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A straightforward and versatile $FeCl_3$ catalyzed Friedel-Crafts *C*-glycosylation process. Application to the synthesis of new functionalized *C*-nucleosides

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ABSTRACT

A new, straightforward and eco-compatible route to *C*-(hetero)aryl nucleosides is reported. This ribosylation process consists of a one-step $FeCl_3$ catalyzed Friedel-Crafts β-*C*-glycosydation reaction. This reaction occurs trough an oxonium intermediate from readily available protected sugars leading to functionalized *C*-nucleosides with high stereocontrol. The expected new *C*-nucleosides were obtained in good yields within a short reaction time (10 min). Moreover, this approach is compatible with the use of a range of bulky (poly)aromatics such as naphthalene, anthracene and pyrene, which are not easily accessible via classical routes. These new *C*-aryl-nucleosides exhibit interesting photophysical properties, underling their potential use for further nucleic acids labelling.

Synthetic nucleosides are extensively used in medicinal chemistry and drug discovery programs due to their ability to mimic their natural counterparts. However, *C*-nucleosides may be considered as better pharmacophores than *N*-nucleosides, since their carbon-carbon glycosidic bond confers to these molecules greater stability and resistance towards chemical and enzymatic hydrolysis.[1] Thereby, in the last decades, several *C*-nucleosides have emerged as therapeutic agents, including antiviral (e.g. BCX-4430),[2] antibiotic (e.g. pyrazomicin, showdomycin),[3] anti-protozoan (e.g. formycin)[4] and anticancer drugs (e.g. tiazofurin).[5] In addition, their use as building blocks for the synthesis of DNA- and RNA-containing artificial nucleobases allowed the emergence of new therapeutic solutions through the regulation of genes expression.[6]

Moreover, artificial *C*-nucleosides have also been used in the design of biochemical and biophysical probes for RNA and DNA labelling.[7,8] Such tools have recently been used as nucleases chemosensors,[9] as well as probes for monitoring DNA repair[10] and DNA/RNA-Protein interactions.[11] Among them, one can discriminate between the fluorescent expanded natural base analogs, whose scaffolds include one or more (hetero)aromatic ring fused to the natural base, and the non-polar analogs, whose scaffold does not retain part of the natural base scaffold.[7b]

Therefore, several synthetic routes to *C*-aryl-nucleosides have been disclosed in the literature. Among these different approaches, which have been recently reviewed by Yang and Yu,[12] Bokor and coll.,[13] Hocek,[14] Adamo and Pergoli,[15] the following may be highlighted due to their versatility: (i) the addition of nucleophilic aryl groups (usually a lithiated derivative) to an electrophilic/carbocationic carbohydrate, but this strategy leads only to a decreased stereocontrol; (ii) the intramolecular rearrangements (e.g. Claisen or Wittig reactions), which requires the prior synthesis of elaborated intermediates; (iii) the coupling of halobenzene derivatives mediated by palladium catalysts is also a convenient strategy, but its use is restricted to the 2'-deoxy series only; and (iv) the stereoselective Heck reaction for the syntheses of 2'-deoxy-*C*-nucleosides and 2',3'-dideoxy-*C*-nucleosides (Scheme 1).

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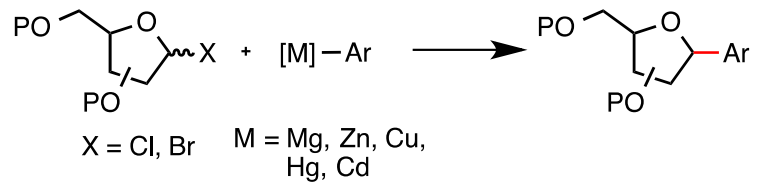
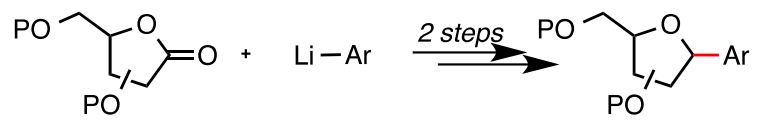
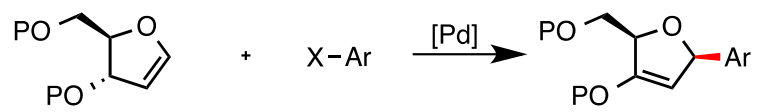
a) addition of organometallic reagents to halosugars



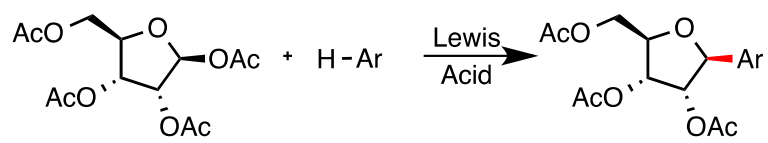
b) Li-Ar addition to (2-deoxy)ribonolactones



c) Heck-type coupling



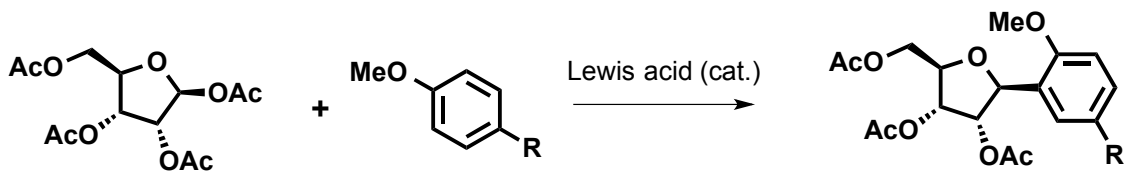
d) Friedel-Crafts type reactions, including ***this work***



Scheme 1. Examples of strategies to access *C*-nucleosides.[12-15]

In summary, despite the numerous synthetic option towards *C*-nucleosides, there is only limited examples using a direct strategy, *i.e.*, a stereoselective one-step preparation of *C*-aryl-β-D-ribosides. In this context, we formerly reported a pioneer work using a Friedel-Crafts ribosylation reaction, mediated by a stoichiometric amount of $SnCl_4$ as Lewis acid (1.1 eq., Table 1, Line 1).[16] This process paved the way to short syntheses of *C*-nucleosides, bearing a (hetero)aryl aglycone, selectively functionalized on their β-face. This methodology was subsequently extended to the preparation bioactive *O*- and *N*-nucleosides, that are structurally related to the anti-cancer agent AICAR (acadesine).[17] However, despite its advantages, this ribosylation process requires the use of a very toxic Lewis acid ($SnCl_4$), and thereby is not compatible with the development of modern eco-compatible organic reactions. Therefore, in continuation of our efforts in the development of greener processes,[18] we report herein an optimization of this Friedel-Crafts reaction, and its use for the synthesis of non-polar fluorescent probes.

Table 1. Optimization of the ribosylation catalyzed by metal salts.



1 **R = I, 2a**
R = OMe, 2b
R = I, 3a
R = OMe, 3b

Entry	R	Catalyst, (mol %)	Solvent	Conditions (T°, Time)	Yield [a]
1	I	$SnCl_4$, (110)	CH_2Cl_2	0°C, 16h.	72%[b]
2	OMe	$SnCl_4$, (50)	CH_2Cl_2	r.t., 30 min.	55%
3	I	$SnBr_4$, (50)	CH_3NO_2	Reflux, 12h.	50%
4	I	$FeCl_3$, (50)	CH_3NO_2	Reflux, 10 min.	68%
5	I	$CuCl_2$, (50)	CH_3NO_2	Reflux, 12h.	-[c]
6	I	$AlCl_3$, (50)	CH_3NO_2	Reflux, 12h.	-[c]
7	I	$ZnCl_2$, (50)	CH_3NO_2	Reflux, 12h.	45%
8	I	$InCl_3$, (50)	CH_3NO_2	Reflux, 12h.	40%
9	I	$FeCl_3$, (20)	CH_3NO_2	Reflux, 10 min.	73%
10	I	$FeCl_3$, (10)	CH_2Cl_2	Reflux, 10 min.	65%
11	OMe	$FeCl_3$, (10)	CH_2Cl_2	Reflux, 10 min.	62%
12	OMe	$FeCl_3$, (5)	CH_2Cl_2	Reflux, 10 min.	27%
13	OMe	$FeCl_3$, (10)	CH_2Cl_2	r.t., 24 h.	26%
14	I	Fe_2O_3, (50)	CH_3NO_2	Reflux, 12h.	-[c]
15	I	$FeSO_4$, (50)	CH_3NO_2	Reflux, 12h.	-[c]
16	I	$FeCl_3$, (20)	Xylene	Reflux, 12h.	-[c]
17	I	$FeCl_3$, (20)	$CH_3C_6H_5$	Reflux, 12h.	20%
18	I	$FeCl_3$, (20)	ClC_6H_5	Reflux, 12h.	-[c]
19	I	$FeCl_3$, (20)	DMF	Reflux, 12h.	-[c]

[a] Yield of isolated product; [b] See reference 16; [c] no reaction observed via TLC monitoring.

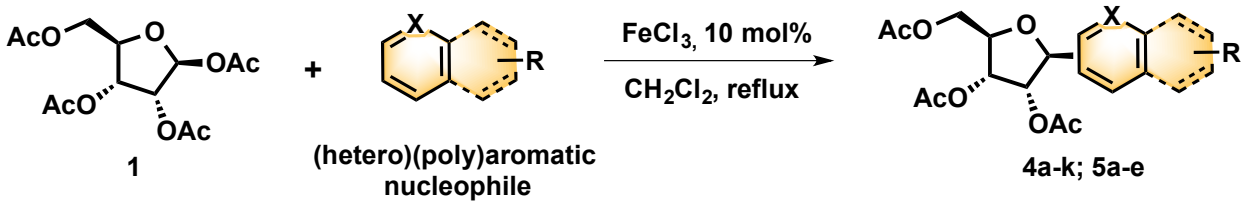
In line with our previous work, we selected as the benchmark reactions the Friedel-Crafts condensation between 1'-β-ribofuranose-1',2',3',5'-tetraacetate (**1**, 1.0 eq.) and 1-iodo-4-methoxybenzene or 1,4-dimethoxybenzene (**2a-b**, 2.0 eq.), a better nucleophile due to the presence of the second methoxy group. In both cases, we observed conversion rates to the corresponding products (**3a-b**) in the 50% range, when reduced amounts of $SnCl_4$ and $SnBr_4$ were employed (0.5 eq., Table 1, entries 2 & 3). Based on these initial results, we next evaluated a series of metal salts as Lewis acids for comparison studies. We selected $CuCl_2$,[19] $AlCl_3$,[20] $InCl_3$[21] and $ZnCl_2$,[22] which all are known to efficiently promote Friedel-Crafts reactions (Table 1, entries 4-8). However, in our hands, the ribosylation preformed in presence of $CuCl_2$ and $AlCl_3$ completely failed, and when performed under $InCl_3$ and $ZnCl_2$ catalysis, it only led to moderate conversion rates (40-45%).

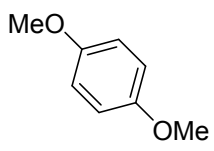
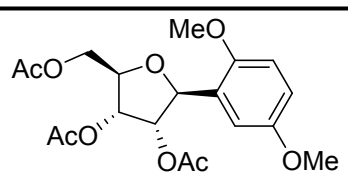
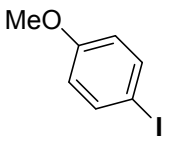
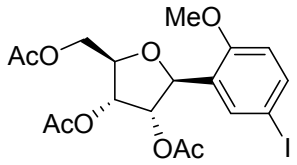
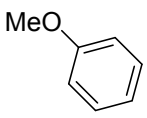
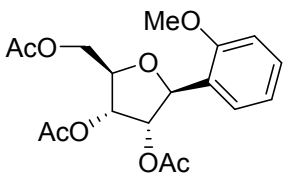
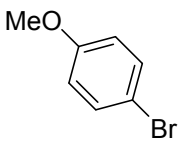
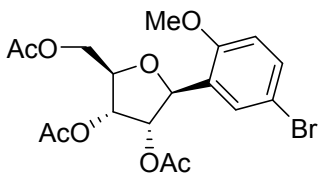
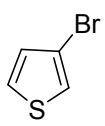
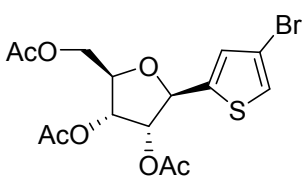
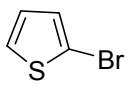
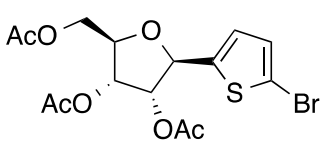
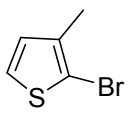
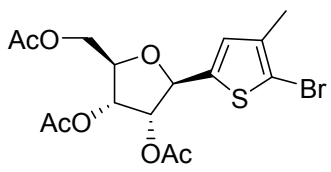
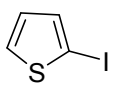
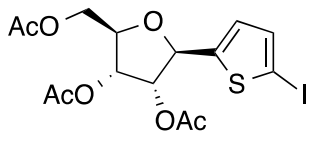
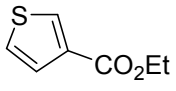
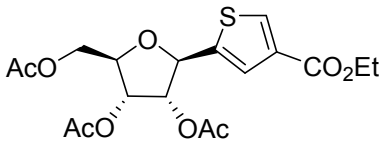
Then, we focused our attention on iron salts, since we already reported the use of a catalytic amounts of $FeCl_3$ to efficiently promote the anomeric azidation of **1** (78% yield).[17a,c] Moreover, it is noteworthy that $FeCl_3$ is a costless, poorly toxic and easy to handle Lewis acid; hence it is perfectly relevant in the context of the development of eco-compatible chemistry processes. Interestingly, using $FeCl_3$, at 20 mol% loading, **1** and **2a** could be efficiently coupled in good yields (Table 1, entry 9, 73%). Lowering the catalyst charge to 10 mol% still promoted the Friedel-Crafts ribosylations of both **2a** and **2b** in good yields (65% and 62% respectively, Table 1, entries 10 & 11) and short reaction times (10 min.). Importantly, these reactions occurred at moderate temperature. We next assayed other Fe(II) and Fe(III) iron salts (Fe_2O_3 and $FeSO_4$), known to catalyze Friedel-Crafts reactions.[23] However, even when using larger catalytic charges (50 mol%), increased reaction times (up to 12 h.) and higher temperature (refluxing nitromethane), we did not observe any conversion (Table 1, entries 14-15). Finally, we tried to perform the ribosylation catalyzed by $FeCl_3$ in other solvents than dichloromethane (Table 1, entries 16-19). However, even in refluxing xylene or DMF, no reaction occurred. These latter results may be due to solvation problems.

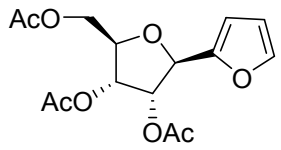
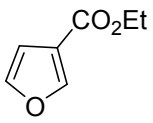
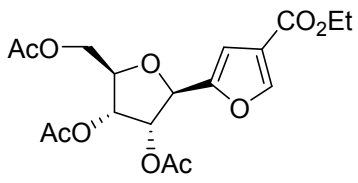
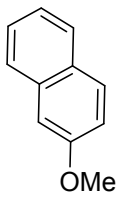
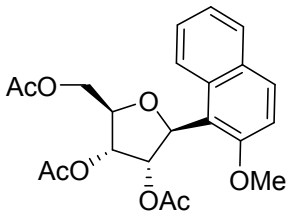
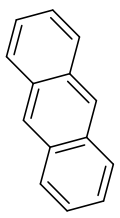
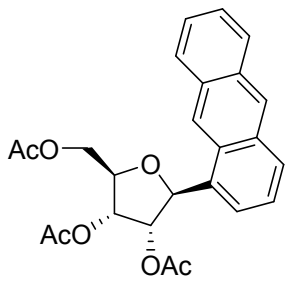
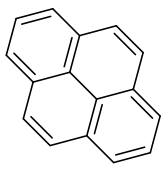
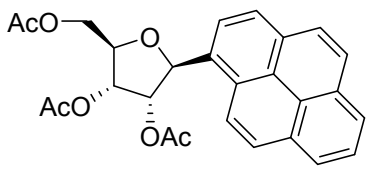
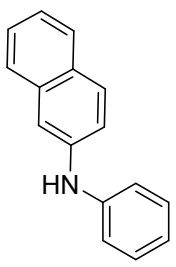
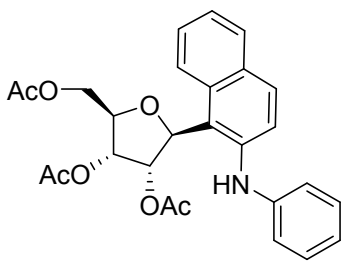
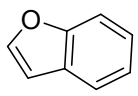
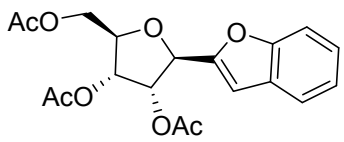
From the mechanistic point of view, it is to note that the ribosylation occurs with a marked stereoselectivity. Indeed, the α/β molar ratio of purified product have been estimated as 2/8 for **3a** and 4/6 for **3b** by ^{1}H NMR spectroscopy. This interesting result may be related to the mechanism of this

reaction. It likely proceeds through the formation of an oxonium intermediate, that may be partially stabilized by anchimeric assistance (neighboring group effect), before its trapping by the nucleophile (aryl).[17a,c]

Table 2. Scope of the *C*-Glycosylation: a survey of nucleophiles.[a]



Entry	Nucleophile	Isolated C-Glycoside	Reaction time (min)	Yield	Ratio β/α
1		 **4a**	10	62%	6/4
2		 **4b**	10	65%	8/2
3		 **4c**	10	45%	6/4
4		 **4d**	30	40%	9/1
5		 **4e**	10	49%	7/3
6		 **4f**	10	30%	8/2
7		 **4g**	10	47%	9/1
8		 **4h**	10	33%	9/1
9		 **4i**	10	48%	7/3

10		 **4j**	10	32%	9/1
11		 **4k**	10	61%	10/0
12		 **5a**	10	35%	10/0
13		 **5b**	20	45%	95/5
14		 **5c**	30	58%	9/1
15		 **5d**	30	53%	10/0
16		 **5e**	25	72%	10/0

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[a] *Reaction conditions:* β-D-ribose tetraacetate **1** (1 mmol), nucleophile (2 mmol), $FeCl_3$ (10 mol%), CH_2Cl_2 (8 mL), 40°C.

Next, we explored the scope of this ribosylation process on a set of six-membered and five-membered (hetero)aromatic compounds (Table 2, compounds **4a-k**). In all cases, the expected products were obtained, in moderate-to-good yields (30-60%), after 10 – 30 min. reaction in refluxing CH_2Cl_2. These compounds were isolated as a mixture of anomers, in α/β ratio ranging from 4/6 to 0/10. The scope of the (hetero)arene glycosyl acceptor encompasses activated (electron-rich) and non-activated benzene derivatives (Table 2, entries 1-4). These may feature bromo- and iodo-moieties that are suited for further transformations (e.g. [Pd] catalyzed cross-couplings). In addition, 5-membered heteroaryl ribosyl acceptor were successfully employed. Indeed, these 5-membered heteroaryl rings include a variety of thiophene and furane moieties bearing methyl, halide or ester functions (Table 2, entries 5-11).[24] Of note, compounds **4i** and **4k** can be converted, in one step, into thiophenfurine and furanfurine which are known anticancer analogues of tiazofurin.[25]

Interestingly, Yokoyama and *coll.* have previously reported a multi-step synthesis of **4j**.[26] Their synthetic path to **4j** was based on the addition of the 2-lithiated furan to the 2,3,5-tri-*O*-benzyl-β-D-ribose, leading to an open ribitol chain, whose subsequent treatment with *p*-toluenesulfonic acid affords the 2-ribofuranosylfurane. Lastly, the interconversion of the protecting groups (benzyl to acetyl) gives compound **4j**. However, by comparison with our Friedel-Crafts single step synthesis, this methodology appears time-consuming, and suffers from low yields (7-30%) and poor stereoselectivity (α/β ratio of 1/3).[27]

We next tested our conditions on the ribosylation of bulky polyaromatic molecules such as 2-methoxynaphthalene, benzofuran, anthracene and pyrene (Table 2, compounds **5a-e**). Satisfactorily, compounds **5a-5e** could be prepared in moderate to good yields (35-72%) and short reaction times (10-30 min.). It is worth noting that **5a-5e** were obtained with a high stereoselectivity; the anomeric α/β ratio ranged from 1/9 to 0/10.

These results are well complementing the glycosylation reaction arsenal as it was already reported, that using a highly reactive 1-chlorosugar, the glycosylation of anthracene (and fluorene) proved difficult.[28] In fact, the use of mildly Lewis acid conditions could not promote the reaction, whereas stronger Lewis acid, *i.e.* $SnCl_4$, induces the decomposition of the glycosyl donor. In sharp contrast, under our specific conditions, *i.e.* 10 mol% of $FeCl_3$ in refluxing dichloromethane, the glycosylation of anthracene provides the desired anthracenyl-C-nuleoside **5b** in 45% yield, as a 95/5 mixture of β/α anomers.

Importantly, anthracene[29] and pyrene[30] have been extensively used as non-polar nucleobase analogues for DNA-labelling. Indeed, even if the pyrene has a larger size than the natural nucleobases, recent structural analyses revealed that, in DNA duplexes, this polyaromatic scaffold can be used as a Watson-Crick base pair surrogate when facing an abasic site on the complementary strand.[31] In addition, pyrene exhibits very strong chemical stability and its fluorescence parameters are highly related to the chemical properties of its local environment. Thereby, tetra-pyrene deoxynucleotide sensors, also called oligodeoxyfluoroside, have been synthesized by Kool and co-workers, and used to monitor catalytic activity of polymerases, deoxynucleotidyl transferases and esterases.[31] However, to the best of our knowledge, we report herein the first single-step, eco-friendly and stereoselective synthesis of 2,3,5-tri-*O*-acetyl-β-D-riboses functionalized on their anomeric position, and on the β-face, by these two motifs (anthracene and pyrene). Moreover, to date such tools have been used as RNA fluorescent probes.

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In this context, to get insights about the photophysical properties of the compounds **5b** and **5c**, UV-vis absorption and steady state fluorescence emission spectra in solution were acquired in solvents with distinct polarity (Figure 1). The main spectroscopic data are given in Table 3. The UV−vis spectra of the pyrene and anthracene derivatives present similar spectral shape compared with the parent unsubstituted molecules.[32] As already reported in the literature,[33] it seems that the inductive effect along the glycosidic bond controls the red shift absorption band. Apart from that, emission spectra revealing the characteristics mirror image of the parent absorption spectra were observed for both fluorophores. Additionally, concerning the pyrene glycoside, no strong evidence indicating a putative excimer emission in solution was observed regardless of the broad range of concentrations evaluated in extremely non-polar environment (*ca.* cyclohexane, Figure S1). Nevertheless, these observations do not rule out the possibilities of a fluorescent ratiometric monomer-excimer emitting probe that could be obtained using **5c** under different conditions. As reported by Chiba and co-workers,[28d] even without evidences of the excited state dimer emission in a pure monomer-containing solution, the excimer and heteroexcimer emissions could be observed when alkynyl pyrene, anthracene and perylene nucleosides were incorporated in oligonucleotide sequences. Finally, any noticeable solvent dependency was observed on the main photophysical parameters (λ_{abs}, λ_{em} and ϕ_f) and both probes were less emissive when compared with their non-substituted analogues.

In conclusion, we report herein a straightforward and eco-compatible route to *C*-(poly)aromaic nucleosides. This single-step synthetic pathway proceeding through a Friedel-Crafts reaction, occurs stereoselectively on the β-face of the carbohydrate, and the expected products have been isolated in good yields. Interestingly, this versatile methodology allows the unprecedented introduction on the ribose scaffold of bulky poly-aromatic derivatives, such as the anthracene and pyrene ones. Such highly functionalized *C*-nuleosides present interesting photophysical properties, including fluorescence. Their use for RNA labeling to afford new biological probes and sensors, is currently investigated by our team, and will be reported in due course.

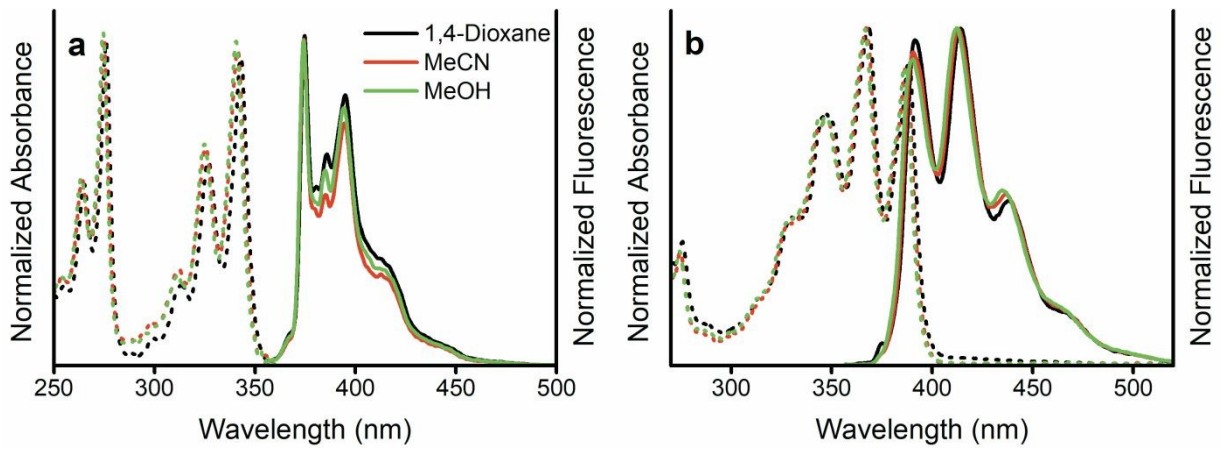

Figure 1. Normalized UV-vis absorption (dashed line) and fluorescence emission spectra (full line) for compounds **5c** (a) and **5b** (b) in organic solvents.

Table 3. Spectroscopic properties of compounds **5b** and **5c** in solution.

Compound	Solvent	λ_{abs} (nm)	λ_{em} (nm)	ε (x 10^3)[a]	ϕ_f[b]
Anthracene	Cyclohexane	275, 329, **345**, 367, 386		6.1	0.25
5b	1,4-Dioxane	275, 330, **347**, 368, 388	392, 414, 438, 466	5.8	0.39
	MeCN	274, 329, **347**, 367, 387	390, 413, 437, 463	5.5	0.30
	MeOH	274, 330, **347**, 366, 386	392, 411, 435, 465	5.6	0.28
Pyrene	Cyclohexane	242, 264, 275, 312, 326, **342**	375, 286, 393, 415	47.0	0.05
5c	1,4-Dioxane	242, 265, 276, 313, 327, **343**	373, 385, 395, 416	45.0	0.14
	MeCN	240, 263, 274, 311, 325, **341**	373, 385, 395, 415	44.0	0.05
	MeOH	239, 262, 273, 310, 324, **340**	373, 385, 393, 415	47.0	0.05

[a] Molar extinction coefficients ($L.mol^{-1}.cm^{-1}$) are related to the highlighted absorption maxima; [b] fluorescence quantum yield values were determined by using quinine sulfate in 0.1 M H_2SO_4 solution (ϕ_f = 0.54)[34] as standard; The highlighted absorption maxima were used as the excitation wavelengths.

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# Equal contribution of the authors

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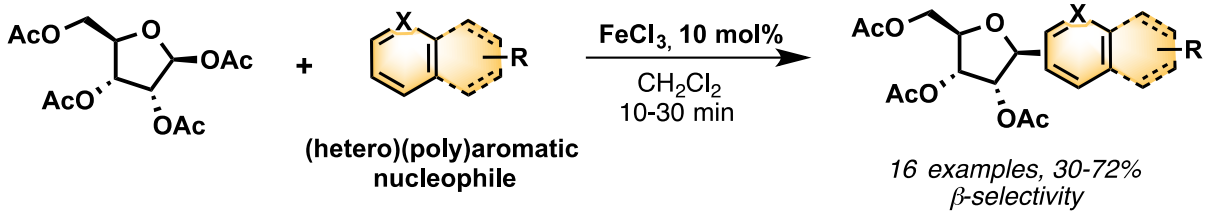

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