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A general and efficient method for the synthesis of benzo-(*iso*)quinoline derivatives

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ABSTRACT

A new, short and efficient synthesis of substituted benzo-(*iso*)quinoline derivatives is reported. The methodology is based on a Suzuki or Negishi cross-coupling followed by a cyclization reaction induced by *t*-BuOK in DMF to form the central ring. This approach allowed the synthesis of all four benzo-(*iso*)quinoline isomers and the substitution of each ring of the benzo-(*iso*)quinoline core.

1. Introduction

Benzoquinoline derivatives are very useful compounds in various fields of chemistry, including biological and pharmacological chemistry.[1] Moreover, some derivatives exhibit very interesting photophysical properties[2] and a recent work showed their utility as ligands for the preparation of helical complexes.[3]

In view of the importance of benzoquinoline derivatives, several methods have been developed for their synthesis. Most of them are based on the construction of the pyridine ring implying starting from substituted naphthalenes, which are not always easily available.[4] An alternative approach starting from a quinoline derivative was also proposed by using a Diels–Alder reaction.[5] In contrast, methods based on the construction of the central ring are quite limited. This approach allowed an efficient synthesis of toddaquinoline by an intramolecular radical cyclization.[6] Analogously to the phenanthrene synthesis, benzoquinoline derivatives were produced efficiently through a photocyclization–oxidation process.[7] Both methods were recently used to prepare monoazahelicenes.[8] As model reaction products of azacorannulenes, benzoquinolines were obtained by flash vacuum pyrolysis of ethynylpyridines.[9] A nice entry to benzoquinolines and other aza-polycyclic aromatic compounds was recently described via superelectrophilic cyclizations.[10]

Herein we described a general method to synthesize all four benzo-(*iso*)quinoline isomers. Our approach, which has proven to be efficient for the preparation of ferroceno-(*iso*)quinolines[11] involves a two-step process including: (i) a palladium-catalyzed cross-coupling reaction to bring together the pyridine and the aryl moieties and (ii) a base-promoted cyclization to build the central ring. This convergent strategy facilitates the introduction of substituents on each cycle of the benzoquinoline core including the central ring due to the facile deprotonation of the methyl group of picolines (Fig. 1).[12]

The base-promoted cyclization step has been previously used in the benzene series by de Koning and co-workers.[13] They found that *t*-BuOK in DMF at 80 °C in presence of light could allow the intramolecular condensation between a methyl group attached to a benzene ring and an aldehyde. The same base was used with success in our work and we noted that irradiation and heating were not necessary due to the higher reactivity of the methyl group in picolines.

2. Results and discussion

Our initial efforts were focused on the synthesis of benzo-(*iso*)quinoline derivatives possessing an unsubstituted central ring. Among the palladium-catalyzed cross-coupling methods available to generate the aryl–heteroaryl bond, the Suzuki reaction[14] was

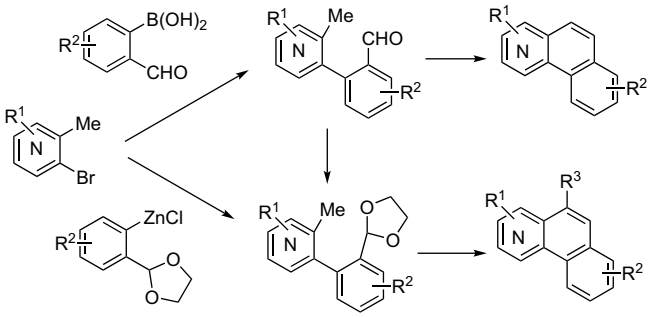

Figure 1. General approach to substituted benzo-(*iso*)quinolines.

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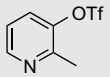
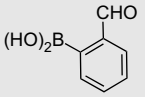
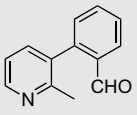
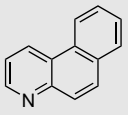
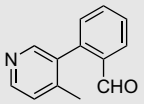
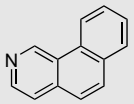
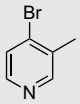
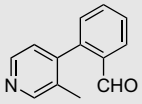
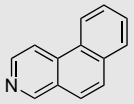
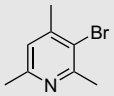
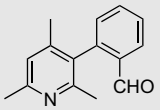
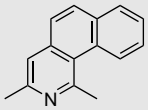
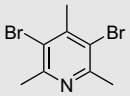
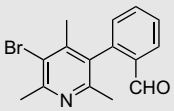
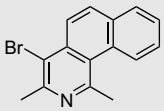
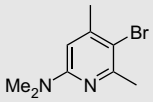
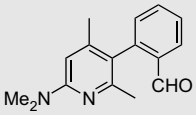
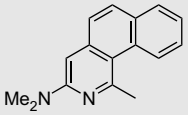
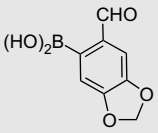
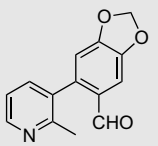
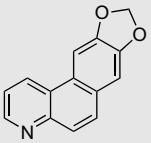
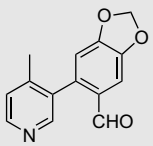
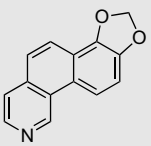
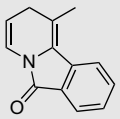
Table 1
Scope of the two-step sequence leading to the benzo-(*iso*)quinoline derivatives

Entry	Pyridines **1**	Boronic acids **2**	Coupling products **3**[a]	Cyclization products **4**[b]	Yield of **3** (%)	Yield of **4** (%)
1	 **1a**	 **2a**	 **3a**	 **4a**	80	75
2	 **1b**	**2a**	 **3b**	 **4b**	94	78
3	 **1c**	**2a**	 **3c**	 **4c**	90	60
4	 **1d**	**2a**	 **3d**	 **4d**	93	51
5	 **1e**	**2a**	 **3e**	 **4e**	53[c]	44
6	 **1f**	**2a**	 **3f**	 **4f**	42	42
7	**1a**	 **2b**	 **3g**	 **4g**	72[d]	65
8	**1b**	**2b**	 **3h**	 **4h**	98[d]	88
9[e]	 **1g**	**2a**	 **5**	—	43	

[a] General conditions: **1** (1 mmol), **2** (1.1 mmol, 1 M in MeOH), 5 mol % $Pd(PPh_3)_4$, Na_2CO_3 (2 mmol, 1 M in H_2O), toluene, 90 °C.
[b] General conditions: **3** (0.5 mmol, 1 M in DMF), *t*-BuOK (1 mmol, 1 M in DMF), rt.
[c] Compound **2a** (2.2 equiv) was used.
[d] Boronic acid (1.5 equiv) was used.
[e] Compound **5** was formed during the Suzuki reaction.

chosen for its high efficiency and because aldehyde protection was not necessary. Standard conditions (5 mol % $Pd(PPh_3)_4$, 1 M Na_2CO_3, toluene/methanol, 90 °C) were used in all cases and no optimization of the catalyst was necessary. For the cyclization step, a two-fold excess of *t*-BuOK in DMF was used to achieve complete conversions. The scope of this two-step methodology is presented in Table 1.

The Suzuki protocol was very efficient for coupling picolines **1a–c**[15] with boronic acid **2a** thus producing aldehydes **3a–c**, which upon treatment with *t*-BuOK delivered the desired benzo[*f*]quinoline **4a**, benzo[*h*]isoquinoline **4b**, and benzo[*f*]isoquinoline **4c** (entries 1–3). This two-step sequence allowed a rapid access to several substituted benzo-(*iso*)quinoline derivatives only by adjusting the two reaction components, i.e., the boronic acid and the pyridine ring. Easily available polysubstituted bromopyridines **1d–f**[16] have been successfully used in this sequence with boronic acid **2a** to generate highly substituted benzo[*h*]isoquinolines **4d–f** (entries 4–6). In the first step, 1,1′,2-trisubstituted biaryl systems were produced with moderate to good yields using standard conditions. Note that the double Suzuki coupling with substrate **1e** did not work and only the mono-coupling product **3e** was formed. In the second step we observed that the cyclization reaction occurred selectively with the methyl group *para* to the nitrogen.[17] Although the yields are moderate, the syntheses remain very attractive for these three compounds because they bear several functional groups as the methyl group,[18] the bromine atom or the dimethylamino group. The substitution of the external aromatic ring was obtained by employing boronic acid **2b**. Benzo-(*iso*)quinoline derivatives **4g** and **4h** were formed with good to excellent yields (entries 7 and 8). With picoline **1g**, the expected aldehyde was not observed and instead the cyclized product **5** was produced through a cascade process (entry 9).[19]

It is noteworthy that our method presents only one limitation because benzo[*h*]quinoline derivatives are not accessible due to a parasite reaction between pyridine **1g** and boronic acid **2a**. To avoid the intramolecular attack of the aldehyde by the pyridine nitrogen, we decided to protect the aldehyde function and in that case we found more convenient to use the Negishi reaction[20] to perform the cross-coupling. This strategy was proven successful in the case of ferrocenyl analogues since the aldehyde intermediate could be isolated to give ferroceno[*h*]quinoline after a *t*-BuOK-promoted cyclization (Fig. 2).[11]

The same methodology applied to bromoacetal **6** furnished the cross-coupling product **7**, which upon treatment with *p*-TSA did not yield the desired compound aldehyde. Quenching the reaction mixture with $NaHCO_3$ furnished again derivative **5** with 37% yield. When the mixture was treated with pH7 buffer, ^1H and ^{13}C NMR analyses showed that no aldehyde nor cyclization product was formed but probably the cyclized product **8** as previously proposed by Igeta and co-workers.[21] It seems that this reaction is very sensitive to structural changes[22] and we anticipated that introducing an electron-withdrawing substituent *ortho* to the nitrogen could lower its nucleophilicity. Thus, repeating the Negishi coupling with pyridine **9**[11] bearing a chlorine in 2-position delivered acetal **10** and after hydrolysis in presence of *p*-TSA we could isolate aldehyde **11** in good yield. Finally, treating **11** with 2 equiv of *t*-BuOK in DMF furnished 2-chlorobenzo[*h*]quinoline **12** (Scheme 1).

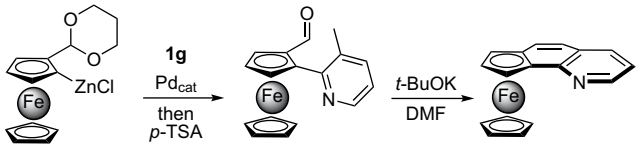
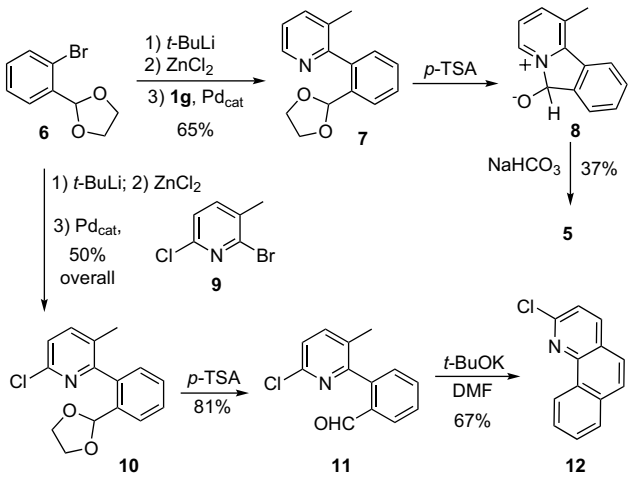
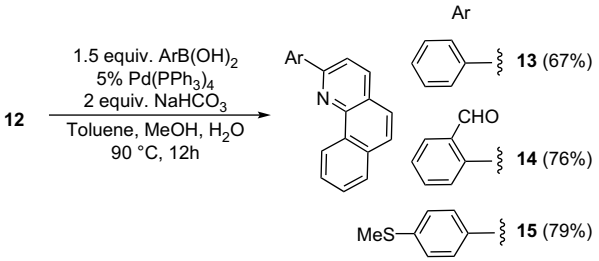


Figure 2. Synthesis of ferroceno[*h*]quinoline through Negishi coupling.



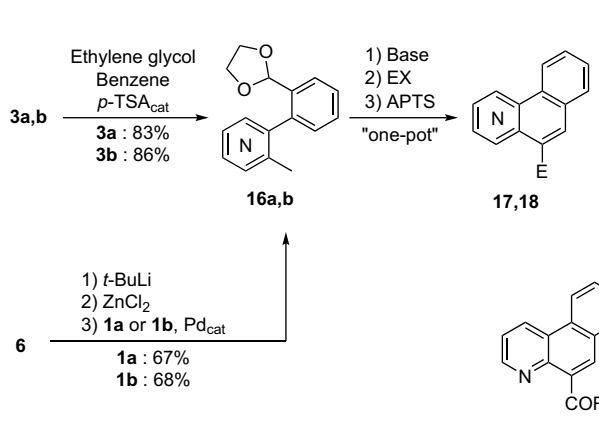
Scheme 1. Synthesis of 2-chlorobenzo[*h*]quinoline **12**.

The presence of a chlorine in 2-position of compound **12** allows a range of functional groups to be incorporated. It was already shown that piperidine or piperazine derivatives can be used to displace the chlorine atom by nucleophilic substitution.[1e,f,23] We then wanted to expand the potential synthetic utility of benzoquinoline **12** by introducing aromatic rings in 2-position. The Suzuki cross-coupling of **12** with different arylboronic acids furnished 2-arylbenzo[*h*]quinolines **13–15** with good yields. It is interesting to note that compound **14** did not cyclize during the Suzuki reaction in contrast to 2-chloroquinoline[19a] showing again the extreme sensitivity of this reaction to structural changes (Scheme 2).



Scheme 2. Preparation of 2-arylbenzo[*h*]quinoline derivative.

Finally, we turned our attention to the elaboration of the central ring of benzo-(*iso*)quinolines (Scheme 3). Acetals **16a**,**b** were obtained by protecting aldehydes **3a**,**b** in benzene. This solvent was preferred to toluene because we observed partial acid-promoted cyclization of **3a** to **4a** caused by the use of a more elevated temperature during the azeotropic distillation. Alternatively, these compounds could be obtained directly from **6** by using a Negishi cross-coupling reaction. Starting from **16a**,**b** we developed a 'one-pot' procedure to access directly benzo-(*iso*)quinoline derivatives **17** and **18** bearing an electron-withdrawing group on the central ring.[24] We found that the methyl functionalization step was very substrate- and electrophile-dependant. Acetal **16a** could be deprotonated on the methyl group by *n*-BuLi but the lithiated intermediate reacted with DMA (dimethylacetamide) while being unreactive with dimethylcarbonate. In this last case, prior metalation with NDA (sodium diisopropylamide) was necessary to achieve good conversion.[15a,18] When using acetal **16b**, *n*-BuLi was not effective even with DMA as the electrophile and again NDA was necessary to give good conversions. It is worth noting that with NDA as the base, DMA did not react and the use of EtOAc was necessary in that case. After the end of the metalation-electrophilic



Acetal	Base (n equiv.)	EX	APTS (n equiv.)	Product	Yield (%)
16a	*n*-BuLi (2)	DMA	10	**17a**	55
16a	NDA (3.5)	$(MeO)_2CO$	20	**18a**	73
16b	NDA (3.5)	EtOAc	20	**17b**	44
16b	NDA (3.5)	$(MeO)_2CO$	20	**18b**[a]	40

[a] A transesterification step (K_2CO_3, EtOH) was necessary to separate the product from the starting aldehyde **3b**

Scheme 3. Fonctionnalization of the central ring of benzo-(*iso*)quinolines.

trapping step, excess *p*-TSA was added causing deprotection of the aldehyde and subsequent cyclization to give compounds **17b** and **18a**,**b** with moderate to good yields.

3. Summary

We have developed a short and efficient synthesis of substituted benzo-(*iso*)quinolines. Our approach based on the construction of the central ring by a base-promoted cyclization allowed the introduction of substituents on each cycle of the benzo-(*iso*)quinoline core. All four isomers depending on the nitrogen position on the pyridine ring were accessible by this methodology, which make it very attractive for biological studies.

4. Experimental part

4.1. General

Melting points were measured on a Totoli apparatus. ^{1}H NMR spectra were recorded on a Brucker AC200 (200 MHz) and data are reported as follows: chemical shifts in parts per million from TMS as an internal standard, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet or overlap of non-equivalent resonances), integration. ^{13}C NMR spectra were recorded at 50 MHz and data are reported as follows: chemical shifts in parts per million from TMS as an internal indicator ($CDCl_3$, δ 77.0 ppm). Mass spectra with electronic impact (MS-EI) were recorded from a Shimadzu QP 2010 apparatus. High resolution mass spectra were recorded from a Brucker micrOTOF-Q. THF was distilled from sodium/benzophenone and stored on sodium wire before use. Diisopropylamine, toluene, benzene, DMA (dimethylacetamide), ethyl acetate, and dimethylcarbonate were distilled over CaH_2. Methanol, DMF, and ethylene glycol were used as received. All reagents were used as received. TLC was performed on silica gel plates and visualized with a UV lamp (254 nm). Chromatography was performed on silica gel (70–230 mesh).

4.2. Preparation of aldehydes 3

*4.2.1. A representative procedure for the Suzuki coupling of pyridine **1** with boronic acid **2**: preparation of 2-(4-methyl-pyridin-3-yl)-benzaldehyde (**3b**)*

3-Bromo-4-methyl-pyridine **1b** (860 mg, 5 mmol) was added to a degazed toluene solution (20 mL) containing $Pd(PPh_3)_4$ (290 mg, 0.25 mmol). To the mixture under N_2 were added successively a degazed solution of boronic acid **2a** (825 mg, 5.5 mmol) in methanol (10 mL) and a degazed solution of Na_2CO_3 (1.06 g, 10 mmol) in water (10 mL). After heating for 15 h at 90 °C, the reaction mixture was cooled to room temperature, extracted with ethyl acetate (30 mL) and dried over $MgSO_4$. After concentration, the residue was purified by chromatography (hexanes/ethyl acetate/triethylamine 8:1:1) to give compound **3b** as a yellow solid (930 mg, 94%). Mp: 77 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.78 (s, 1H), 8.54 (d, J=5 Hz, 1H), 8.42 (s, 1H), 8.06 (d, J=8.2 Hz, 1H), 7.70 (t, J=7.4 Hz, 1H), 7.58 (t, J=7.4 Hz, 1H), 7.31 (d, J=7.6 Hz, 1H), 7.26 (d, J=5 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 191.0, 149.5, 149.1, 145.4, 140.8, 133.9, 133.8, 130.9, 128.5, 128.1, 124.7, 19.6. MS (EI) m/z 197 (M^+, 95%), 196 ($[M-1]^+$, 100), 182 (40), 168 (39), 167 (42), 115 (29). HRMS m/z calcd for $C_{13}H_{11}NO$: 197.0841, found: 198.0913 (MH^+).

*4.2.2. 2-(2-Methyl-pyridin-3-yl)-benzaldehyde (**3a**)*

Yellow solid. Yield: 80%. Mp: 62 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.75 (s, 1H), 8.55 (d, J=4.6 Hz, 1H), 7.99 (d, J=7.8 Hz, 1H), 7.65 (t, J=7.4 Hz, 1H), 7.51 (m, 2H), 7.21 (m, 2H), 2.32 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 190.4, 155.5, 148.2, 142.2, 137.0, 133.4, 133.1, 130.2, 127.9, 127.7, 120.2, 22.6. MS (EI) m/z 197 (M^+, 95%), 196 ($[M-1]^+$, 100), 182 (75), 168 (65), 167 (58), 128 (48). HRMS m/z calcd for $C_{13}H_{11}NO$: 197.0841, found: 198.0913 (MH^+).

*4.2.3. 2-(3-Methyl-pyridin-3-yl)-benzaldehyde (**3c**)*

Yellow solid. Yield: 90%. Mp: 65 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.75 (s, 1H), 8.56 (s, 1H), 8.53 (d, J=4.8 Hz, 1H), 8.06 (d, J=7.6 Hz, 1H), 7.71 (t, J=7.2 Hz, 1H), 7.59 (t, J=7.4 Hz, 1H), 7.27 (d, J=7.6 Hz, 1H), 7.15 (d, J=4.8 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 190.9, 150.7, 147.0, 145.9, 136.1, 134.0, 133.0, 131.5, 129.8, 128.7, 128.1, 124.3, 17.0. MS (EI) m/z 197 (M^+, 100%), 182 (37), 167 (25), 127 (14), 115 (22). HRMS m/z calcd for $C_{13}H_{11}NO$: 197.0841, found: 198.0913 (MH^+).

*4.2.4. 2-(2,4,6-Trimethyl-pyridin-3-yl)-benzaldehyde (**3d**)*

White solid. Yield: 93%. Mp: 58 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.70 (s, 1H), 8.03 (d, J=7.6 Hz, 1H), 7.68 (t, J=7.4 Hz, 1H), 7.53 (t, J=7.6 Hz, 1H), 7.19 (d, J=7.6 Hz, 1H), 6.96 (s, 1H), 2.54 (s, 3H), 2.18 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 191.3, 157.0, 155.1, 145.8, 142.4, 134.4, 133.6, 130.1, 129.7, 128.2, 128.1, 122.0, 24.0, 23.5, 20.1. MS (EI) m/z 225 (M^+, 100%), 210 (50), 196 (83), 115 (22). HRMS m/z calcd for $C_{15}H_{15}NO$: 225.1154, found: 226.1226 (MH^+).

*4.2.5. 2-(5-Bromo-2,4,6-trimethyl-pyridin-3-yl)-benzaldehyde (**3e**)*

White solid. Yield: 53%. Mp: 108 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.74 (s, 1H), 8.06 (d, J=7 Hz, 1H), 7.72 (t, J=7 Hz, 1H), 7.60 (t, J=6.8 Hz, 1H), 7.20 (d, J=7 Hz, 1H), 2.73 (s, 3H), 2.14 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 190.7, 156.1, 153.4, 145.4, 141.6, 134.5, 133.5, 131.5, 130.5, 128.7, 128.6, 122.0, 25.7, 23.2, 21.4. MS (EI) m/z 305 (M^+ [^{81}Br], 97%), 303 (M^+ [^{79}Br], 100), 290 (50), 288 (55),

276 (92), 274 (95), 224 (32), 209 (30), 194 (35), 181 (27), 152 (38), 115 (26), 76 (36). HRMS *m*/*z* calcd for $C_{15}H_{14}BrNO$: 303.0259, found: 304.0332 (MH^+).

*4.2.6. 2-(6-Dimethylamino-2,4-dimethyl-pyridin-3-yl)-benzaldehyde (**3f**)*

Yellow oil. Yield: 42%. ^1H NMR (200 MHz, $CDCl_3$) δ 9.78 (s, 1H), 8.01 (d, *J*=7.6 Hz, 1H), 7.63 (t, *J*=7.4 Hz, 1H), 7.47 (t, *J*=7.4 Hz, 1H), 7.20 (d, *J*=7.4 Hz, 1H), 6.31 (s, 1H), 3.11 (s, 6H), 2.09 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 192.2, 158.5, 153.9, 146.5, 143.9, 134.4, 134.1, 131.6, 127.6, 127.2, 120.2, 103.7, 37.7, 23.7, 20.9. MS (EI) *m*/*z* 254 (M^+, 100%), 239 (74), 225 (100), 211 (36), 182 (22). HRMS *m*/*z* calcd for $C_{16}H_{18}N_2O$: 254.1419, found: 255.1492 (MH^+).

*4.2.7. 6-(2-Methyl-pyridin-3-yl)-benzo[1,3]dioxole-5-carbaldehyde (**3g**)*

Colorless oil. Yield: 72%. ^1H NMR (200 MHz, $CDCl_3$) δ 9.47 (s, 1H), 8.53 (d, *J*=4.2 Hz, 1H), 7.48 (d, *J*=7.6 Hz, 1H), 7.41 (s, 1H), 7.21 (t, *J*=5 Hz, 1H), 6.67 (s, 1H), 6.10 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 189.0, 156.3, 152.3, 148.7, 148.0, 137.7, 132.4, 128.6, 120.5, 109.8, 106.1, 102.1, 22.9. MS (EI) *m*/*z* 241 (M^+, 75%), 226 (100), 154 (17). HRMS *m*/*z* calcd for $C_{14}H_{11}NO_3$: 241.0739, found: 242.0812 (MH^+).

*4.2.8. 6-(4-Methyl-pyridin-3-yl)-benzo[1,3]dioxole-5-carbaldehyde (**3h**)*

White solid. Yield: 98%. Mp: 134 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 948 (s, 1H), 8.51 (d, *J*=4.8 Hz, 1H), 8.39 (s, 1H), 7.44 (s, 1H), 7.24 (d, *J*=4.8 Hz, 1H), 6.69 (s, 1H), 6.12 (s, 2H), 2.15 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 189.0, 152.3, 149.5, 148.8, 148.2, 145.9, 138.0, 133.5, 129.0, 124.7, 110.1, 106.2, 102.2. MS (EI) *m*/*z* 241 (M^+, 100%), 226 (55), 212 (15), 154 (17). HRMS *m*/*z* calcd for $C_{14}H_{11}NO_3$: 241.0739, found: 242.0812 (MH^+).

4.3. Preparation of benzo-(*iso*)quinolines 4

*4.3.1. A representative procedure for the t-BuOK-promoted cyclization of aldehydes **3**: preparation of benzo[h]isoquinoline (**4b**)[9]*

To a solution of compound **3b** (788 mg, 4 mmol) in DMF (4 mL) was slowly added at room temperature a solution of *t*-BuOK (896 mg, 8 mmol) in DMF (8 mL) and the mixture was stirred overnight. The reaction mixture was quenched by addition of water (1 mL) and extracted with dichloromethane (4×20 mL). After drying over $MgSO_4$ and concentration, the residue was purified by chromatography (hexanes/ethyl acetate/triethylamine 8:1:1) to afford **4b** as a white solid (560 mg, 78%). Mp: 50 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.82 (d, *J*=8.4 Hz, 1H), 8.72 (d, *J*=5.2 Hz, 1H), 7.96 (d, *J*=8.8 Hz, 2H), 7.73 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.5, 144.8, 135.5, 131.8, 131.3, 128.9, 128.6, 127.5, 127.1, 124.5, 124.7, 121.6, 120.9. MS (EI) *m*/*z* 179 (M^+, 100%), 151 (19), 76 (15).

*4.3.2. Benzo[f]quinoline (**4a**)[9]*

White solid. Yield: 80%. Mp: 93 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.94 (d, *J*=6.2 Hz, 1H), 8.62 (m, 1H), 7.99 (s, 1H), 7.96 (dd, *J*=6.6, 2.2 Hz, 1H), 7.92 (d, *J*=2.2 Hz, 1H), 7.67 (m, 2H), 7.55 (dd, *J*=8.4, 4.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.9, 149.4, 131.8, 131.0, 130.8, 129.8, 128.8, 128.3, 127.5, 127.2, 125.6, 122.7, 121.4. MS (EI) *m*/*z* 179 (M^+, 100%), 151 (22), 76 (18).

*4.3.3. Benzo[f]isoquinoline (**4c**)[9]*

White solid. Yield: 60%. Mp: 90 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.69 (d, *J*=5.6 Hz, 1H), 8.53 (t, *J*=4.6 Hz, 1H), 8.27 (d, *J*=5.4 Hz, 1H), 7.84 (m, 1H), 7.80–7.55 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 151.5, 145.0, 134.6, 133.3, 128.6, 128.5, 128.2, 127.0, 126.8, 124.5, 123.0, 115.9. MS (EI) *m*/*z* 179 (M^+, 100%), 151 (16), 89 (13), 76 (18).

*4.3.4. 1,3-Dimethylbenzo[h]isoquinoline (**4d**)*

White solid. Yield: 51%. Mp: 112 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 8.71 (d, *J*=8.2 Hz, 1H), 8.81 (d, *J*=7 Hz, 1H), 7.72 (d, *J*=8.8 Hz, 1H), 7.57 (t, *J*=7.6 Hz, 1H), 7.43 (d, *J*=8.8 Hz, 1H), 7.28 (s, 1H), 3.23 (s, 3H), 2.64 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.2, 151.6, 138.3, 133.0, 131.3, 130.4, 128.9, 128.4, 126.8, 126.7, 126.0, 125.6, 125.2, 125.1, 118.6, 30.2, 23.8. MS (EI) *m*/*z* 206 ($[M-1]^+$, 100%), 191 (10). HRMS *m*/*z* calcd for $C_{15}H_{13}N$: 207.1048, found: 208.1121 (MH^+).

*4.3.5. 4-Bromo-1,3-dimethylbenzo[h]isoquinoline (**4e**)*

White solid. Yield: 44%. Mp: 98 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 8.68 (d, *J*=8 Hz, 1H), 8.06 (d, *J*=9 Hz, 1H), 7.83 (m, 2H), 7.61 (m, 2H), 3.17 (s, 3H), 2.81 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.6, 150.9, 132.7, 132.5, 129.9, 128.9, 127.1, 126.7, 126.6, 124.5, 122.8, 118.2, 29.9, 25.5. MS (EI) *m*/*z* 285 (M^+, 100%), 205 (42), 190 (20), 163 (20), 103 (27), 82 (25). HRMS *m*/*z* calcd for $C_{15}H_{12}BrN$: 285.0153, found: 286.0226 (MH^+).

*4.3.6. 3-Dimethylamino-1-methylbenzo[h]isoquinoline (**4f**)*

Greenish solid. Yield: 42%. Mp: 80 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 8.59 (d, *J*=8.6 Hz, 1H), 7.72 (d, *J*=7.4 Hz, 1H), 7.58 (d, *J*=9 Hz, 1H), 7.52 (d, *J*=8.6 Hz, 1H), 7.37 (t, *J*=8.2 Hz, 2H), 3.15 (s, 3H), 3.13 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.6, 156.5, 140.8, 131.5, 130.9, 128.8, 126.7, 126.2, 126.1, 125.9, 124.4, 98.4, 37.9, 30.2. MS (EI) *m*/*z* 236 (M^+, 100%), 221 (66), 207 (100), 193 (29), 165 (45), 118 (23). HRMS *m*/*z* calcd for $C_{16}H_{16}N_2$: 236.1313, found: 237.1386 (MH^+).

*4.3.7. [1,3]Benzodioxolo[5,6-f]quinoline (**4g**)[6a]*

White solid. Yield: 65%. Mp: 193 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 8.90 (d, *J*=3.8 Hz, 1H), 8.68 (d, *J*=8.4 Hz, 1H), 7.84 (m, 3H), 7.47 (dd, *J*=8.2 4.2 Hz, 1H), 7.21 (s, 1H), 6.10 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.9, 148.5, 148.1, 147.1, 130.3, 130.1, 128.0, 126.3, 125.8, 125.0, 120.8, 105.7, 101.5, 100.5. MS (EI) *m*/*z* 223 (M^+, 100%), 164 (16), 138 (14), 111 (17).

*4.3.8. [1,3]Benzodioxolo[5,6-h]isoquinoline (**4h**)[6a]*

White solid. Yield: 88%. Mp: 178 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 9.75 (s, 1H), 8.56 (d, *J*=5.2 Hz, 1H), 7.99 (s, 1H), 7.70 (d, *J*=8.8 Hz, 1H), 7.58 (d, *J*=5.2 Hz, 1H), 7.48 (d, *J*=8.8 Hz, 1H), 7.14 (s, 1H), 6.07 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.9, 148.1, 146.5, 143.7, 134.8, 130.9, 128.7, 126.3, 124.8, 123.0, 121.0, 105.9, 101.6, 99.9. MS (EI) *m*/*z* 223 (M^+, 100%), 164 (18), 138 (15), 111 (17).

4.4. Preparation of 2-chlorobenzo[*h*]quinoline 12

*4.4.1. A representative procedure for the Negishi reaction of **6** with bromopyridines. Preparation of 2-(2-[1,3]dioxolan-2-yl-phenyl)-3-methyl-pyridine (**7**)*

A solution of **6** (486 mg, 2 mmol) in dry THF (1 mL) was added to a cooled solution of *t*-BuLi (1.7 M in pentane, 2.35 mL, 4 mmol) in dry THF (4 mL) at −78 °C under nitrogen. After 30 min at −78 °C, a solution of freshly dried $ZnCl_2$ in THF (0.5 M, 4.3 mL, 4.28 mmol) was added slowly and the temperature was raised to room temperature and stirred for 2 h. To the clear solution were successively added pyridine **1g** (287 mg, 1.67 mmol) and $Pd(PPh_3)_4$ (77 mg, 0.067 mmol) and the mixture was stirred at reflux overnight. Brine was added, the mixture was extracted with ethyl acetate (15 mL), dried over $MgSO_4$, and concentrated. The residue was purified by chromatography (hexanes/ethyl acetate 4:1) to afford **7** as a colorless oil (262 mg, 65%). ^1H NMR (200 MHz, $CDCl_3$) δ 8.43 (d, *J*=4.2 Hz, 1H), 7.67 (m, 1H), 7.47 (d, *J*=7.6 Hz, 1H), 7.34 (m, 2H), 7.11 (m, 2H), 5.56 (s, 1H), 3.89 (m, 2H), 3.68 (m, 2H), 2.07 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.5, 145.5, 139.5, 136.9, 134.9, 131.4, 128.1, 128.0,

127.3, 125.9, 121.7, 100.4, 64.4, 18.6. MS (EI) m/z 240 ($[M-H]^+$, 5%), 182 (15), 168 (100).

*4.4.2. 6-Chloro-2-(2-[1,3]dioxolan-2-yl-phenyl)-3-methyl-pyridine (**10**)*

Yellow solid. Yield: 50%. Mp: 107 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.63 (m, 1H), 7.48 (d, J=8 Hz, 1H), 7.37 (d, J=5 Hz, 1H), 7.36 (d, J=4.6 Hz, 1H), 7.14 (m, 2H), 5.61 (s, 1H), 3.90 (m, 2H), 3.78 (m, 2H), 2.05 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.5, 147.2, 140.3, 138.5, 135.5, 131.1, 128.7, 128.6, 128.2, 126.5, 122.6, 101.1, 65.0, 18.4. MS (EI) m/z 202 ($[M-C_3H_6O_2]^+$, 100%), 166 (20). HRMS m/z calcd for $C_{15}H_{14}ClNO_2$: 275.0713, found: 276.0786 (MH^+).

*4.4.3. 2-(6-Chloro-3-methyl-pyridin-2-yl)-benzaldehyde (**11**)*

Compound **10** (100 mg, 0.344 mmol) was dissolved in THF (2 mL), water (0.2 mL) and *p*-TSA (130 mg, 0.688 mmol) were added and the mixture was stirred at room temperature for 2 h. A saturated solution of $NaHCO_3$ was added and the mixture was extracted with ethyl acetate (10 mL), dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (hexanes/ethyl acetate 4:1) to afford aldehyde **11** (70 mg, 81%), which was used directly in the cyclization step. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.98 (d, J=7.4 Hz), 7.70–7.50 (m, 3H), 7.35 (d, J=7.2 Hz, 1H), 7.27 (d, J=8 Hz, 1H), 2.10 (s, 3H).

*4.4.4. 2-Chlorobenzo[h]quinole (**12**)[1f]*

This compound was obtained using the same procedure as for **4**. Yellow solid. Yield: 67%. Mp: 105 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.17 (d, J=8.3 Hz, 1H), 8.02 (d, J=8.3 Hz, 1H), 7.67–7.79 (m, 4H), 7.57 (d, J=8.7 Hz, 1H), 7.43 (d, J=8.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.6, 149.8, 138.5, 133.9, 130.4, 128.8, 128.1, 127.8, 127.3, 124.9, 124.7, 124.5, 122.6. MS (EI) m/z 214 (M^+, 100%), 178 (72).

4.5. Suzuki coupling of 12

*4.5.1. Representative procedure. Preparation of 2-phenylbenzo[h]quinole (**13**)[4f]*

2-Chlorobenzo[*h*]quinole **12** (100 mg, 0.47 mmol) was added to a degazed toluene solution (2 mL) containing $Pd(PPh_3)_4$ (27 mg, 0.024 mmol). To the mixture under N_2 were added successively a degazed solution of boronic acid **2a** (110 mg, 0.7 mmol) in methanol (1 mL) and a degazed solution of $NaHCO_3$ (80 mg, 0.94 mmol) in water (1 mL). After heating for 15 h at 90 °C, the reaction mixture was cooled to room temperature, extracted with ethyl acetate (10 mL) and dried over $MgSO_4$. After concentration, the residue was purified by chromatography (hexanes/ethyl acetate 4:1) to give compound **13** as a white solid (76 mg, 67%). Mp: 65 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.48 (d, J=7.9 Hz, 1H), 8.29 (d, J=7.2 Hz, 1H), 8.04 (d, J=8.4 Hz, 1H), 7.86 (d, J=8.2 Hz, 1H), 7.83 (d, J=8.2 Hz, 1H), 7.42–7.70 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.4, 146.2, 139.7, 136.5, 133.9, 131.9, 129.3, 128.9, 128.2, 127.8, 127.5, 127.4, 126.9, 125.2, 125.1, 124.8, 118.8. MS (EI) m/z 255 (M^+, 100%), 127 (18).

*4.5.2. 2-Benzo[h]quinolin-2-yl-benzaldehyde (**14**)*

White solid. Yield: 76%. Mp: 115 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.36 (s, 1H), 9.20 (d, J=8.3 Hz, 1H), 8.29 (d, J=8.4 Hz, 1H), 8.06 (d, J=7.6 Hz, 1H), 7.50–8.00 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 193.2, 154.2, 143.0, 137.0, 136.3, 133.9, 133.5, 132.8, 131.6, 129.9, 129.1, 128.9, 128.6, 128.5, 128.4, 127.9, 127.6, 125.0, 124.9, 121.9. MS (EI) m/z 255 ($[M-CO]^+$, 100%), 127 (18). HRMS m/z calcd for $C_{20}H_{13}NO$: 283.0997, found: 284.1070 (MH^+).

*4.5.3. 2-(4-Thiomethyl-phenyl)benzo[h]quinoline (**15**)*

White solid. Yield: 79%. Mp: 128 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.46 (d, 7.9 Hz, 1H), 8.24 (d, J=7.7 Hz, 1H), 8.12 (d, J=8.4 Hz, 1H), 7.85–7.95 (m, 2H), 7.60–7.80 (m, 4H), 7.38 (d, J=8.7 Hz, 2H), 2.53 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.9, 146.3, 140.3, 136.5, 133.9, 133.0, 131.9, 128.6, 128.3, 127.7, 127.1, 127.0, 126.4, 126.2, 125.1, 124.6, 118.4, 14.2. MS (EI) m/z 301 (M^+, 100%), 253 (12), 226 (15), 142 (22), 127 (21). HRMS m/z calcd for $C_{20}H_{15}NS$: 301.0925, found: 302.0998 (MH^+).

4.6. Preparation of acetals 16

*4.6.1. 3-(2-[1,3]Dioxolan-2-yl-phenyl)-2-methyl-pyridine (**16a**)*

Aldehyde **3a** (320 mg, 1.624 mmol) was dissolved in benzene (60 mL). Ethylene glycol (15 mL) and *p*-TSA (15.6 mg, 0.08 mmol) were added and the mixture was heated at 100 °C with a Dean–Stark apparatus overnight. After cooling the reaction, a saturated solution of $NaHCO_3$ (30 mL) was added and the organic phase was separated and dried over $MgSO_4$. After filtration and concentration, the crude was purified by chromatography on silica gel (hexane/ethyl acetate 1:1) to give **16a** as a colorless oil (323 mg, 83%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.46 (d, J=3.8 Hz, 1H), 7.64 (m, 1H), 7.44 (d, J=7.8 Hz, 1H), 7.40 (d, J=7.4 Hz, 1H), 7.36 (d, J=3.6 Hz, 1H), 7.10 (m, 2H), 5.38 (s, 1H), 3.90–3.70 (m, 4H), 2.30 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.4, 148.1, 139.1, 137.5, 135.1, 134.7, 129.5, 129.0, 128.0, 126.9, 120.2, 101.5, 65.2, 65.1, 23.2. MS (EI) m/z 240 ($[M-1]^+$, 35%), 226 (100), 196 (64), 180 (92), 167 (54), 148 (96), 139 (20), 104 (26), 73 (36). HRMS m/z calcd for $C_{15}H_{15}NO_2$: 241.1103, found: 242.1176 (MH^+).

*4.6.2. 3-(2-[1,3]Dioxolan-2-yl-phenyl)-4-methyl-pyridine (**16b**)*

Colorless oil. Yield: 86%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.43 (d, J=5 Hz, 1H), 8.38 (s, 1H), 7.67 (m, 1H), 7.40 (m, 2H), 7.15 (d, J=5 Hz, 1H), 7.09 (m, 1H), 5.41 (s, 1H), 3.90–3.75 (m, 4H), 2.08 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.7, 148.3, 145.5, 137.1, 135.6, 135.5, 129.8, 128.8, 128.0, 126.8, 124.4, 101.4, 65.1, 19.5. MS (EI) m/z 240 ($[M-1]^+$, 100%), 196 (38), 168 (31), 148 (62), 104 (14), 73 (17). HRMS m/z calcd for $C_{15}H_{15}NO_2$: 241.1103, found: 242.1176 (MH^+).

Compounds **16a** and **16b** were also obtained using the same procedure as for **7** and **10**; **16a** (67%) and **16b** (68%).

4.7. Preparation of benzo-(*iso*)quinolines 17 and 18

*4.7.1. 1-Benzo[f]quinolin-5-yl-ethanone (**17a**)*

Acetal **16a** (100 mg, 0.415 mmol) was dissolved in THF (2 mL) and the solution was cooled to −30 °C. *n*-BuLi (1.6 M in hexanes, 0.52 mL, 0.83 mmol) was added slowly and the mixture was stirred at −20 °C for 1 h. After cooling to −78 °C, DMA (85 μL, 0.913 mmol) was added and the solution was stirred for 1 h. Hydrolysis was performed at −78 °C then the temperature was raised to ambiant. *p*-TSA (800 mg, 4.2 mmol) was added and the mixture was stirred at room temperature overnight. $NaHCO_3$ satd (5 mL) was added and the mixture was extracted with ethyl acetate (20 mL), dried over $MgSO_4$ and concentrated. The crude was purified by chromatography (hexanes/ethyl acetate 4:1) to give **17a** as a yellow solid (50 mg, 55%). Mp: 110 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.96 (d, J=4.2 Hz, 1H), 8.91 (d, J=8.6 Hz, 1H), 8.55 (d, J=8 Hz, 1H), 8.17 (s, 1H), 7.96 (d, J=7 Hz, 1H), 7.72 (m, 2H), 7.56 (dd, J=8.4, 4.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 190.9, 156.4, 149.1, 138.5, 132.4, 130.7, 130.2, 129.8, 129.2, 128.5, 127.7, 125.4, 122.4, 121.5, 32.4. MS (EI) m/z 221 (M^+, 100%), 206 (94), 178 (60), 151 (46), 75 (16). HRMS m/z calcd for $C_{15}H_{11}NO$: 221.0841, found: 222.0913 (MH^+).

*4.7.2. A representative procedure for the reaction of acetals **16** with NDA. Preparation of benzo[f]quinoline-5-carboxylic acid methyl ester (**18a**)*

t-BuONa (140 mg, 1.45 mmol) was dried for 2 h at 100 °C in vacuo. THF (3 mL) and diisopropylamine (187 μL, 1.45 mmol) were added and the mixture was cooled to −78 °C. *n*-BuLi (1.6 M in hexane, 0.9 mL, 1.45 mmol) was added dropwise and the mixture

was stirred for 15 min at the same temperature. Acetal **16b** (100 mg, 0.415 mmol) dissolved in THF (2 mL) was added dropwise and the resulting solution was stirred for 30 min at −78 °C. Dimethylcarbonate (200 μL, 1.66 mmol) was added and the mixture was stirred for 1 h. Water (1 mL) was added at −78 °C and the temperature was raised to ambient temperature before addition of *p*-TSA (1.6 g, 8.4 mmol) and stirring was maintained overnight. $NaHCO_3$ satd (10 mL) was added and the mixture was extracted with ethyl acetate (30 mL), dried over $MgSO_4$ and concentrated. The crude was purified by chromatography (hexanes/ethyl acetate 4:1) to give **18a** as a yellow oil (72 mg, 73%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.02 (d, J=4.2 Hz, 1H), 8.83 (d, J=8.4 Hz, 1H), 8.47 (d, J=8.2 Hz, 1H), 8.26 (s, 1H), 7.88 (d, J=7.2 Hz, 1H), 7.63 (m, 2H), 7.51 (dd, J=8.4, 4.4 Hz, 1H), 4.08 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.0, 149.8, 132.1, 130.6, 130.4, 130.0, 129.6, 129.1, 128.5, 127.5, 125.3, 122.3, 121.5, 52.5. MS (EI) m/z 237 (M^+, 40%), 206 (46), 179 (100), 151 (28), 89 (13), 75 (17). HRMS m/z calcd for $C_{15}H_{11}NO_2$: 237.0790, found: 238.0863 (MH^+).

*4.7.3. 1-Benzo[h]isoquinolin-5-yl-ethanone (**17b**)*

Yellow solid. Yield: 44%. Mp: 135 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.94 (s, 1H), 8.68 (m, 3H), 8.36 (s, 1H), 7.93 (d, J=7.4 Hz, 1H), 7.78 (t, J=7.2 Hz, 1H), 7.66 (t, J=7 Hz, 1H), 2.79 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 199.8, 146.5, 145.9, 135.8, 132.6, 131.3, 130.9, 130.2, 130.1, 129.8, 128.6, 127.9, 125.0, 121.7, 119.5, 29.1. MS (EI) m/z 221 (M^+, 60%), 206 (100), 178 (49), 151 (30). HRMS m/z calcd for $C_{15}H_{11}NO$: 221.0841, found: 222.0913 (MH^+).

*4.7.4. Benzo[h]isoquinoline-5-carboxylic acid ethyl ester (**18b**)*

White solid. Yield: 40%. Mp: 95 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.78 (m, 3H), 8.69 (s, 1H), 7.99 (d, J=7.8 Hz, 1H), 7.82 (t, J=7.2 Hz, 1H), 7.68 (t, J=7 Hz, 1H), 4.51 (q, J=7 Hz, 2H), 1.50 (t, J=7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.3, 146.8, 145.8, 137.0, 131.2, 130.4, 130.2, 128.7, 128.5, 127.9, 125.1, 124.2, 121.9, 119.3, 61.4, 14.4. MS (EI) m/z 251 (M^+, 83%), 223 (22), 206 (100), 178 (42), 151 (28). HRMS m/z calcd for $C_{16}H_{13}NO_2$: 251.0946, found: 252.1019 (MH^+).

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