 Hz, 2H, $H_{2''/6''}$); 6.53 (d, J=8.5 Hz, 2H, $H_{3''/5''}$); 3.70 (s, 3H, OCH_3); IR: ν 1529, 1511, 1351, 1241, 1028, 806, 692 cm^{-1}. Anal. calcd for $C_{21}H_{15}N_3O_3$ (357.37): C, 70.59; N, 11.76; H, 4.20. Found: C, 70.95; N, 11.41; H, 4.55.

2.4.14. 5-(4″-Methoxyphenyl)-4-(2′-pyridyl)quinazoline (16). Cross-coupling reaction of 4-methoxyphenylboronic acid (1.3 equiv.) with **12** (125 mg, 0.35 mmol) according to the general procedure C (t=60 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate 5/5) 31 mg (28%) of **16** as a yellow solid, mp 106–107 °C; ^{1}H NMR ($CDCl_3$): δ 9.35 (s, 1H, H_2); 8.20 (d, J=3.8 Hz, 1H, $H_{6'}$); 8.07 (dd, J=8.7 and 1.1 Hz, 1H, H_8); 7.90 (dd, J=8.7, 7.1 Hz, 1H, H_7); 7.56 (dd, J=7.1, 1.5 Hz, 1H, H_6); 7.42–7.32 (m, 2H, $H_{3'}$ /$_{4'}$); 6.94–6.91 (m, 3H, $H_{2''/6''/5'}$); 6.49 (d, J=8.7 Hz, 2H, $H_{3''/5''}$); 3.71 (s, 3H, OCH_3); IR: ν 1606, 1565, 1512, 1465, 1359, 1246, 1031, 799 cm^{-1}. Anal. calcd for $C_{20}H_{15}N_3O$ (313.36): C, 76.46; N, 13.41; H, 4.82. Found: C, 76.22; N, 12.98; H, 4.44.

2.4.15. 5-(2″-Thienyl)-4-(4′-trifluoromethylphenyl)quinazoline (17). Cross-coupling reaction of (2-thienyl)-trimethylstannane (1.3 equiv.) with **10** (150 mg, 0.36 mmol) according to the general procedure D (t=24 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate 5/5) 85 mg (67%) of **17** as a pale yellow solid, mp 137–138 °C; ^{1}H NMR ($CDCl_3$): δ 9.41 (s, 1H, H_2); 8.19 (dd, J=8.4, 1.2 Hz, 1H, H_8); 7.98 (dd, J=8.4, 7.2 Hz, 1H, H_7); 7.77 (dd, J=7.2, 1.2 Hz, 1H, H_6); 7.43 (m, 4H, $H_{2'/3'/5'/6'}$); 7.09 (dd, J=5, 1 Hz, 1H, $H_{5''}$); 6.56 (dd, J=5, 3.6 Hz, 1H, $H_{4''}$); 6.39 (dd, J=3.6, 1 Hz, 1H, $H_{3''}$); ^{19}F NMR ($CDCl_3$): δ −63.3; IR: ν 1537, 1325, 1108, 1065, 828, 706 cm^{-1}. Anal. calcd for $C_{19}H_{11}F_3N_2S$ (394.48): C, 64.04; N, 7.86; H, 3.11. Found: C, 64.31; N, 7.59; H, 3.46.

2.4.16. 2-*tert*-Butyl-5-(1-hydroxyethyl)quinazolin-4(3*H*)-one (19). Metallation of **18** (50 mg, 0.24 mmol) according to the procedure B with *sec*-BuLi 1.3 M (4.2 equiv., 0.80 mL), TMEDA (4.0 equiv., 0.149 mL), T_1=−78 °C, followed by reaction with acetaldehyde (5 equiv., 0.07 mL), t_1=1 h, gave after purification by column chromatography (silicagel, eluent: dichloromethane/ethyl acetate (1/1)) 49 mg (82%) of **19** as a white solid, mp 189–190 °C; ^{1}H NMR ($CDCl_3$): δ 10.94 (s, 1H, NH); 7.64 (m, 2H, H_7 and H_8); 7.46 (dd, J_{H6-H7}=6.41 Hz and J_{H6-H8}=2.26 Hz, 1H, H_6); 5.45 (quint, J=6.78 Hz, 1H, C*H*OH); 5.07 (d, J=7.54 Hz, 1H, OH); 1.57 (d, J=6.78 Hz, 3H, Me); 1.43 (s, 9H, *tert*-butyl); ^{13}C NMR ($CDCl_3$): δ 165.4 (C_{qui}), 161.8 (C_{qui}), 152.1 (C_{qui}), 147.3 (C_{qui}), 134.9 (CH_{qui}), 128.3 (CH_{qui}), 125.4 (CH_{qui}), 117.9 (C_{qui}), 69.66 (CHOH), 37.5 (*C*Me_3), 28.6 ($3Me_{tert\text{-butyl}}$), 23.8 (Me). Anal. calcd for $C_{14}H_{18}N_2O_2$ (246.30): C, 68.27; H, 7.37; N, 11.99. Found: C, 67.97; H, 7.31; N, 11.61.

2.4.17. 2-*tert*-Butyl-5-(1-hydroxyphenyl)quinazolin-4(3*H*)-one (20). Metallation of **18** (50 mg, 0.24 mmol) according to the procedure B with *sec*-BuLi 1.3 M (4.2 equiv., 0.80 mL), TMEDA (4.0 equiv., 0.149 mL), T_1=−78 °C, followed by reaction with benzaldehyde (5 equiv., 0.126 mL), t_1=1 h, gave after purification by column chromatography (silicagel, eluent: dichloromethane/ethyl acetate (8/2)) 70 mg (92%) of **20** as a white solid, mp 163–164 °C; ^{1}H NMR ($CDCl_3$): δ 10.76 (s, 1H, NH); 7.61 (m, 2H, H_7 and H_8); 7.24 (m, 5H, Ph); 7.13 (dd, J_{H6-H7}=7.16 Hz and J_{H6-H8}=1.51 Hz, 1H, H_6); 6.39 (d, J=7.91 Hz, 1H, C*H*OH); 5.73 (d, J=7.91 Hz, 1H, OH); 1.34 (s, 9H, *tert*-butyl); ^{13}C NMR ($CDCl_3$): δ 165.2 (C_{qui}), 161.9 (C_{qui}), 152.2 (C_{qui}), 145.1 (C_{qui}), 143.3 (C_{Ph}), 134.7 (CH_{qui}), 128.8 (CH_{qui}), 128.4 ($2CH_{Ph}$), 128.3 (CH_{Ph}), 127.5 (CH_{qui}), 127.2 ($2CH_{Ph}$), 118.5 (C_{qui}), 75.1 (CHOH), 37.5 (*C*Me_3), 28.5 ($3Me_{tert\text{-butyl}}$). Anal. calcd for $C_{19}H_{20}N_2O_2$ (308.38): C, 74.00; H, 6.54; N, 9.08. Found: C, 74.13; H, 6.56; N, 8.69.

2.4.18. 2-*tert*-Butyl-5-phenylsulfanylquinazolin-4(3*H*)-one (21). Metallation of 18. (50 mg, 0.24 mmol) according to the procedure B with *sec*-BuLi 1.3 M (4.2 equiv., 0.80 mL), TMEDA (4.0 equiv., 0.149 mL), T_1=−78 °C, followed by reaction with benzaldehyde (5 equiv., 0.126 mL), t_1=1 h, gave after purification by column chromatography (silicagel, eluent: petromeum ether/ethyl acetate (7/3)) 13 mg (17%) of **21** as a white solid, mp >250 °C; ^{1}H NMR ($CDCl_3$): δ 10.85 (s, 1H, NH); 7.57 (m, 2H, H_7 and H_8); 7.42 (m, 3H); 7.29 (d, J=4.52 Hz, 2H); 6.51 (dq, J=4.53 Hz, 1H); 1.42 (s, 9H, *tert*-butyl); ^{13}C NMR ($CDCl_3$): δ 164.2 (C_{qui})162.5 (C_{qui}), 151.3 (C_{qui}), 144.2 (C_{qui}), 136.7 ($2CH_{Ph}$), 133.9 (CH_{qui}), 132.5 (C_{qui}), 130.3 ($2CH_{Ph}$), 129.8 (CH_{qui}), 123.7 (CH),123.3 (CH), 37.7 (*C*Me_3), 28.6 ($3Me_{tert\text{-butyl}}$). Anal. calcd for $C_{18}H_{18}N_2OS$ (310.42): C, 69.65; H, 5.84; N, 9.02; S, 10.33. Found: C, 69.37; H, 5.93; N, 8.87; S, 10.58.

2.4.19. 2-*tert*-Butyl-5-(tri-*n*-butylstannyl)quinazolin-4(3*H*)-one (22). Metallation of **18** (50 mg, 0.24 mmol)

according to the procedure B with *sec*-BuLi 1.3 M (4.2 equiv., 0.80 mL), TMEDA (4.0 equiv., 0.149 mL), T_1=−78 °C, followed by reaction with tri-*n*-butylstannyl chloride (5 equiv., 0.34 mL), t_1=1 h, gave after purification by column chromatography (silicagel, eluent: petroleum ether/ethyl acetate (7/3)) 13 mg (17%) of **22** as a vitrous solid, mp 54–55 °C; ^{1}H NMR ($CDCl_3$): δ 8.72 (s, 1H, NH); 7.59 (m, 3H, $H_{6/7/8}$); 1.48 (m, 6H, CH_2); 1.34 (s, 9H, *tert*-butyl); 1.13 (2m, 12H, CH_2); 0.79 (t, J=7.16–7.54 Hz, 9H, CH_3); ^{13}C NMR ($CDCl_3$): δ 164.2 (C_{qui}), 160.5 (C_{qui}), 149.5 (C_{qui}), 145.1 (C_{qui}), 135.8 (CH_{qui}), 134.0 (CH_{qui}), 127.9 (CH_{qui}), 125.5 (C_{qui}), 37.4 ($C_{tert\text{-}butyl}$), 29.6 (CH_2), 28.7 (3×$CH_{3\,tert\text{-}butyl}$), 27.8 ($CH_2$), 14.1 ($CH_3$), 11.8 ($CH_2$). Anal. calcd for $C_{24}H_{40}N_2OSn$ (491.30): C, 58.67; H, 8.21; N, 5.70. Found: C, 58.68; H, 8.23; N, 5.27.

2.4.20. 2-*tert*-Butyl-5-iodoquinazolin-4(3*H*)-one (23). Metallation of **18** (50 mg, 0.24 mmol) according to the procedure B with *sec*-BuLi 1.3 M (4.2 equiv., 0.80 mL), TMEDA (4.0 equiv., 0.149 mL), T_1=−78 °C, followed by reaction with iodine in THF (5 equiv., 314 mg), t_1=1 h, gave after purification by column chromatography (silicagel, eluent: ethyl ether/dichloromethane (1/9)) 30 mg (37%) of **23** as a white solid, mp 245–246 °C; ^{1}H NMR ($CDCl_3$): δ 11.40 (s, 1H, NH); 7.99 (dd, J_{H6-H7}=7.53–7.53 Hz and J_{H6-H8}=0.75–1.13 Hz, 1H, H_6); 7.63 (dd, J_{H8-H7}=7.91–8.29 Hz and J_{H8-H6}=0.75–1.13 Hz, 1H, H_8); 7.24 (t, J=7.9 Hz, H_7); 1.44 (s, 9H, *tert*-butyl); ^{13}C NMR ($CDCl_3$): δ 162.7 (C_{qui}), 162.6 (C_{qui}), 151.0 (C_{qui}), 140.9 (CH_{qui}), 135.0 (CH_{qui}), 129.2 (CH_{qui}), 120.4 (C_{qui}), 91.3 (C_{qui}), 38.0 ($C_{tert\text{-}butyl}$), 28.6 (3×$CH_{3\,tert\text{-}butyl}$). Anal. calcd for $C_{12}H_{13}N_2OI$ (328.15): C, 43.92; H, 3.99; N, 8.54. Found: C, 43.98; H, 3.97; N, 8.35.

2.4.21. 2-*tert*-Butyl-4-oxo-3,4-dihydroquinazolin-5-boronic acid (24). Metalation of **18** (100 mg, 0.5 mmol) according to the procedure B with *sec*-BuLi 1.3 M (4.2 equiv., 1.6 mL), TMEDA (4.0 equiv., 0.3 mL), T_1=−20 °C, t_1=1 h, followed by reaction with tri-*iso*propylborate (6 equiv., 564 mg), T_2=−78 °C to rt, t_2=15 h, gave after purification by washing with DCM 84 mg (68%)of **24**, mp °C; ^{1}H NMR (d_6-DMSO): δ 11.88 (s, 1H, NH), 9.35 (s, 2H, 2×OH), 7.72 (t, J=7.9 Hz, 1H, H_7), 7.54 (dd, J=7.9, 1.1 Hz, 1H, H_{Ar}), 7.42 (dd, J=7.9, 1.1 Hz, 1H, H_{Ar}), 1.37 (s, 9H, *tert*-butyl); IR: ν 3346, 3173, 3069, 2973, 2922, 1640, 1583, 1409, 1375 cm^{-1}.

2.4.22. 2-*tert*-Butyl-5-(4′-methoxyphenyl)quinazolin-4(3*H*)-one (25). Coupling of heteroarylboronic acid **24** (640 mg, 1.3 equiv.) with 4-iodoanisole (468 mg, 2 mmol) according to the general procedure C (DME, t=60 h) gave after purification by column chromatography (silica gel, eluent petroleum ether/ethyl acetate 6/4) 246 mg (40%) of **25** as a white solid, mp >250 °C; ^{1}H NMR ($CDCl_3$): δ 11.17 (s, 1H, NH); 7.66 (m, 2H, $H_{6/8}$); 7.22 (d, J=8.7 Hz, 2H, $H_{2'/6'}$); 7.19 (t, 1H, H_7); 6.89 (d, J=8.7 Hz, 2H, $H_{3'/5'}$); 3.86 (s, 3H, OCH_3); 1.18 (s, 9H, *tert*-butyl); ^{13}C NMR ($CDCl_3$): δ 163.9 (C_4), 162.8 (C_2), 158.8 ($C_{4'}$), 151.0 (C_{8a}), 143.5 (C_5), 135.0 ($C_{1'}$), 133.4 (C_6), 130.1 ($C_{2'}$, $C_{6'}$), 129.9 (C_7), 127.6 (C_8), 118.1 (C_{4a}), 113.2 ($C_{3'}$, $C_{5'}$), 55.5 (OCH_3), 37.2 ($C_{tert\text{-}butyl}$), 28.4 (3×$CH_{3\,tert\text{-}butyl}$); IR: ν 3173, 3090, 3053, 2973, 2951, 2832, 1669, 1616, 1592, 1515, 1465, 1286, 1238, 827 cm^{-1}. MS (IC): 309 $(MH)^+$. Anal. calcd for $C_{19}H_{20}N_2O_2$ (308.38): C, 74.00; N, 9.08; H, 6.54. Found: C, 73.88; N, 8.82; H, 6.34.

2.4.23. 2-*tert*-Butyl-5-(2′-thienyl)quinazolin-4(3*H*)-one (26). Coupling of heteroarylboronic acid **24** (640 mg, 1.3 equiv.) with 2-iodothiophene (421 mg, 2 mmol) according to the general procedure F (DME, t=60 h) gave after purification by column chromatography (silica gel, eluent petroleum ether/ethyl acetate 7/3) 341 mg (60%) of **26** as a beige solid, mp 242–243 °C; ^{1}H NMR ($CDCl_3$): δ 11.87 (s, 1H, NH); 7.70 (m, 2H, $H_{6/8}$); 7.35 (m, 2H, $H_{2'/7}$); 7.03 (m, 2H, $H_{3'/4'}$); 1.25 (s, 9H, *tert*-butyl); ^{13}C NMR ($CDCl_3$): δ 163.7 (C_4), 163.1 (C_2), 150.9 (C_{8a}), 142.8 (C_5), 135.5 ($C_{1'}$), 133.0 (C_6), 131.1 (C_7), 128.7 (C_8), 126.8 ($C_{3'}$ or $C_{4'}$), 126.6 ($C_{3'}$ or $C_{4'}$), 125.2 ($C_{2'}$), 118.8 (C_{4a}), 37.2 ($C_{tert\text{-}butyl}$), 28.3 (3×$CH_{3\,tert\text{-}butyl}$); IR: ν 3175, 1660, 1614, 1592, 1570, 1310, 976, 822, 786 cm^{-1}. Anal. calcd for $C_{16}H_{16}N_2OS$ (284.38): C, 67.58; N, 9.85; H, 5.67. Found: C, 67.23; N, 9.37; H, 5.13.

2.4.24. 2-*tert*-Butyl-5-(4′-*N*,*N*-dimethylaminophenyl)-quinazolin-4(3*H*)-one (27). Coupling of heteroarylboronic acid **24** (640 mg, 1.3 equiv.) with 4-bromo-*N*,*N*-dimethylaniline (400 mg, 2 mmol) according to the general procedure F (DME, t=60 h) gave after purification by recrystalization in diethyl ether 454 mg (71%) of **27** as a solid, mp >250 °C; ^{1}H NMR ($CDCl_3$): δ 11.33 (s, 1H, NH); 7.64 (m, 2H, $H_{6/8}$); 7.20 (m, 3H, $H_{2'/6'/7}$); 6.74 (d, J=8.7 Hz, 2H, $H_{3'/5'}$); 3.00 (s, 6H, $N(CH_3)_2$); 1.22 (s, 9H, *tert*-butyl); ^{13}C NMR ($CDCl_3$): δ 163.9 (C_4), 162.6 (C_2), 151.0 (C_{8a}), 144.2 (C_5), 133.4 (C_6), 130.6 (C_7), 129.9 ($C_{1'}$), 129.8 ($C_{2'}$, $C_{6'}$), 126.9 (C_8), 118.0 (C_{4a}), 111.9 ($C_{3'}$, $C_{5'}$), 40.9 (2×CH_3), 37.2 ($C_{tert\text{-}butyl}$), 28.5 (3×$CH_{3\,tert\text{-}butyl}$). Anal. calcd for $C_{20}H_{23}N_3O$ (321.43): C, 74.74; N, 13.07; H, 7.21. Found: C, 74.52; N, 12.60; H, 6.98.

2.4.25. 2-*tert*-Butyl-4-chloro-5-(4′-methoxyphenyl)quinazoline (28). Reaction of **25** (900 mg, 2.9 mmol) with $POCl_3$ (50 mL) under reflux for 6 h, followed by removal of excess of $POCl_3$ under reduced pressure and partitionning of the residue between CH_2Cl_2 and cold aqueous K_2CO_3 solution, gave after purification by column chromatography (silica gel, eluent petroleum ether/ethyl acetate 6/4) 682 mg (72%) of **28** as a yellow solid, mp 98–99 °C; ^{1}H NMR ($CDCl_3$): δ 8.01 (d, J=8.3 Hz, 1H, H_8); 7.82 (dd, J=8.3, 7.2 Hz, 1H, H_7); 7.47 (d, J=7.2 Hz, 1H, H_6); 7.24 (d, J=8.3 Hz, 2H, $H_{2'/6'}$); 6.96 (d, J=8.3 Hz, 2H, $H_{3'/5'}$); 3.89 (s, 3H, OCH_3); 1.50 (s, 9H, *tert*-butyl); ^{13}C NMR ($CDCl_3$): δ 171.9 (C_2), 160.7 (C_4), 159.2 ($C_{4'}$), 152.8 (C_{8a}), 140.2 (C_5), 133.5 ($C_{1'}$), 132.7 (C_6), 131.0 ($C_{2'}$, $C_{6'}$), 130.5 (C_8), 128.3 (C_7), 120.1 (C_{4a}), 113.2 ($C_{3'}$, $C_{5'}$), 55.3 (OCH_3), 39.2 ($C_{tert\text{-}butyl}$), 29.3 (3×$CH_{3\,tert\text{-}butyl}$); IR: ν 1608, 1563, 1510, 1460, 1290, 1240, 1170, 881, 832, 744 cm^{-1}. Anal. calcd for $C_{19}H_{19}ClN_2O$ (326.83): C, 69.83; N, 8.57; H, 5.86. Found: C, 69.87; N, 8.49; H, 5.98.

2.4.26. 2-*tert*-Butyl-4-chloro-5-(2′-thienyl)quinazolin-4(3*H*)-one (29). Reaction of **26** (284 mg, 1 mmol) with $POCl_3$ (15 mL) under reflux for 6 h, followed by removal of excess of $POCl_3$ under reduced pressure and partitionning of the residue between CH_2Cl_2 and cold aqueous K_2CO_3 solution, gave after purification by column chromatography (silica gel, eluent petroleum ether/ethyl acetate 7/3) 121 mg

(40%) of **29** as a yellow solid, mp 134–135 °C; ^{1}H NMR ($CDCl_3$): δ 8.05 (d, J=8.3 Hz, 1H, H_8); 7.83 (dd, J=8.3, 7.2 Hz, 1H, H_7); 7.63 (d, J=7.2 Hz, 1H, H_6); 7.44 (d, J=5.3 Hz, 1H, $H_{2'}$); 7.11 (m, 1H, $H_{3'}$); 7.02 (m, 1H, $H_{4'}$); 1.49 (s, 9H, 3×$CH_{3\,tert\text{-butyl}}$); ^{13}C NMR ($CDCl_3$): δ 172.3, 160.6, 152.9, 141.2, 132.6 (C_7), 132.5 (C_6), 132.4, 129.9 (C_8), 128.9 ($C_{4'}$), 127.1 ($C_{3'}$), 126.4 ($C_{2'}$), 121.2 (C_{4a}), 39.5 ($C_{tert\text{-butyl}}$), 29.5 (3×$CH_{3\,tert\text{-butyl}}$); IR: ν 1563, 1444, 1280, 827, 744, 712 cm^{-1}. Anal. calcd for $C_{16}H_{15}ClN_2S$ (302.83): C, 63.46; N, 9.25; H, 4.99. Found: C, 63.96; N, 8.93; H, 5.09.

2.4.27. 2-*tert*-Butyl-4-(4′-cyanophenyl)-5-(4″-methoxyphenyl)quinazoline (30). Coupling of 4-cyanophenylboronic acid (1.3 equiv.) with **28** (474 mg, 2 mmol) according to the general procedure C (t=60 h) gave after purification by column chromatography (silica gel, eluent petroleum ether/ethyl acetate 8/2)) 618 mg (90%) of **30** as a yellow solid, mp 149–150 °C; ^{1}H NMR ($CDCl_3$): δ 8.07 (d, J=8.3 Hz, 1H, H_8); 7.89 (dd, J=8.3, 7.2 Hz, 1H, H_7); 7.53 (d, J=7.2 Hz, 1H, H_6); 7.33 (m, 4H, $H_{2'/3'/5'/6'}$); 6.92 (d, J=8.7 Hz, 2H, $H_{2''/6''}$); 6.56 (d, J=8.7 Hz, 2H, $H_{3''/5''}$); 3.73 (s, 3H, OCH_3); 1.54 (s, 9H, *tert*-butyl); ^{13}C NMR ($CDCl_3$): δ 171.8 (C_2), 165.4 (C_4), 159.1 ($C_{4''}$), 153.1 (C_{8a}), 144.9 ($C_{1'}$), 139.9 (C_5), 132.8 (C_7), 131.1 ($C_{2''}$, $C_{6''}$), 131.0 ($C_{2'}$, $C_{6'}$), 130.7 ($C_{3'}$, $C_{5'}$), 130.0 (C_6), 128.4 (C_8), 119.2 (CN), 118.8 (C_{4a}), 113.6 ($C_{3'}$, $C_{5'}$), 111.5 ($C_{4'}$), 55.6 (OCH_3), 39.5 ($C_{tert\text{-butyl}}$), 29.7 (3×$CH_{3\,tert\text{-butyl}}$); IR: ν 3073, 3008, 2966, 2931, 2863, 2230, 1609, 1538, 1513, 1470, 1368, 1296, 1249, 1175, 1035, 827, 812 cm^{-1}. Anal. calcd for $C_{26}H_{23}N_3O$ (343.49): C, 79.36; N, 5.89; H, 10.68. Found: C, 78.99; N, 10.33; H, 6.13.

2.4.28. 2-*tert*-Butyl-4-(4′-cyanophenyl)-5-(2″-thienyl)quinazoline (31). Coupling of 4-cyanophenylboronic acid (1.3 equiv.) with **29** (mg, 2 mmol) according to the general procedure C (t=60 h) gave after purification by column chromatography (silica gel, eluent petroleum ether/ethyl acetate)) 221 mg (30%) of **31** as a yellow solid, mp 120–121 °C; ^{1}H NMR ($CDCl_3$): δ 8.09 (d, J=8.3 Hz, 1H, H_8); 7.87 (dd, J=8.3, 7.2 Hz, 1H, H_7); 7.63 (d, J=7.2 Hz, 1H, H_6); 7.46 (d, J=8.3 Hz, 2H, $2H_{PhCN}$); 7.39 (d, J=8.3 Hz, 2H, $2H_{PhCN}$); 7.08 (d, J=5.3 Hz, 1H, $H_{2''}$); 6.56 (m, 1H, $H_{3''}$); 6.38 (m, 1H, $H_{4''}$); 1.54 (s, 9H, *tert*-butyl); ^{13}C NMR ($CDCl_3$): δ 172.1 (C_2), 165.2 (C_4), 153.1 (C_{8a}), 145.0 ($C_{1'}$), 142.0 ($C_{1''}$), 132.7 (C_5), 132.4 (C_7), 131.2 (2×CH_{PhCN}), 131.0 (C_6), 130.0 (2×CH_{PhCN}), 129.7 ($C_{4''}$), 129.4 (C_8), 127.5 ($C_{3''}$), 126.4 ($C_{2''}$), 119.7 (CN), 119.0 (C_{4a}), 111.9 ($C_{2''}$), 39.6 ($C_{tert\text{-butyl}}$), 29.8 (3×$CH_{3\,tert\text{-butyl}}$). HRMS(IC) calculated for $C_{23}H_{20}N_3S$: 370.1378. Found: 370.1380.

2.4.29. 2-*tert*-Butyl-5-(4″-methoxyphenyl)-4-(2′-pyridyl)-quinazoline (32). Coupling of (2-pyridyl)-tributylstannane (1.3 equiv.) with **28** (474 mg, 2 mmol) according to the general procedure D (t=48 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate 8/2) 236 mg (32%) of **32** as a yellow solid, mp 107–108 °C; ^{1}H NMR ($CDCl_3$): δ 8.11 (d, J=4.9 Hz, 1H, $H_{3'}$); 8.05 (d, J=8.3 Hz, 1H, H_8); 7.86 (dd, J=8.3, 7.5 Hz, 1H, H_7); 7.66 (d, J=7.9 Hz, 1H, $H_{6'}$); 7.53 (m, 2H, $H_{6/5'}$); 6.95 (m, 3H, $H_{2''/6''/4'}$); 6.54 (d, J=8.3 Hz, 2H, $H_{3''/5''}$); 3.72 (s, 3H, OCH_3); 1.56 (s, 9H, *tert*-butyl); ^{13}C NMR ($CDCl_3$): δ 171.6 (C_2), 165.8 (C_4), 158.4 ($C_{4''}$ or $C_{1'}$), 158.3 ($C_{4''}$ or $C_{1'}$),153.1 (C_{8a}), 148.6 ($C_{3'}$), 140.4 (C_5), 135.8 ($C_{5'}$), 134.6 ($C_{1''}$), 132.6 (C_7), 130.6 ($C_{2''}$, $C_{6''}$), 129.9 (C_6), 128.0 (C_8), 124.9 ($C_{6'}$), 122.5 ($C_{4'}$), 119.3 (C_{4a}), 113.2 ($C_{3'}$, $C_{5'}$), 55.4 (OCH_3), 39.4 ($C_{tert\text{-butyl}}$), 29.8 (3×$CH_{3\,tert\text{-butyl}}$); IR: ν 3058, 3014, 2960, 2926, 2864, 2837, 1610, 1550, 1512, 1470, 1368, 1348, 1292, 1245, 1183, 1026, 827, 804, 790, 744 cm^{-1}. MS (EI): 369 $(M)^+$. Anal. calcd for $C_{24}H_{23}N_3O$ (369.47): C, 78.02; N, 11.37; H, 6.27. Found: C, 77.69; N, 10.97; H, 6.51.

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