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AN EFFICIENT DOMINO SONOGASHIRA/DOUBLE CARBOPALLADATION/C–H-ACTIVATION REACTION LEADING TO FLUORESCENT POLYCYCLIC AROMATIC HYDROCARBONS

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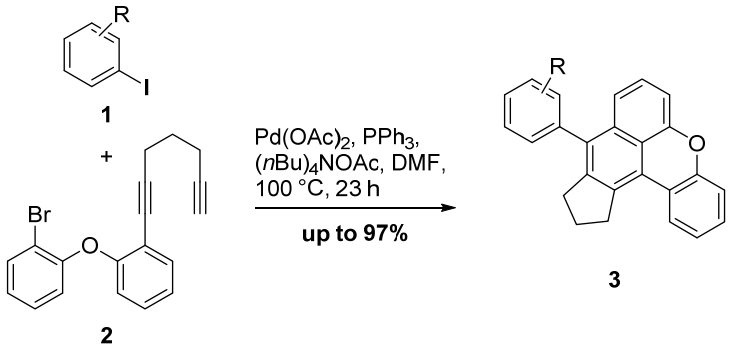
Abstract – A facile synthesis of fluorescent polycyclic aromatic hydrocarbons through a highly productive palladium-catalyzed fourfold domino Sonogashira/double carbopalladation/C–H-activation process was developed.

Dedicated to Professor Isao Kuwajima on the occasion of his birthday

INTRODUCTION

Domino reactions allow the transformation of simple organic building blocks into complex functional structures within few steps.[1] Beside this compelling characteristic of efficiency the concept is also reassuring due to its economic and environmental sustainability, since two or more reactions are included in one process without the need of any intermediate purification. Moreover, domino reactions can proceed via unstable intermediates, which is usually not possible in a step-wise approach. In addition to the development of domino Knoevenagel/hetero-Diels-Alder reactions,[2] domino imine formation/hydride shift/alkylation reactions,[3] domino amidation/spirocyclization/electrophilic aromatic substitution reactions[4] and domino acetalization/allylation reactions,[5] in the last years we have focused especially on palladium-catalyzed domino processes.[6] In this aspect, it was one of our goals to include C–H-activation reactions[7] in domino processes for the synthesis of natural products and functional materials. C–H activation reactions that are part of palladium-catalyzed domino processes have persuading advantages compared to typically used transition-metal catalyzed cross-coupling reactions, as no functionalization of the precursors is necessary.

Quite recently, we have developed a domino Sonogashira/carbopalladation/C–H-activation reaction for the synthesis of tetra-substituted helical alkenes as potential switches[8] and domino Sonogashira/double carbopalladation/C–H-activation reactions for the preparation of condensed aromatic systems.[9] Herein we report even more productive domino Sonogashira/double carbopalladation/C–H activation reactions that convert aryl iodides **1** and dialkyne **2** into polycyclic aromatic hydrocarbons **3** in up to 97% yield (Scheme 1).

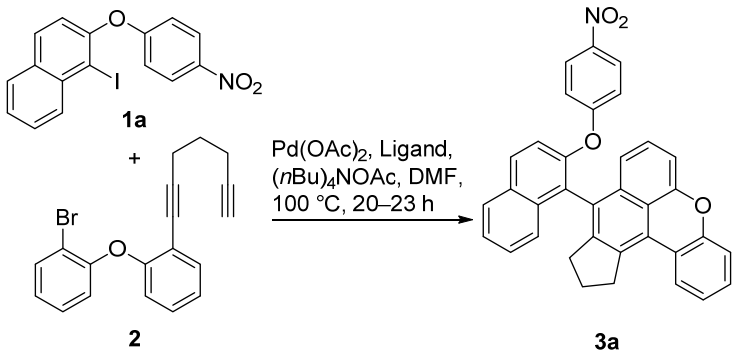


Scheme 1. Domino Sonogashira/double carbopalladation/C–H-activation reactions

RESULTS AND DISCUSSION

For the optimization of the reaction conditions, we investigated the domino reaction of **1a** and **2** as coupling partners in the presence of a combination of $Pd(OAc)_2$ and PPh_3 in a ratio of 1:5 as catalytic system and $(n\text{Bu})_4\text{NOAc}$ as base in DMF at 100 °C. A catalyst loading of 10 mol% $Pd(OAc)_2$ furnished the domino product **3a** in 81% yield as the best result for this system (Table 1, Entry 1). Reduction of the catalyst loading to 5 mol% of $Pd(OAc)_2$ led to **3a** in 67% yield while 1 mol% of $Pd(OAc)_2$ furnished **3a** in 66% yield (Entries 2 and 3). Moreover, a higher catalyst loading of 20 mol% of $Pd(OAc)_2$ was also not advantageous, since the yield of the domino reaction dropped to 60% (Entry 4). In order to further optimize the reaction conditions, we tested several ligands with a 20 mol% loading of $Pd(OAc)_2$. Electron rich PCy_3 led to **3a** in 53% yield (Entry 5), while the electron rich and bulky SPhos ligand as well as the ionic species $[P\textit{t}Bu_4][BF_4]$ gave 49% yield (Entries 6 and 7). The use of bidentate dppe furnished **3a** in only 16% (Entry 8). Thus, PPh_3 showed the best results and was used in the further investigations employing different substrates.

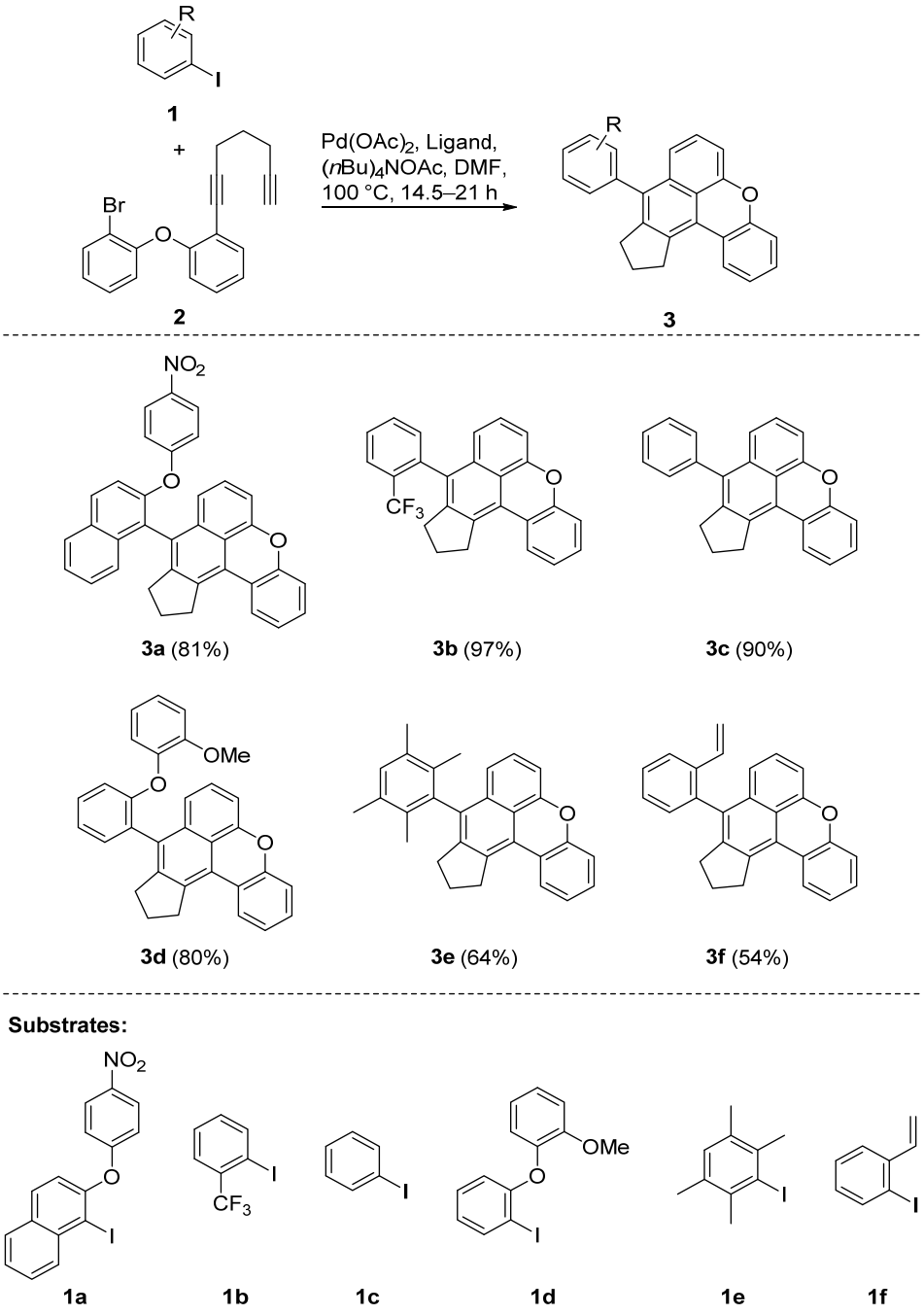
Table 1. Optimization of the reaction conditions[a]



Entry	$Pd(OAc)_2$ (mol%)	Ligand	Ligand (mol%)	Yield [%][b]
1	10	PPh_3	50	81
2	5	PPh_3	25	67
3	1	PPh_3	5	66
4	20	PPh_3	100	60
5	20	PCy_3	100	53
6	20	SPhos	100	49
7	20	$[PtBu_4][BF_4]$	100	49
8	20	dppe	50	16

[a] **1a** (1.00 equiv.), **2** (1.05 equiv.), $Pd(OAc)_2$, ligand, $(nBu)_4NOAc$ (6.00 equiv.), DMF, 100 °C, 20–23 h; [b] isolated yields following flash column chromatography.

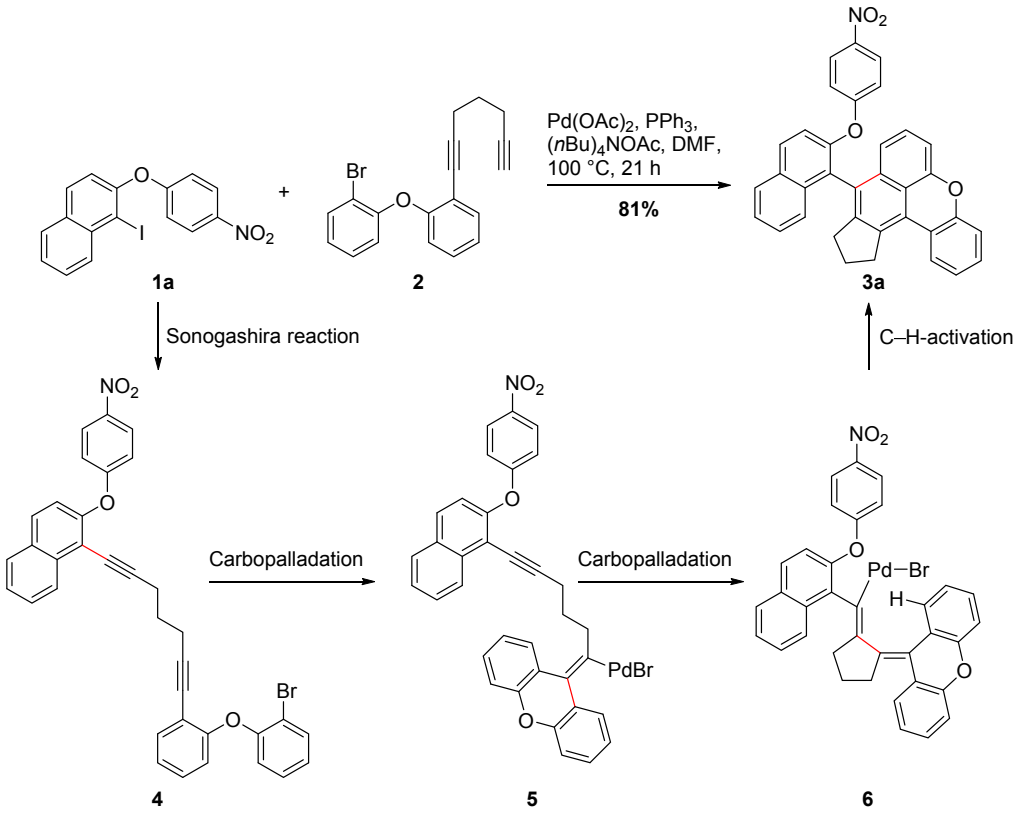
In the following, we extended the scope of the fourfold domino reaction using differently substituted substrates **1b-f**. The corresponding polycyclic aromatic hydrocarbons **3b-f** were obtained highly selectively and in good to excellent yield ranging from 54 – 97% (Scheme 2). Moreover, the results show that functional groups having electron-accepting and electron-donating properties are tolerated. Thus, the already mentioned naphthyl iodide **1a** containing a 4-nitro-phenoxy group in the *ortho* position gave **3a** in 81% yield and the 2-trifluorophenyl iodide **1b** led to **3b** in 97% yield. Excellent yields of 90% and 80%, respectively, were also obtained with the electron neutral **1c** and the phenyl iodide **1d** containing a 2-methoxyphenoxy group in the *ortho* position. Interesting examples are the phenyl iodides **1e** and **1f**. Compound **1e** containing four methyl groups is sterically highly hindered and in **1f** there is a competing vinyl group which might undergo an intermolecular Mizoroki-Heck reaction after the primary oxidative addition. However, the Sonogashira reaction of **1f** with **2** seems to be much faster than the also possible Mizoroki-Heck reaction. Anyhow, in both cases the yields with 64% and 54% were slightly lower.



Scheme 2. Domino Sonogashira/double carbopalladation/C–H activation process of **1a**-**f** and **2**

The domino Sonogashira/double carbopalladation/C–H activation process as described for the reaction of aryl iodide **1a** and dialkyne **2** starts with a Sonogashira reaction that couples **1a** with **2** to form intermediate **4** (Scheme 3). After an oxidative addition at the C–Br bond in **4**, a first carbopalladation takes place at one of the two triple bonds in **4** to provide vinyl-palladium species **5** which contains a newly generated six-membered heterocycle. The vinyl-palladium species then undergoes a carbopalladation at the second triple bond furnishing dialkene **6** containing another vinyl-palladium

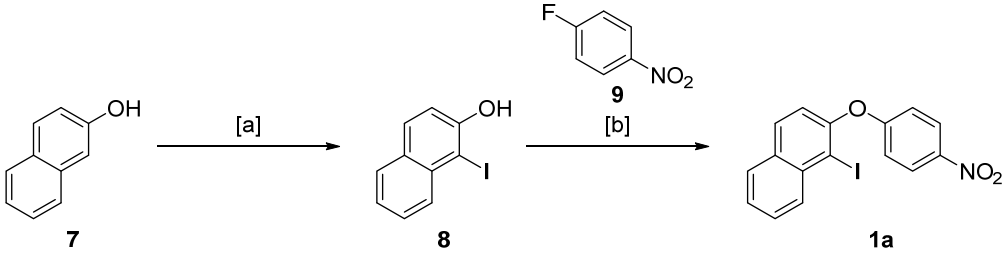
species and a five-membered ring which is built up during the carbopalladation process. Finally, a C–H-activation reaction transforms **6** into the desired polycyclic aromatic hydrocarbon **3a** whereupon the two newly formed double bonds become part of the aromatic naphthalene system in **3a**. This fact might act as a driving force and could explain the smooth and high yielding course of the domino process.



Scheme 3. Postulated mechanism of the domino Sonogashira/double carbopalladation/C–H activation reaction. The ligands at the Pd-atom are omitted for clarity.

The syntheses of the substrates **1** and **2** for the domino reactions either followed literature known protocols[8–11] or the necessary compounds were commercially available as **1b, c** and **e**.

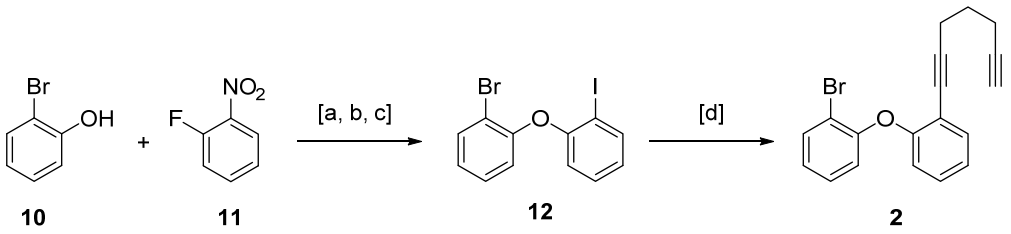
Building block **1a** was prepared through an iodination of naphthol **7** and a subsequent nucleophilic aromatic substitution coupling naphthol **8** with 4-fluoronitrobenzene **9** to give **1a** in 78% yield (Scheme 4).



Scheme 4. Synthesis of **1a**

Reaction conditions: [a] KI, H_2O_2, H_2SO_4, MeOH, 0 °C, 1 h, 72%; [b] **9**, K_2CO_3, DMSO, 95 °C, 24 h, 78%.

The sequence leading to building block **2** started with a nucleophilic aromatic substitution of phenol **10** and 2-fluoronitrobenzene (**11**), which was followed by a reduction of the nitro group and a Sandmeyer reaction to give the aryl iodide **12**. Then, compound **12** was converted into the dialkyne **2** through a Sonogashira reaction using 1,6-heptadiyne as coupling partner (Scheme 5).



Scheme 5. Synthesis of **2**

Reaction conditions: [a] K_2CO_3, DMSO, 95 °C, 23 h, quant.; [b] Zn, conc. HCl, conc. AcOH, EtOAc, 0 °C → rt, 15 min, 86%; [c] *p*TsOH·H_2O, KI, $NaNO_2$, MeCN, H_2O, rt, 30 min, 87%; [d] 1,6-heptadiyne, $PdCl_2(PPh_3)_2$, CuI, NEt_3, rt, 17 h, 72%.

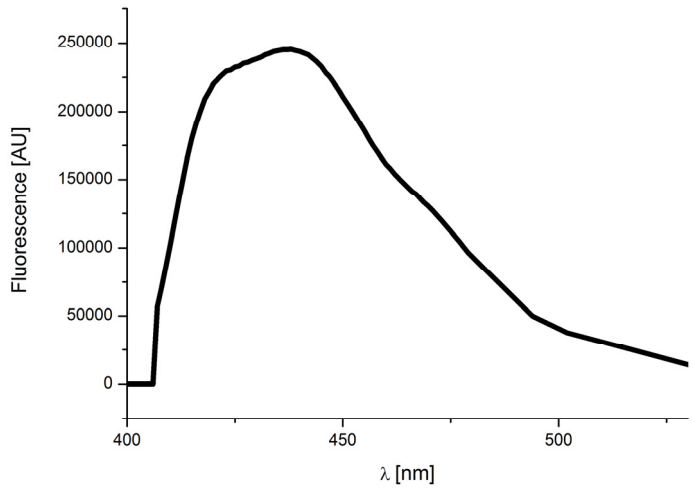


Figure 1. Fluorescence spectrum of **3c** in acetonitrile

Compounds **3b-f** exhibit an interesting fluorescence activity and we investigated molecule **3c** exemplarily by fluorescence spectrometry (Figure 1).[12] Irradiation at a wavelength of 352 nm caused an emission of blue light with a maximum at a wavelength of 436 nm. The fluorescence properties of **3b-f** could be useful for the application of compounds of type **3** as fluorescence dyes or chemical sensors.

In conclusion, we have developed a fourfold domino process with a C–H-activation reaction as the final step to transform simple precursors highly efficiently into polycyclic aromatic hydrocarbons with pronounced fluorescence activity.

EXPERIMENTAL

General method for the domino reaction:

9-[2-(4-Nitrophenoxy)naphthalene-1-yl]-11,12-dihydro-10*H*-indeno[6,5,4-*kl*]xanthene (3a):

A mixture of **1a** (73.6 mg, 189 µmol, 1.00 equiv.), **2** (67.1 mg, 198 µmol, 1.05 equiv.), $Pd(OAc)_2$ (4.22 mg, 18.8 µmol, 0.10 equiv.), PPh_3 (24.7 mg, 94.0 µmol, 0.50 equiv.) and $(n\text{Bu})_4\text{NOAc}$ (341 mg, 1.13 mmol, 6.00 equiv.) in degassed DMF (5 mL) was stirred at 100 °C for 21 h. The reaction mixture was filtered through SiO_2, flushed with EtOAc and the solvent of the filtrate was removed *in vacuo*. Column chromatography (SiO_2, *n*-pentane/EtOAc 20:1) yielded **3a** as a yellow solid (79.9 mg, 153 µmol, 81%).

R_f = 0.40 (*n*-pentane/EtOAc, 20:1); UV/Vis (MeCN) nm (lg ε) = 193 (4.9352), 223 (4.3783), 256 (3.8842), 286 (3.6870), 350 (3.4956), 367 (3.4858); IR (ATR) cm^{-1} = 1580, 1509, 1485, 1463, 1442, 1338, 1307, 1279, 1240, 1166, 1128, 1110, 1066, 1045, 1028, 1012, 958, 860, 852, 836, 821, 808, 768, 761, 750, 734, 703, 688, 667, 645, 629, 618, 530, 522, 514; ^{1}H-NMR (600 MHz, C_6D_6) δ: 1.58–1.70 (m, 2H, 6''-H_2), 2.33 (ddd, *J* = 16.2 and 8.4 and 6.2 Hz, 1H), 2.50 (dt, *J* = 15.9 and 7.9 Hz, 1H), 2.87 (dt, *J* = 15.6 and 7.5 Hz, 1H, 5''-H_a), 2.94 (ddd, *J* = 15.8 and 8.2 and 5.9 Hz, 1H, 5''-H_b), 6.37 (d, *J* = 9.2 Hz, 2H, 2'-H, 6'-H), 6.77 (dd, *J* = 7.9 and 1.6 Hz, 1H, 10''-H), 6.84–6.92 (m, 3H, 3''-H, 8''-H, 9''-H), 6.97 (ddd, *J* = 8.3 and 7.3 and 1.4 Hz, 1H, 2''-H), 7.03–7.09 (m, 2H, 3-H, 1''-H), 7.14 (m_C, 1H, 7-H), 7.26 (ddd, *J* = 8.1 and 6.8 and 1.2 Hz, 1H, 6-H), 7.43 (dd, *J* = 8.5 and 1.1 Hz, 1H, 8-H), 7.59 (d, *J* = 9.2 Hz, 2H, 3'-H, 5'-H), 7.67 (d, *J* = 8.9 Hz, 1H, 4-H), 7.71 (d, *J* = 8.4 Hz, 1H, 4''-H), 7.73 (d, *J* = 8.4 Hz, 1H, 5-H); ^{13}C-NMR (126 MHz, C_6D_6) δ: 25.5 (C-6''), 32.2 (C-7''), 35.3 (C-5''), 108.1 (C-8''), 117.0 (C-2', C-6'), 117.2 (C-1''), 118.2 (C-10''), 120.7 (C-3), 122.4, 122.6 (C-4''a), 123.1 (C-3''), 123.3 (C-4''b), 125.5 (C-3', C-5'), 125.7, 126.1 (C-6, C-8), 127.0, 127.1, 127.6 (C-7, C-4'', C-9''), 127.9 (C-1), 128.3, 128.6 (C-5), 129.6 (C-2''), 130.2 (C-4), 132.0 (C-4a), 133.9 (C-8a, C-4''c/C-7''a), 134.1 (C-7''d), 143.0 (C-1'), 146.4 (C-4''c/C-7''a), 150.2 (C-2), 151.7 (C-10a), 153.4 (C-10''b), 162.7 (C-1'') (*Further signals could not be assigned*); MS (ESI): 544.2 (41) ($M+Na^+$); HRMS (ESI): calcd for $C_{35}H_{23}NO_4+Na^+$: 544.1519. Found: 544.1505.

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12. Fluorescence spectrum: The spectrum was recorded on a fluorimeter FP 6500 by *JASCO*. Light source: 150 W, Xe lamp; photometric system: monochromatic light; monochromator: signal-to-noise ratio (Raman-band of water, 350 nm excitation wavelength, 2 sec response time, 5 nm bandwidth) of 200:1 (excitation and emission monochromator), measuring wavelength range: zero order, 220–750 nm; resolution: 1 nm (excitation and emission), wavelength accuracy: +/- 1.5 nm (excitation and emission); wavelength reproducibility: +/- 0.3 nm (excitation and emission); detector: photomultiplier tube (excitation and emission).