Synthesis of Fluorescent 9-Aryl-Substituted Benzo[*b*]quinolizinium Derivatives

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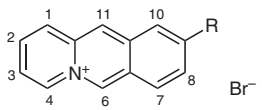
Abstract: The arylation of readily available benzo[*b*]quinolizinium-9-boronic acid with carbocyclic or heterocyclic bromoarenes in the presence of a palladium catalyst [Pd(dppf)Cl_2·CH_2Cl_2 or $Pd(PPh_3)_2Cl_2$] gives the corresponding cationic biaryl products in yields of 15–81%. All aryl-substituted benzo[*b*]quinolizinium (acridizinium) derivatives exhibit a long-wavelength absorption maximum between 409 and 422 nm in water, which change marginally in different solvents ($\Delta\lambda$ <10 nm). As the only exception, the 9-(*N*,*N*-dimethylaminophenyl)benzo[*b*]quinolizinium exhibits pronounced solvatochromic behavior (H_2O: λ_{abs} = 422 nm; MeCN: λ_{abs} = 474 nm; CH_2Cl_2: λ_{abs} = 507 nm) due to the strong donor–acceptor interplay in the cationic chromophore. Depending on the donor strength of the aryl substituent, the benzo[*b*]quinolizinium derivatives exhibit fluorescence bands in water with long-wavelength maxima between λ_{fl} = 452 nm (R = phenyl) and 529 nm (R = 4-methoxyphenyl). The non-fluorescent 9-(*N*,*N*-dimethylaminophenyl)benzo[*b*]quinolizinium may be employed as a pH-sensitive light-up probe (pH 2.8–4.8), since its emission intensity increases by a factor of 130 upon protonation.

Key words: arylations, biaryls, cationic hetarenes, heterocycles, fluorescent probes

Heterocyclic polyaromatic cations with a quaternary nitrogen atom represent attractive and versatile sources for the design of water-soluble materials; for example, as colorimetric or fluorimetric probes.[1] Moreover, annelated azinium and quinolizinium derivatives, i.e. arenes which contain quaternary bridgehead nitrogen atoms, have been shown to bind to DNA and may thus be employed as a central unit in DNA-targeting drugs.[2] To explore the possibilities offered by this particular class of heteroaromatic compounds in detail and to have efficient access to target molecules with a definite substitution pattern, synthetic methods are required that allow the versatile functionalization of the heteroaromatic core. Nevertheless, in many cases the electrophilic aromatic substitution of cationic heteroarenes is an inefficient and rather unselective reaction; in particular as the substrates are often not persistent under the reaction conditions.[3] On the other hand, nucleophilic substitution reactions occasionally give the desired products,[4] but in many cases nucleophilic reagents induce ring-opening reactions that lead to the destruction of the substrate.[5] Notably, only a few successful transition-metal-mediated reactions of cationic hetarenes have been reported. Thus, bromoquinolizinium derivatives have been employed successfully in Stille and Sonogashira coupling reactions.[6,7,8] Considering the latter results, we proposed that the Suzuki–Miyaura cross-coupling reaction[9] may be an appropriate reaction for the synthesis of 9-aryl-substituted benzo[*b*]quinolizinium ions (acridizinium ions),[3] i.e., a class of compounds we are interested in because of their potential application as DNA-binding ligands and as water-soluble fluorescent probes.[2e] As a starting point, we chose the benzo[*b*]quinolizinium-9-boronic acid (**1a**; Figure 1), because the potential coupling reagents, namely halogen-substituted arenes, are readily available with a broad variation of the substitution pattern. The Suzuki–Miyaura coupling of 9-bromobenzo[*b*]quinolizinium bromide (**1b**) with arene boronic acids may also be considered; however, this inverse approach has been shown to be rather inefficient with bromoquinolizinium derivatives.[6b,8] Herein, we demonstrate that, indeed, the benzo[*b*]quinolizinium-9-boronic acid (**1a**) may be employed in palladium-mediated coupling reactions and that the products exhibit promising photophysical properties.



1a: R = $B(OH)_2$
1b: R = Br

Figure 1

The benzo[*b*]quinoliziniumboronic acid **1a** was synthesized from the known (4-bromomethylphenyl)boronic ester (**2**),[10] which was prepared in two steps from commercially available *p*-tolylboronic acid (75% overall yield). The reaction of boronic ester **2** with (1,3-dioxolan-2-yl)pyridine yielded the *N*-benzylpyridinium derivative **3** almost quantitatively (Scheme 1). The cyclodehydration[3b] of the pyridinium salt **3** in refluxing HBr (48%) gave the benzo[*b*]quinoliziniumboronic acid **1a** in 80% yield. The structure of **1a** was confirmed by ^{1}H- and ^{13}C NMR analysis, mass-spectrometric data and elemental analysis.

The first attempts to achieve an aryl–aryl coupling reaction between the benzo[*b*]quinoliziniumboronic acid **1a** and bromobenzene were performed under commonly employed conditions of the Suzuki–Miyaura reaction, i.e., with $Pd(PPh_3)_2Cl_2$ as the catalyst in a refluxing solution of water and 1,4-dioxane. To avoid the known ring-opening

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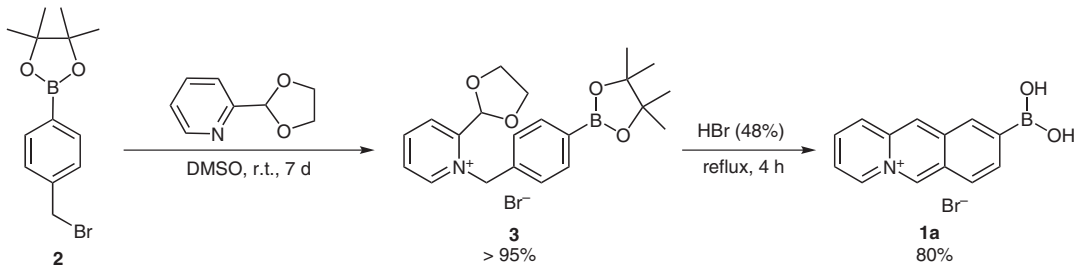
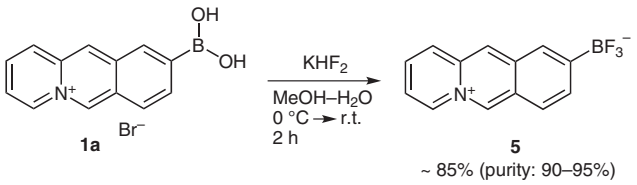


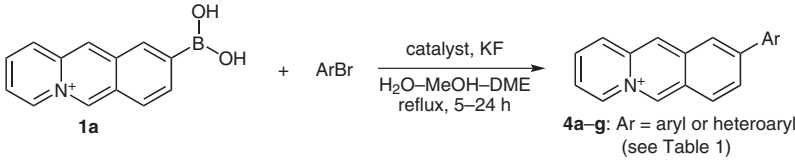
Scheme 1 Synthesis of the benzo[*b*]quinolizinium-9-boronic acid (**1a**)

reaction of the benzo[*b*]quinolizinium ion in the presence of a strong nucleophile,[5a,b] potassium fluoride was used as the additive.[11] However, only traces of cross-coupling product **4a** were generated in the reaction as indicated by ^{1}H NMR spectroscopic analysis of the crude product. The use of potassium phosphate as a rather weak base led to the decomposition of the substrate **1a** (monitored by TLC). The optimization of the reaction conditions revealed that an efficient cross-coupling between **1a** and bromobenzene may be achieved in a solvent mixture of water, methanol and 1,2-dimethoxyethane (DME) with $Pd(PPh_3)_2Cl_2$ as catalyst and potassium fluoride as a base (Scheme 2). Under these particular conditions, the reaction of the boronic acid **1a** with bromobenzene, *p*-bromofluorobenzene or *p*-bromoanisole gave the 9-arylbenzo[*b*]quinolizinium derivatives **4a**–**c** as the main products, which were isolated in moderate yields (21–44%) by precipitation as tetrafluoroborate or perchlorate salts upon addition of aqueous sodium tetrafluoroborate or sodium perchlorate solutions (ion metathesis) and subsequent crystallization (Table 1). In contrast, only traces of the cross-coupling product **4d** were isolated when the reaction was performed with *p*-bromo-*N*,*N*-dimethylaniline as substrate. Presumably, the oxidative addition to the electron-rich bromoarene is not efficient enough to maintain the catalytic cycle.[9a] Nevertheless, the use of $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ as the catalyst increased the yield of the products **4c** and **4d** up to 81% and 40%, respectively, as compared with 21% and 3% with $Pd(PPh_3)_2Cl_2$ (Table 1, entries 3–6). As this observation indicated that $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ may be an appropriate catalyst for the coupling of the boronic acid **1a** and electron-rich bromoarenes, it was also employed for the reaction with 3-bromothiophene, 2-bromothiophene, and 3-bromofuran; however, the corresponding heteroaryl-substituted benzo[*b*]quinolizinium derivatives **4e**–**g** were isolated only in low to moderate yields (15–42%). Although $Pd_2(dba)_3$/PCy_3 has been demonstrated to catalyze Suzuki cross-coupling reactions of nitrogen heterocycles efficiently,[12] this catalyst did not improve the yield of the coupling reaction of the boronic acid **1a** with, for example, 3-bromofuran (Table 1, entry 9 and 10). Except for product **4a**, all products **4b**–**g** are new compounds and were fully characterized. Specifically, the structural assignments were confirmed by ^{1}H and ^{13}C NMR analysis, mass-spectrometric and elemental analysis data. Unfortunately, attempts to synthesize pyridine-substituted benzo[*b*]quinolizinium derivatives in various catalyst systems such as $Pd(PPh_3)_2Cl_2$/KF, $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$/KF, or $Pd_2(dba)_3$/PCy_3/KF, by the reaction of the boronic acid **1a** with 2-bromo-, 3-bromo- or 4-iodopyridine, i.e. reagents which are frequently used for Suzuki–Miyaura coupling reactions, did not provide the corresponding pyridyl-substituted benzo[*b*]quinolizinium derivatives. So far, it is not clear why the coupling reaction with bromopyridine derivatives failed; however, these results are consistent with the observation that the inverse combination of substrates, i.e., bromoquinolizinium ions and pyridine boronic acids, do not react in a Suzuki-type coupling reaction either.[6b]



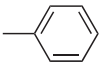
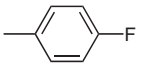
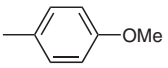
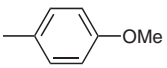
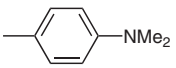
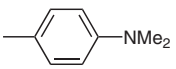
Scheme 3 Synthesis of benzo[*b*]quinolizinium-9-trifluoroborate **5**

As it has been demonstrated that organotrifluoroborates may be employed in Suzuki–Miyaura coupling reactions,[13,14] it was examined whether benzo[*b*]quinoliziniumtrifluoroborate derivatives are synthetically available and whether they may be used for palladium-mediated coupling reactions with bromoarenes. The boronic acid **1a** was reacted with KHF_2 to give the corresponding organotrifluoroborate **5** as the main product (Scheme 3). ^{1}H-, ^{13}C- and ^{19}F NMR spectroscopic data are in agreement with the proposed structure. In particular, the coupling be-



Scheme 2 Synthesis of 9-aryl-substituted benzo[*b*]quinolizinium derivatives by Suzuki–Miyaura cross-coupling (for substituent Ar, see Table 1)

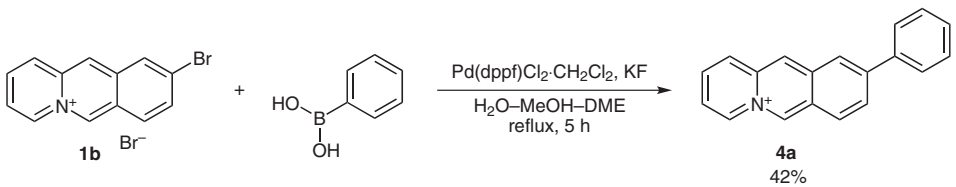
Table 1 Reaction Conditions for the Synthesis of 9-Aryl-Substituted Benzo[*b*]quinolizinium Derivatives According to Scheme 2

Entry	Catalyst	Time (h)	Product		Yield (%)[a]
1	$Pd(PPh_3)_2Cl_2$	5	**4a**	Ar = 	44[b]
2	$Pd(PPh_3)_2Cl_2$	8	**4b**	Ar = 	40[b]
3	$Pd(PPh_3)_2Cl_2$	8	**4c**	Ar = 	21[c]
4	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$	8	**4c**	Ar = 	81[c]
5	$Pd(PPh_3)_2Cl_2$	8	**4d**	Ar = 	3[c]
6	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$	8	**4d**	Ar = 	40[c]
7	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$	24	**4e**	Ar = 	42[c]
8	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$	24	**4f**	Ar = 	28[c]
9	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$	24	**4g**	Ar = 	15[c]
10	$Pd_2(dba)_3/PCy_3$	24	**4g**	Ar = 	14[c]

[a] Yields are the average of two independent experiments; dppf = 1,1′-bis(diphenylphosphino)ferrocene.
[b] Isolated and fully characterized as a tetrafluoroborate salt.
[c] Isolated and fully characterized as a perchlorate salt.

tween fluorine atoms and C-8 (J = 1 Hz), C-10 (J = 2 Hz) along with the chemical shift of the fluoro substituents (δ = –140.8 ppm) are characteristic of the aryltrifluoroborate structure. Nevertheless, the product could not be isolated as a pure sample (purity: 90–95% as determined by ^{1}H NMR spectroscopic analysis). The benzo[*b*]quinoliziniumtrifluoroborate **5** is insoluble in most organic solvents except for DMF or DMSO, presumably due to its zwitterionic nature. Attempts to employ the benzo[*b*]quinoliziniumtrifluoroborate **5** (90% purity) in cross-coupling reactions with aryl bromides in the presence of either potassium fluoride or cesium carbonate as the base were not successful either because no reaction took place (in the presence of KF) or decomposition of the substrate (in the presence of $CsCO_3$) occurred under these conditions.

For comparison, the complementary Suzuki–Miyaura reaction between the 9-bromobenzo[*b*]quinolizinium **1b** and potassium phenyltrifluoroborate was examined under established conditions, i.e., $Pd(OAc)_2/K_2CO_3$/water;[8] however, this reaction failed due to extensive decomposition of the benzo[*b*]quinolizinium substrate under these particular reaction conditions. In contrast, the reaction of 9-bromobenzo[*b*]quinolizinium **1b** with phenylboronic acid with $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ as catalyst and potassium fluoride gave the phenylbenzo[*b*]quinolizinium **1c** in 42% yield (Scheme 4). This observation shows that the synthesis of aryl-substituted benzo[*b*]quinolizinium derivatives may be accomplished by either possible Suzuki–Miyaura approach, i.e. starting with the substrates **1a** or **1b**. Thus, both methods may be used complementarily; however, it should be considered that arylboronic acid derivatives are not as easily available as the corresponding bromoarenes, i.e. the boronic acids are usually significantly more expen-

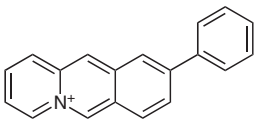
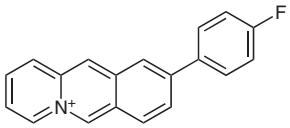
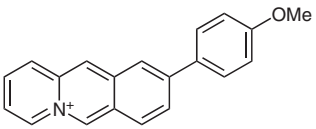
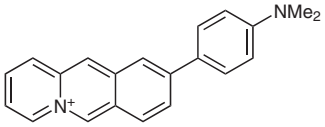
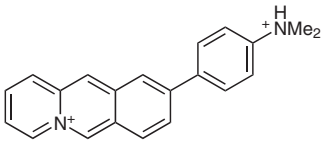
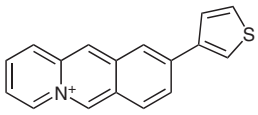
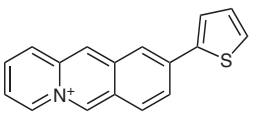
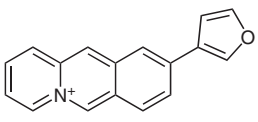


Scheme 4 Synthesis of 9-phenylbenzo[*b*]quinolizinium (**4a**) from the reaction of 9-bromobenzo[*b*]quinolizinium (**1b**) with phenylboronic acid

sive or require additional synthetic steps for their preparation.[9a] In addition, Stille coupling reactions may also offer a possible route to quinolizinium-based biaryl derivatives;[6a,b] however, Suzuki coupling reactions are more attractive from a practical viewpoint because of the low toxicity and facile removal of the boron-containing side product and reasonable yields of the coupling products.

The 9-arylbenzo[*b*]quinolizinium derivatives **4a–c** and **4e–g** exhibit absorption properties that resemble those of the benzo[*b*]quinolizinium chromophore[15] (Table 2); however, depending on the electron-donating character of the aryl substituents, red-shifts of the absorption bands are induced as compared with the parent benzo[*b*]quinolizinium (long-wavelength maximum: 399 nm in EtOH,

Table 2 Absorption and Emission Properties of Compounds **4a–g**

Compound	Solvent	λ_{abs} (nm) (log ε)[a]	λ_{fl} (nm)[b]	ϕ_{fl}
	H_2O[f]	409 (4.12)	431, 452	31[c]
	MeCN	409 (4.11)	434, 453	26[c]
	MeOH	411 (4.11)	435, 455	35[c]
	DMF	413 (4.10)	437, 458	22[c]
	CH_2Cl_2	415 (4.15)	442, 459	21[c]
4a				
	H_2O[f]	409 (4.17)	454	36[c]
	MeCN	409 (4.14)	437, 455	34[c]
	MeOH	410 (4.15)	440, 455	38[c]
	DMF	413 (4.06)	438, 458	24[c]
	CH_2Cl_2	414 (4.17)	451, 459	20[c]
4b				
	H_2O[f]	411 (4.23)	529	29[d]
	MeCN	414 (4.27)	528	44[d]
	MeOH	416 (4.29)	526	62[d]
	DMF	417 (4.26)	531	34[d]
	CH_2Cl_2	421 (4.30)	520	35[d]
4c				
	H_2O	422 (4.23)	–[e]	–[e]
	MeCN	474 (4.33)	–[e]	–[e]
	MeOH	477 (4.38)	–[e]	–[e]
	DMSO	476 (4.36)	–[e]	–[e]
	DMF	475 (4.35)	–[e]	–[e]
	CH_2Cl_2	507 (4.39)	–[e]	–[e]
4d				
	H_2O	408 (4.12)	423, 447	14[c]
4d + H^+				
	H_2O[f]	412 (4.22)	472	23[c]
	MeCN	413 (4.21)	474	26[c]
	MeOH	415 (4.26)	476	28[c]
	DMF	417 (4.24)	479	22[c]
	CH_2Cl_2	420 (4.26)	473	18[c]
4e				
	H_2O[f]	422 (4.22)	495	25[d]
	MeCN	424 (4.28)	497	28[d]
	MeOH	426 (4.30)	496	19[d]
	DMF	428 (4.27)	502	22[d]
	CH_2Cl_2	432 (4.31)	490	11[d]
4f				
	H_2O[f]	408 (4.14)	474	17[c]
	MeCN	409 (4.17)	474	25[c]
	MeOH	410 (4.16)	478	39[c]
	DMF	411 (4.20)	471	4[c]
	CH_2Cl_2	416 (4.17)	467	14[c]
4g				

[a] Long-wavelength absorption maximum (c = 50 μM).
[b] Fluorescence emission maximum (c = 10 μM); excitation wavelength λ_{ex} = 380 nm.
[c] Fluorescence quantum yield relative to Coumarin 1.
[d] Fluorescence quantum yield relative to Coumarin 153.
[e] Too low to be determined.
[f] Containing 1% MeCN.

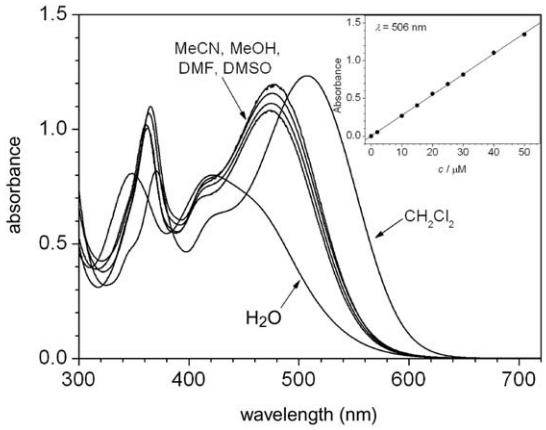


Figure 2 Absorption spectra of compound **4d** in different solvents (c = 50 μM). Inset: Plot of the absorbance of **4d** in dichloromethane at λ = 506 nm versus concentration (r^2 = 0.9996).

log ε = 3.88).[15] In particular, the strong donor–acceptor interplay in the dimethylaminophenyl-substituted benzo[*b*]quinolizinium derivative **4d** results in a pronounced red-shifted absorption maximum of this compound (477 nm in MeOH). In the case of the thienyl-substituted benzo[*b*]quinolizinium ions **4e** and **4f**, the donating effect of the electron-rich thiophene ring is more effective when it is connected with its C2 carbon atom to the benzo[*b*]quinolizinium as indicated by the larger red-shift of the absorption maximum of compound **4f** (424 nm; in MeCN) as compared with the isomer **4e** (413 nm in MeCN).[16]

Compounds **4a–c** and **4e–g** show relatively weak solvatochromism (Table 2). In contrast, the long-wavelength absorption bands of **4d** show a bathochromic and hyperchromic effect upon changing the solvent from water to polar organic solvents.[17] Notably, this effect was most pronounced in dichloromethane, in which the absorption maximum is significantly red-shifted (507 nm, Figure 2). Since the extinction coefficients and the shape of the absorption spectra of compound **4d** in dichloromethane are essentially independent of the concentration (inset of Figure 2), the bathochromic and hyperchromic effect is unlikely the result of aggregation. Similar red-shifted absorption bands have previously been reported for 9-aminobenzo[*b*]quinolizinium and 7-aminoquinolinium derivatives in dichloromethane and explained by the exceptionally high polarizability of this solvent (α = 6.52 Å^3).[2e,4b] Thus, the influence of this solvent on the delicate interplay between the vertical electronic excitation and the immediate vertical conversion to the solvent-relaxed Franck–Condon excited state of charged push-pull polyenes[18] leads to a decrease of the energy of the excited state.

The absorption and emission properties of the dimethylaminophenyl-substituted benzo[*b*]quinolizinium derivative **4d** change significantly upon protonation (Figure 3). Thus, with decreasing pH value of the solution (pH 6.1–1.7) the broad long-wavelength absorption disappeared, along with the development of a new absorption band (λ_{max} = 388 nm) that resembles that of the 9-phenylbenzo[*b*]quinolizinium **4a**, which indicates the disruption of the donor–acceptor system in **4d** by the protonation of the electron-donating amine substituent. On the other hand, the addition of acid to the weakly fluorescent benzo[*b*]quinolizinium derivative **4d** leads to a significant increase of the emission intensity by a factor of 130. This increase of the fluorescence intensity is also caused by protonation of the amino group, which leads to the suppression of the major quenching process in the excited state of compound **4d**, namely the photoinduced electron-transfer between the excited benzo[*b*]quinolizinium and the amine substituent.[2e,17,19] The data from the photometric and fluorimetric titrations were used to determine the pK_a value of the protonated amine **4d** in water (insets of Figure 3) by a numerical fit of the experimental data to the Henderson–Hasselbalch equation.[20] Based on the spectro-

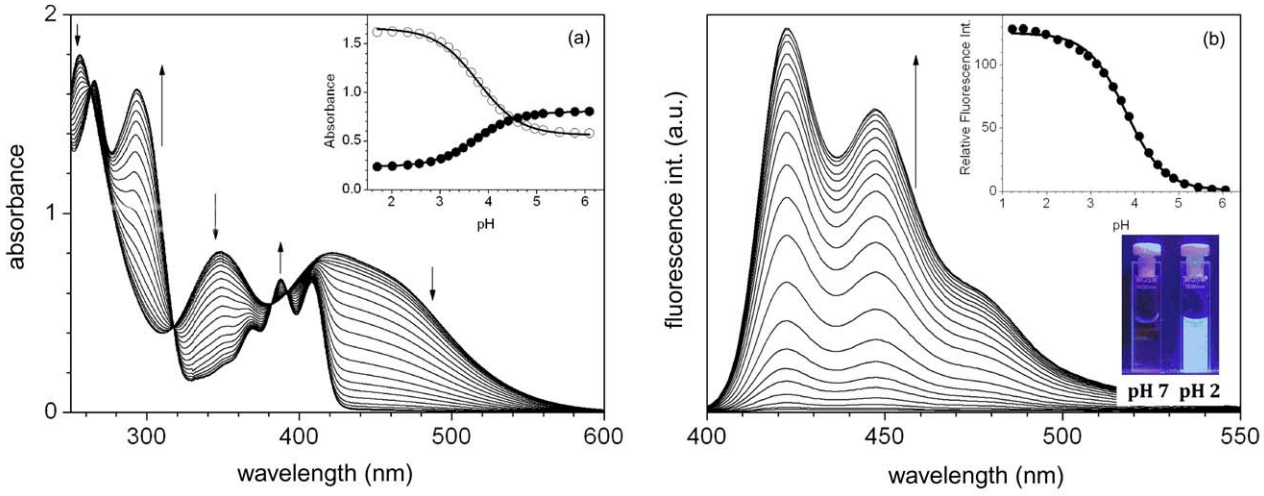


Figure 3 Influence of the pH value on the absorption (a; c = 50 μM) and emission (b; c = 10 μM, λ_{ex} = 381 nm) properties of **4d** in Britton–Robinson buffer; arrows indicate the development of emission bands upon addition of acid. Insets: spectrophotometric titration curves (a; open circles: Absorption at 293 nm; filled circles: Absorption at 350 nm) and spectrofluorimetric titration curve (b); numerical fits calculated for the value pK_a = 3.8. Inset: image showing the fluorescence of **4d** (c = 10 μM) in Britton–Robinson buffer at pH 7.0 (left) and pH 2.0 (right).

metric data, the pK_a was determined to be 3.8, i.e. it is comparable to those of 9-(*p*-amino)phenylacridinium ions (pK_a = 2.5–3.5 in water), which exhibit an increase of the fluorescence intensity upon protonation or complexation with metal cations.[17,21] Thus, compound **4d** represents a water-soluble pH-sensitive fluorescent probe,[22] whose light-up effect may be used at pH 2.8–4.8 with essentially no background fluorecence at higher pH values. It should be noted that the pK_a of **4d** and its range of performance may be modified by substitution of the phenyl ring with electron-donor or electron-acceptor substituents.

In summary, we present one of the rare examples for a successful palladium-mediated arylation of heteroaromatic cations. Specifically, the Suzuki–Miyaura reaction of the readily available benzo[*b*]quinoliziniumboronic acid **1a** may be employed to obtain 9-aryl-substituted benzo[*b*]quinolizinium derivatives. The products exhibit promising absorption and emission properties and represent a useful starting point for the design of fluorescent probes. In particular, it was demonstrated with the dimethylaminophenyl-substituted benzo[*b*]quinolizinium derivative **4d** that this method may be generally used to attach functionality to the benzo[*b*]quinolizinium fluorophore, in this case the pH-sensitive amino substituent, which allows fluorimetric detection of selected analytes. Along these lines, it may be proposed that other selective receptor units may be introduced instead of the aminomethyl substituent, thus leading to a significant fluorimetric response upon complexation of a particular guest molecule.

All commercially available chemicals were reagent grade and used without further purification. 9-Bromobenzo[*b*]quinolizinium bromide (**1b**) was prepared according to published procedures.[23] Melting points were determined with a melting point apparatus (Büchi 510K) and are uncorrected. Mass spectra (ESI in the positive-ion mode, source voltage 6 kV) were recorded with a Finnigan LCQ Deca instrument; only *m*/*z* values in the range of 100–2000 units were analyzed. NMR spectra were measured on a Bruker Avance 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) and a Varian NMR System 600 (^{1}H: 600 MHz, ^{13}C: 150 MHz, ^{19}F: 564 MHz) at 20 °C. Chemical shifts of ^{1}H- and ^{13}C NMR spectra are given in ppm (δ) relative to TMS (δ = 0.00 ppm). Chemical shifts of ^{19}F NMR spectra are given in ppm (δ) relative to a spectrometer reference based on the ^{2}H-frequency according to IUPAC rules.[24] Unambiguous proton NMR assignments were established with the help of {1H, 1H}-COSY, HSQC and HMBC experiments. All couplings given in the ^{13}C NMR spectroscopic data refer to ^{13}C–^{19}F couplings. Elemental microanalyses of all new compounds were performed with a HEKAtech EuroEA combustion analyzer by Mr. H. Bodenstedt (Organische Chemie I, Universität Siegen). TLC analyses were performed on silica gel sheets (Macherey–Nagel Polygram Sil G/UV254; eluent: $CHCl_3$–MeOH–AcOH, 90:10:1 v/v). Purified water with resistivity ≥18 MΩ cm^{-1} was used for spectrophotometric measurements. Absorption spectra were recorded on a Varian Cary 100 double-beam spectrophotometer. Emission spectra were recorded on a Varian Cary Eclipse fluorescence spectrophotometer. All spectrophotometric measurements were performed in thermostated quartz sample cells at 20 °C. The Britton–Robinson buffer solution[25] was prepared from boric acid, phosphoric acid and sodium acetate (0.04 M each) in purified water and neutralized to pH 7.0 by addition of 2 M NaOH solution. Acid–base spectrophotometric and spectrofluorimetric titrations and determination of the pK_a value of compound **4d** were performed according to published methods.[2e] All spectrophotometric measurements were performed at least three times to ensure the reproducibility. Solutions for analysis were prepared by dilution of stock solutions (1.0×10^{-3} M in MeCN or MeOH) immediately before the experiments.

2-(1,3-Dioxolan-2-yl)-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl] Pyridinium Bromide (3)

A solution of 2-(1,3-dioxolan-2-yl)pyridine (4.80 g, 31.8 mmol) and 4-(bromomethyl)benzeneboronic acid pinacol ester (9.40 g, 31.8 mmol) in DMSO (15 mL) was stirred under an argon gas atmosphere at r.t. for 7 d. The reaction mixture was poured into EtOAc (1 L) and the precipitated white solid was collected, washed thoroughly with EtOAc and Et_2O, and dried under vacuum to give the analytically pure product.

Yield: 13.5 g (95%); colorless solid; mp 163–164 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.29 (s, 12 H, CH_3), 4.11 (s, 4 H, CH_2), 6.06 (s, 2 H, CH_2), 6.48 (s, 1 H, CH), 7.33 (d, *J* = 8.0 Hz, 2 H, H-3, H-5), 7.72 (d, *J* = 8.0 Hz, 2 H, H-2, H-6), 8.20–8.27 (m, 1 H, H-5′), 8.34 (dd, *J* = 8.1, 1.3 Hz, 1 H, H-3′), 8.72–8.79 (m, 1 H, H-4′), 9.07 (dd, *J* = 6.2, 1.0 Hz, 1 H, H-6′).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.5 (CH_3), 59.8 (CH_2), 65.6 (CH_2), 83.8 (CH), 97.0 (CH), 126.0 (CH_{Ar}), 127.4 (CH_{Ar}), 128.6 (CH_{Ar}), 129.0 (C_q), 134.9 (CH_{Ar}) 136.8 (CH_{Ar}), 147.2 (CH_{Ar}), 147.3 (CH_{Ar}), 152.0 (C_q).

MS (ESI$^+$): *m*/*z* (%) = 368 (100) [M]$^+$.

Anal. Calcd for $C_{21}H_{27}BBrNO_4$: C, 56.28; H, 6.07; N, 3.13. Found: C, 56.15; H, 6.11; N, 3.13.

Benzo[*b*]quinolizinium-9-boronic Acid Bromide (1a)

The pyridinium derivative **3** (1.00 g, 2.23 mmol) was dissolved in aq HBr (48%, 10 mL) and the reaction mixture was stirred under reflux for 4.5 h. After cooling to r.t., the reaction mixture was poured into THF (500 mL) and the yellow precipitate was collected, washed with THF and EtOAc and dried to give the product (0.61 g, 91%), which was pure by ^{1}H NMR. An analytically pure sample was obtained by two-fold recrystallization from H_2O.

Yellow needles; mp 228–230 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.95–8.02 (m, 1 H, H-3), 8.13–8.05 (m, 1 H, H-2), 8.27 (d, *J* = 9.3 Hz, 1 H, H-8), 8.42 (d, *J* = 8.8 Hz, 1 H, H-7), 8.61 (d, *J* = 8.6 Hz, 1 H, H-1), 8.76 (br s, 3 H, H-10, 2 × OH), 9.28 (s, 1 H, H-11), 9.31 (d, *J* = 6.8 Hz, 1 H, H-4), 10.45 (s, 1 H, H-6).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 122.4 (CH_{Ar}), 125.1 (CH_{Ar}), 126.2 (C_q), 126.2 (CH_{Ar}), 126.9 (CH_{Ar}), 130.8 (CH_{Ar}), 133.5 (CH_{Ar}), 134.0 (CH_{Ar}), 134.5 (C_q), 134.6 (CH_{Ar}), 137.4 (C_q), 139.6 (CH_{Ar}), 141.7 (C_q).

MS (ESI$^+$): *m*/*z* (%) = 224 (100) [M]$^+$.

Anal. Calcd for $C_{13}H_{11}BBrNO_2 \cdot H_2O$: C, 48.50; H, 4.07; N, 4.35. Found: C, 48.71; H, 3.91; N, 4.45.

Suzuki Coupling of Benzo[*b*]quinolizinium-9-boronic Acid Bromide (1a) and Aryl Bromides; General Procedure

Under an inert gas atmosphere, a solution of benzo[*b*]quinoliziniumboronic acid (**1a**; 303 mg, 1.00 mmol), the corresponding aryl or heteroaryl bromide (1.50 mmol), $Pd(PPh_3)_2Cl_2$ (21 mg, 0.03 mmol) or $Pd(dppf)Cl_2 \times CH_2Cl_2$ (40.8 mg, 0.05 mmol) and KF (232 mg, 4.00 mmol) in DME–MeOH–H_2O (2:1:1; 12 mL) was stirred under reflux for 5–24 h (reaction monitored by TLC). After cooling to r.t., MeOH (10 mL) was added to the reaction mixture. The precipitated palladium-black was removed by filtration and sat. aq $NaBF_4$ or $NaClO_4$ (5 mL) was added to the filtrate until no more precipitation

was observed. The yellow precipitate was collected, washed with H_2O, EtOAc, and Et_2O. The analytically pure product was separated by recrystallization of the precipitate from MeCN–EtOAc or by column chromatography (Al_2O_3, Activity I; MeCN) and subsequent recrystallization from MeCN–EtOAc.

9-Phenylbenzo[*b*]quinolizinium Tetrafluoroborate (4a)
Catalyst: $Pd(PPh_3)_2Cl_2$.

Yield: 152 mg (44%); yellow prisms; mp 203–204 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.57 (t, *J* = 7.2 Hz, 1 H, H-4′), 7.64 (dd, *J* = 7.9, 7.6 Hz, 2 H, H-3′, H-5′), 7.93–7.97 (m, 1 H, H-3), 8.02 (d, *J* = 7.3 Hz, 2 H, H-2′, H-6′), 8.08 (dd, *J* = 9.0, 7.2 Hz, 1 H, H-2), 8.40 (dd, *J* = 9.0, 1.5 Hz, 1 H, H-8), 8.58 (d, *J* = 9.2 Hz, 1 H, H-7), 8.60 (d, *J* = 9.5 Hz, 1 H, H-1), 8.71 (s, 1 H, H-10), 9.20 (s, 1 H, H-11), 9.27 (d, *J* = 7.0 Hz, 1 H, H-4), 10.42 (s, 1 H, H-6).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 122.2 (CH_{Ar}), 123.6 (CH_{Ar}), 124.6 (CH_{Ar}), 125.0 (C_q), 126.8 (CH_{Ar}), 127.7 (CH_{Ar}), 129.0 (CH_{Ar}), 129.5 (CH_{Ar}), 129.7 (CH_{Ar}), 130.5 (CH_{Ar}), 131.1 (CH_{Ar}), 134.4 (CH_{Ar}), 135.8 (C_q), 137.8 (C_q), 137.8 (C_q), 140.0 (CH_{Ar}), 145.3 (C_q).

MS (ESI$^+$): *m*/*z* (%) = 256 (100) $[M]^+$.

Anal. Calcd for $C_{19}H_{14}BF_4N{\cdot}0.5H_2O$: C, 64.81; H, 4.29; N, 3.98. Found: C, 64.47; H, 4.22; N, 3.79.

9-(*p*-Fluorophenyl)benzo[*b*]quinolizinium Tetrafluoroborate (4b)
Catalyst: $Pd(PPh_3)_2Cl_2$.

Yield: 143 mg (40%); yellow prisms; mp 235–237 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.44–7.51 (m, 2 H, H-2′, H-6′), 7.92–9.97 (m, 1 H, H-3), 8.05–8.10 (m, 3 H, H-2, H-3′, H-5′), 8.38 (dd, *J* = 9.1, 1.7 Hz, 1 H, H-8), 8.57 (d, *J* = 8.9 Hz, 1 H, H-7), 8.60 (d, *J* = 8.8 Hz, 1 H, H-1), 8.68 (s, 1 H, H-10), 9.17 (s, 1 H, H-11), 9.26 (d, *J* = 6.8 Hz, 1 H, H-4), 10.40 (s, 1 H, H-6).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 116.3 (d, *J* = 22 Hz, CH_{Ar}), 122.1 (CH_{Ar}), 123.4 (d, *J* = 1 Hz, CH_{Ar}), 124.5 (CH_{Ar}), 124.8 (C_q), 126.7 (CH_{Ar}), 128.9 (CH_{Ar}), 129.9 (d, *J* = 8 Hz, CH_{Ar}), 130.2 (CH_{Ar}), 131.1 (CH_{Ar}), 134.1 (d, *J* = 3 Hz, C_q), 134.3 (CH_{Ar}), 135.6 (C_q), 137.7 (C_q), 139.8 (CH_{Ar}), 144.0 (C_q), 163.0 (d, *J* = 248 Hz, C_q).

MS (ESI$^+$): *m*/*z* = 274 (100) $[M]^+$.

Anal. Calcd for $C_{19}H_{13}BF_5N$: C, 63.19; H, 3.63; N, 3.88. Found: C, 62.79; H, 3.30; N, 3.89.

9-(*p*-Methoxyphenyl)benzo[*b*]quinolizinium Perchlorate (4c)
Catalyst: $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$.

Yield: 312 mg (81%); yellow prisms; mp 218–220 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 3.88 (s, 3 H, CH_3), 7.16–7.22 (m, 2 H, H-2′, H-6′), 7.88–7.94 (m, 1 H, H-3), 7.98–8.08 (m, 3 H, H-2, H-3′, H-5′), 8.40 (dd, *J* = 9.0, 1.6 Hz, 1 H, H-8), 8.53 (d, *J* = 9.3 Hz, 1 H, H-7), 8.56 (d, *J* = 8.8 Hz, 1 H, H-1), 8.64 (s, 1 H, H-10), 9.12 (s, 1 H, H-11), 9.23 (d, *J* = 6.9 Hz, 1 H, H-4), 10.36 (s, 1 H, H-6).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 55.4 (CH_3), 114.9 (CH_{Ar}), 121.9 (CH_{Ar}), 122.0 (CH_{Ar}), 124.1 (CH_{Ar}), 124.8 (C_q), 126.7 (CH_{Ar}), 128.8 (CH_{Ar}), 129.1 (CH_{Ar}), 129.7 (C_q), 130.2 (CH_{Ar}), 131.0 (CH_{Ar}), 134.3 (CH_{Ar}), 136.0 (C_q), 137.7 (C_q), 139.7 (CH_{Ar}), 144.9 (C_q), 160.7 (C_q).

MS (ESI$^+$): *m*/*z* = 286 (100) $[M]^+$.

Anal. Calcd for $C_{20}H_{16}ClNO_5$: C, 62.26; H, 4.18; N, 3.63. Found: C, 62.50; H, 3.86; N, 3.68.

9-(*p*-*N*,*N*-Dimethylaminophenyl)benzo[*b*]quinolizinium Perchlorate (4d)
Catalyst: $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$.

Yield: 160 mg (40%); dark-red powder; mp >300 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 3.04 (s, 6 H, CH_3), 6.89 (d, *J* = 8.9 Hz, 2 H, H-2′, H-6′), 7.80–7.86 (m, 1 H, H-3), 7.91 (d, *J* = 9.3 Hz, 2 H, H-3′, H-5′), 7.95–8.02 (m, 1 H, H-2), 8.35–8.50 (m, 3 H, H-1, H-7, H-8), 8.51 (s, 1 H, H-10), 8.99 (s, 1 H, H-11), 9.14 (d, *J* = 6.9 Hz, 1 H, H-4), 10.24 (s, 1 H, H-6).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 39.5 (CH_3), 112.2 (CH_{Ar}), 119.4 (CH_{Ar}), 121.1 (CH_{Ar}), 123.0 (CH_{Ar}), 123.4 (C_q), 124.2 (C_q), 126.3 (CH_{Ar}), 128.2 (CH_{Ar}), 128.3 (CH_{Ar}), 129.5 (CH_{Ar}), 130.4 (CH_{Ar}), 133.8 (CH_{Ar}), 136.0 (C_q), 137.4 (C_q), 139.0 (CH_{Ar}), 145.1 (C_q), 151.0 (C_q).

MS (ESI$^+$): *m*/*z* = 299 (100) $[M]^+$.

Anal. Calcd for $C_{21}H_{19}ClN_2O_4$: C, 63.24; H, 4.80; N, 7.02. Found: C, 62.94; H, 4.72; N, 7.07.

9-(3-Thienyl)benzo[*b*]quinolizinium Perchlorate (4e)
Catalyst: $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$.

Yield: 152 mg (42%); yellow needles; mp 238–240 °C (dec.).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.82 (dd, *J* = 5.2, 2.9 Hz, 1 H, H-4′), 7.88–7.93 (m, 2 H, H-3, H-5′), 8.02–8.07 (m, 1 H, H-2), 8.41–8.45 (m, 2 H, H-8, H-2′), 8.49 (d, *J* = 9.0 Hz, 1 H, H-7), 8.55 (d, *J* = 8.7 Hz, 1 H, H-1), 8.66 (s, 1 H, H-10), 9.06 (s, 1 H, H-11), 9.22 (d, *J* = 6.9 Hz, 1 H, H-4), 10.31 (s, 1 H, H-6).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 121.9 (CH_{Ar}), 122.0 (CH_{Ar}), 124.0 (CH_{Ar}), 124.9 (C_q), 126.3 (CH_{Ar}), 126.3 (CH_{Ar}), 126.7 (CH_{Ar}), 128.5 (CH_{Ar}), 128.8 (CH_{Ar}), 130.1 (CH_{Ar}), 131.1 (CH_{Ar}), 134.3 (CH_{Ar}), 136.1 (C_q), 137.8 (C_q), 139.3 (CH_{Ar}), 139.6 (C_q), 139.9 (C_q).

MS (ESI$^+$): *m*/*z* = 262 (100) $[M]^+$.

Anal. Calcd for $C_{17}H_{12}ClNO_4S$: C, 56.44; H, 3.34; N, 3.87; S, 8.86. Found: C, 56.45; H, 3.29; N, 4.09; S, 8.59.

9-(2-Thienyl)benzo[*b*]quinolizinium Perchlorate (4f)
Catalyst: $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$.

Yield: 100 mg (28%); yellow prisms; mp 214–216 °C (dec.).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.32 (dd, *J* = 4.9, 3.7 Hz, 1 H, H-4′), 7.88 (dd, *J* = 5.0, 0.9 Hz, 1 H, H-3′), 7.89–7.92 (m, 1 H, H-3), 8.01 (dd, *J* = 3.5, 0.9 Hz, 1 H, H-5′), 8.04 (dd, *J* = 9.0, 7.4 Hz, 1 H, H-2), 8.36 (dd, *J* = 8.9, 1.6 Hz, 1 H, H-8), 8.46–8.52 (m, 2 H, H-1, H-7), 8.55 (s, 1 H, H-10), 9.10 (s, 1 H, H-11), 9.20 (d, *J* = 7.0 Hz, 1 H, H-4), 10.30 (s, 1 H, H-6).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 120.7 (CH_{Ar}), 122.0 (CH_{Ar}), 124.0 (CH_{Ar}), 124.8 (C_q), 126.7 (CH_{Ar}), 128.2 (CH_{Ar}), 129.0 (CH_{Ar}), 129.1 (CH_{Ar}), 129.4 (CH_{Ar}), 130.1 (CH_{Ar}), 131.3 (CH_{Ar}), 134.3 (CH_{Ar}), 135.9 (C_q), 137.9 (C_q), 138.7 (C_q), 139.6 (CH_{Ar}), 141.1 (C_q).

MS (ESI$^+$): *m*/*z* = 262 (100) $[M]^+$.

Anal. Calcd for $C_{17}H_{12}ClNO_4S$: C, 56.44; H, 3.34; N, 3.87; S, 8.86. Found: C, 56.38; H, 3.28; N, 3.83; S, 8.59.

9-(3-Furyl)benzo[*b*]quinolizinium Perchlorate (4g)
Catalyst: $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$.

Yield: 50 mg (15%); yellow powder; mp 234–236 °C (dec.).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.29–7.34 (m, 1 H, H-4′), 7.88–7.93 (m, 1 H, H-3), 7.93–7.96 (m, 1 H, H-5′), 8.05 (dd, *J* = 8.5, 7.0 Hz, 1 H, H-2), 8.32 (dd, *J* = 9.0, 1.2 Hz, 1 H, H-8), 8.49 (d, *J* = 8.9 Hz, 1 H, H-7), 8.56 (s, 1 H, H-2′), 8.57 (d, *J* = 9.0 Hz, 1 H,

H-1), 8.69 (s, 1 H, H-10), 9.04 (s, 1 H, H-11), 9.23 (d, *J* = 7.0 Hz, 1 H, H-4), 10.30 (s, 1 H, H-6).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 108.5 (CH_{Ar}), 121.1 (CH_{Ar}), 122.0 (CH_{Ar}), 123.7 (CH_{Ar}), 124.8 (C_q), 124.9 (C_q), 126.7 (CH_{Ar}), 128.7 (CH_{Ar}), 129.6 (CH_{Ar}), 131.2 (CH_{Ar}), 134.3 (CH_{Ar}), 136.1 (C_q), 137.8 (C_q), 137.9 (C_q), 139.6 (CH_{Ar}), 143.3 (CH_{Ar}), 145.6 (CH_{Ar}).

MS (ESI$^+$): *m*/*z* = 246 (100) [M]$^+$.

Anal. Calcd for $C_{17}H_{12}ClNO_5$: C, 59.06; H, 3.50; N, 4.05. Found: C, 58.52; H, 3.42; N, 3.95.

9-Phenylbenzo[*b*]quinolizinium Tetrafluoroborate (4a) from 9-Bromobenzo[*b*]quinolizinium Bromide (1b)

Under an inert gas atmosphere, a solution of **1b** (303 mg, 1.00 mmol), phenyl boronic acid (122 mg, 1.00 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (24.5 mg, 0.03 mmol) and KF (232 mg, 4.00 mmol) in DME–MeOH–H_2O (2:1:1; 12 mL) was stirred under reflux for 5 h (reaction monitored by TLC). After cooling to r.t., MeOH (10 mL) was added to the reaction mixture and the precipitated palladium-black was removed by filtration. Sat. aq $NaBF_4$ (5 mL) was added to the filtrate until no more precipitation was observed. The yellow precipitate was collected and washed with H_2O, EtOAc, and Et_2O. The analytically pure product was separated by recrystallization of the precipitate from MeCN–EtOAc (145 mg, 42%). The spectroscopic data and melting point are identical with those of the product from the Pd-catalyzed reaction of benzo[*b*]quinolizinium-9-boronic acid bromide (**1a**) and bromobenzene (see above).

Benzo[*b*]quinolizinium-9-trifluoroborate (5)

Under an inert gas atmosphere, a solution of benzo[*b*]quinolizinium-9-boronic acid (**1a**; 303 mg, 1.00 mmol) and KHF_2 (234 mg, 3.00 mmol) in MeOH (5 mL) was stirred at 0 °C. H_2O (5 mL) was added dropwise to the solution at 0 °C, and the reaction mixture was stirred at r.t. for 2 h. The solvent was evaporated in vacuo and the resulting solid was collected and washed thoroughly with H_2O and MeOH, and dried to give the crude product with 90–95% purity (determined by ^{1}H NMR spectroscopic analysis) as pale-yellow solid (233 mg, 85%). The crude product was used for the coupling reaction without further purification.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.78–7.86 (m, 1 H, H-3), 7.90–7.98 (m, 1 H, H-2), 8.04 (d, *J* = 8.5 Hz, 1 H, H-8), 8.19–8.27 (m, 2 H, H-7, H-10), 8.44 (d, *J* = 8.8 Hz, 1 H, H-1), 9.05 (s, 1 H, H-11), 9.16 (d, *J* = 7.0 Hz, 1 H, H-4), 10.27 (s, 1 H, H-6).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 121.2 (CH_{Ar}), 123.3 (CH_{Ar}), 125.1 (CH_{Ar}), 125.4 (C_q), 126.6 (CH_{Ar}), 127.7 (q, *J* = 2 Hz, CH_{Ar}), 129.7 (CH_{Ar}), 133.7 (CH_{Ar}), 135.4 (C_q), 136.1 (q, *J* = 1 Hz, CH_{Ar}), 136.9 (C_q), 139.2 (CH_{Ar}).

^{19}F NMR (564 MHz, DMSO-d_6): δ = –140.8.

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