Palladium-Catalyzed Cross-Coupling/Annulation Cascade for Synthesis of 9-Hydroxy and 9-Aminofluorenes

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Palladium-Catalyzed Cross-Coupling/Annulation Cascade for Synthesis of 9-Hydroxy and 9-Aminofluorenes.

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Abstract. 9-Hydroxyfluorenes are easily synthesized via a tandem Suzuki/phenolic aldolisation sequence. This process was extended to 9-aminofluorenes by simply adding various amines as third partners. X-ray structures and NMR studies confirmed the presence of intermolecular O-H···N hydrogen bonding.

Keywords: Suzuki coupling; Mannich reaction; cascade process; fluorene; Betti bases.

Introduction

Due to remarkable optical and electronic properties, polycyclic aromatic hydrocarbons (PAHs) have found abundant applications, as organic field-effect transistors, light-emitting devices, organic photovoltaic cells or biosensors.[1] Numerous studies have been also devoted to their precise environmental impact.[2] Fluorene is one of the simplest PAHs with a planar rigid biphenyl core. In addition to their extensive use as functional materials, fluorene-containing compounds have been also employed as protecting groups in peptide chemistry or building blocks in organic synthesis.[3] Furthermore, they constitute the common substructure of a number of biologically active substances. Thus, notable examples of bioactive 9-amino substituted derivatives include inhibitors of cyclophilin A, **1**,[4] InhA and *Mycobacterium tuberculosis* growth, **2**,[5] and Hsp90, **3**.[6] As regards their oxygenated analogs, guanidine **4** showed potent affinity for 5-HT_{2B} and 5-HT_7 receptors,[7] and glycosides **5** displayed significant antiviral properties against HSV-1 and HSV-2 (Figure 1).[8]

These remarkable pharmacological properties have attracted considerable attention from synthetic and medicinal chemists that led to the development of efficient strategies for accessing this class of 9-heterosubstituted fluorenes. Usual methods for hydroxy derivatives mostly rely on the reduction of the corresponding fluoren-9-ones, which were typically prepared by Friedel-Crafts reactions catalyzed by Lewis acids [7,9], directed remote metalation[10] or via a palladacycle–catalyzed sequential reaction of 2-bromobenzaldehydes with arylboronic acids.[11] Other main strategies consist of [1,2]-Wittig rearrangements,[12] intramolecular [4+2]-cycloadditions,[13] cyclotrimerisation,[14] photoredox-catalyzed tandem cyclizations,[15] intramolecular dehydroaromatization,[16] or dehydrogenative cyclization.[17] Regarding the 9-aminofluorenes, they were essentially synthesized by nucleophilic substitution on the corresponding halogeno derivatives,[18] reductive amination, metal-free C(sp^3)-H arylation and Ugi condensation of fluorenones,[19,20,21] dehydrogenative cyclization,[22] and intramolecular aza Friedel Craft from *N*-sulfonyl imines,[23] *N*-sulfinyl imines [24] or *N*-sulfonylhydrazones.[25]

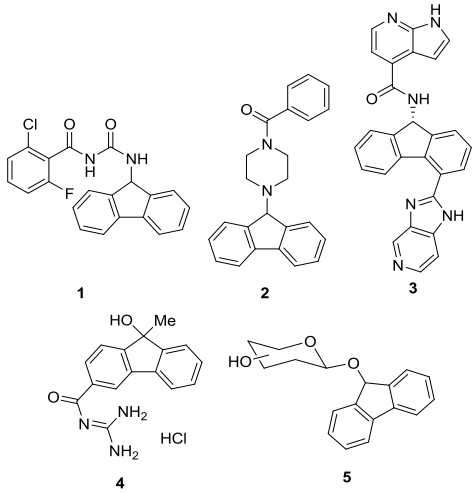
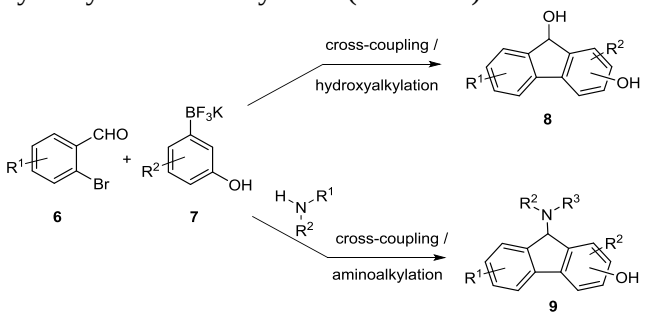


Figure 1. Some bioactive 9-heterosubstituted fluorenes.

In this context, we report herein a new approach to 9-heterosubstituted fluorenes **8** and **9** from commercially or easily available starting materials, which are based on a cascade sequence: palladium-catalyzed Suzuki cross-coupling/intramolecular hydroxy- or aminoalkylation (Scheme 1).



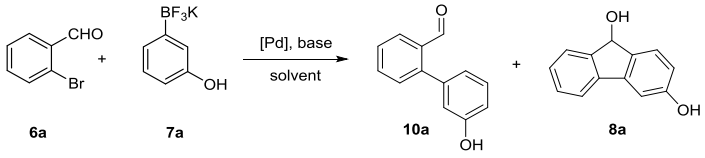
Scheme 1. Synthesis of 9-hydroxy- and 9-aminofluorenes **8** and **9**.

Results and discussion

Our initial efforts started with the 9-hydroxy derivatives and the screening of coupling conditions of 2-bromobenzaldehyde **6a** with potassium 3-hydroxyphenyl trifluoroborate **7a**, selected as boron partner due to its recognized advantages over the corresponding boronic acids and boronate esters.[26] Various solvents, palladium sources and bases were tested in order to optimize the direct and efficient formation of the cyclized product (Table 1). The use of palladium acetate and potassium triphosphate as base in a mixture dioxane/water (1/1) afforded only the cross-coupled material **10a** in a modest yield after 5 hours at 65°C (entry 1). An increase of the reaction time resulted in the minor formation of the expected fluorenyl derivative (entry 2), while the replacement of the initial catalytic species by tetrakis(triphenylphosphine)palladium(0) at higher temperature cleanly delivered **10a** in a better yield without any detected formation of **8a** (entry 3). Fortunately, the reaction conducted in methanol provided a convenient access to this fluorene derivative with a spectacular increase of the yield (entries 4 and 5). Other modifications failed to improve these results (entries 6, 7 and 8). In each case, the formation of 1,9-dihydroxyfluorene **8'a** was also observed in ratio varying from 7 to 10% under the best conditions for cyclization (entries 4 and 5). The two isomers were easily separated by column chromatography. The assignment of their respective structures was done on the basis of their ^{1}H and ^{13}C NMR spectra, mass spectroscopy and comparison with literature data the for **8'a.**[27]

A plausible mechanism for the formation of the fluorene cycle is depicted in Scheme 2. A first Suzuki coupling afforded the aldehyde **10a**. Deprotonation generated the phenolate **A**, which can undergo a nucleophilic addition to the aldehyde moiety according to a phenolic aldol-type condensation, mainly by the *para* position.[28] Rearomatization and protonolysis afforded **8a**, the formation of the other isomer **8'a** occurring via an attack from the carbon *ortho* to the phenolic oxygen atom.

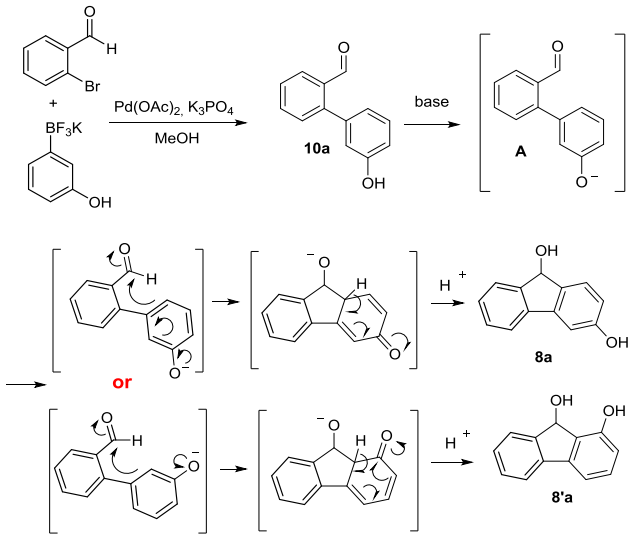
Table 1. Optimization of the cascade process for the synthesis of 9-hydroxyfluorene **8a**.



Entry	Solvent	Catalyst (mol %)	Temp (°C)	Time (h)	Base	Yield (%)[a]	
						10a	**8a**
1	Dioxane/ H_2O (4/1)	$Pd(OAc)_2$ (0.5)	65	5	K_3PO_4	35	0
2	Dioxane/ H_2O (4/1)	$Pd(OAc)_2$ (0.5)	65	62	K_3PO_4	53 (50) [b]	14[c]
3	Dioxane/ H_2O (4/1)	$Pd(PPh_3)_4$ (5.0)	100	5	K_3PO_4	82 (69) [b]	0
4	MeOH	$Pd(OAc)_2$ (0.5)	65	5	K_3PO_4	6	87 (74) [b,c]
5	MeOH	$Pd(OAc)_2$ (0.5)	65	5	K_2CO_3	0	84 (61) [b,d]
6	H_2O	$Pd(OAc)_2$ (0.5)	65	5	K_2CO_3	0	10
7	EtOH	$Pd(dppf)Cl_2$ (1)	65	5	iPr$_2$NEt	35	4
8	EtOH	$Pd(dppf)Cl_2$ (1)	65	22	iPr$_2$NEt	29	29

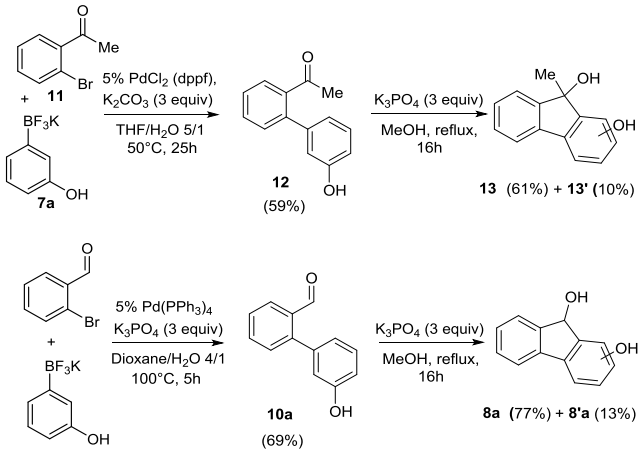
[a] Yields in the crude mixture determined with 4-nitroanisole as an internal standard.
[b] Values within parentheses are yields of the isolated pure product **8a** or **10a** purified by column chromatography on silica gel.
[c] 93/7 Regioisomeric ratio (3-OH/1-OH) measured by ^{1}H NMR on the crude material.

[d] 90/10 Regioisomeric ratio (3-OH/1-OH) measured by ^{1}H NMR on the crude material.



Scheme 2. Plausible mechanism for the synthesis of 9-hydroxyfluorenes **8a** and **8'a**.

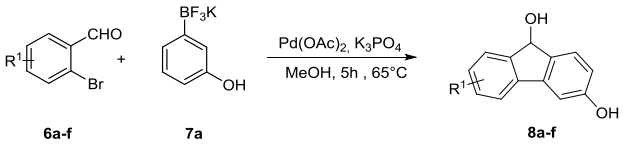
To extend the scope of this sequence, we then tested 2'-bromoacetophenone **11** as substrate. First attempts with previously used catalytic system: $Pd(OAc)_2$, K_3PO_4, only resulted in the observation of the starting ketone and biphenyl-3,3'-diol,[29] the homocoupling product of the trifluoroborate **7a**. Using another combination ($PdCl_2(dppf)$, K_2CO_3, THF/H_2O) allowed obtaining the biphenyl **12** without any tricyclic compound. When this ketone was treated with potassium triphosphate tribasic in methanol at reflux for 16h, cyclization occurred giving the expected fluorene derivatives **13** and **13'** in a 71% yield (mixture of two regiosomers 85/15) (Scheme 3). The same observation was made with the aldehyde **10a**, thus confirming that open species **10** were most likely intermediates in the formation of compounds **8** and **8'**.

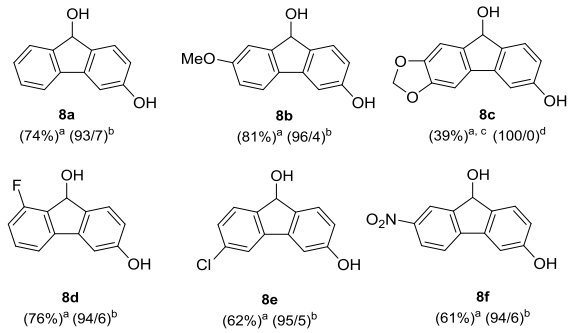


Scheme 3. Two steps synthesis of 9-hydroxyfluorenes **8a** and **13**.

The scope of the cascade sequence was then evaluated under the previously optimized conditions (entry 4, Table 1). A range of 2-bromobenzaldehydes possessing various substitution patterns in different position provided the corresponding fluorene derivatives **8b-f** in good to moderate yields without any obvious effect of the nature of the aromatic ring substituent. In all cases, minor amounts of regioisomers **8'** were also present in the crude mixtures (Table 2).

Table 2. Substrate scope of the one-pot synthesis of 9-hydroxyfluorenes **8**.



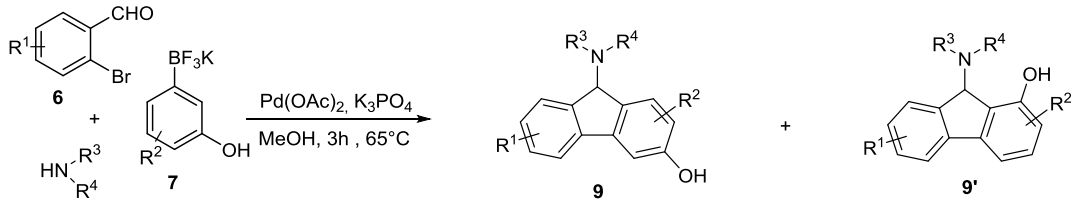


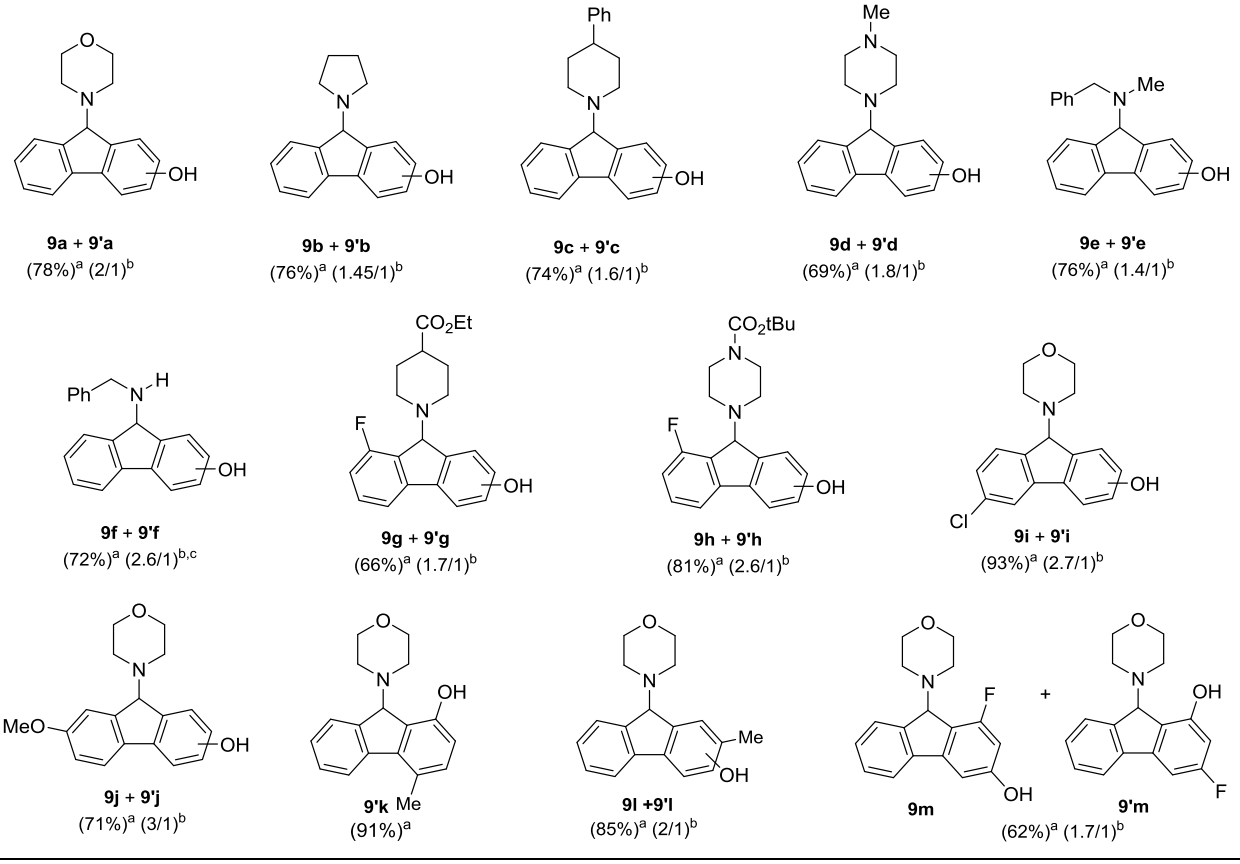
[a] Yields of pure isolated regioisomers purified by column chromatography on silica gel. [b] Ratio of regioisomers (3-OH/1-OH) determined by ^{1}H NMR on the crude material. [c] This low yield was due to problems of purification. A 63% crude yield of **8c** was determined by the use of 4-nitroanisole as an internal standard.

On the other hand, the Betti reaction, which usually involves 2-naphtol, amines and aldehydes, is a well known process that gives easy access to a variety of useful building blocks for organic synthesis.[30,31] On the basis of the commonly accepted mechanism of this three component condensation, we envisioned the participation of a third partner in the above reported palladium-catalyzed cross-coupling/annulation cascade. Complete conversion and moderate to very good yields were achieved in all examined cases for a range of secondary amines (Table 3). As for the hydroxy derivatives, but with a more balanced ratio, the 9-aminofluorene derivatives are systematically obtained as a mixture of two regiosiomers **9** and **9'**. The structural determination of each isomer was based on the proton ^{1}H NMR data (characteristic doublet around 7.2 ppm (J≈2 Hz) for **9**), comparison with literature data [5a,25] and X-ray diffraction studies.[32] This reaction is efficient with both cyclic and acyclic amines, the presence of supplementary heteroatoms and an ester group on the amino partner having no obvious impact on the yield. Unfortunately, no significant asymmetric induction was observed

with the chiral (*S*)-*N*-methyl-α-methylbenzylamine as amino partner.

Table 3. Substrate scope of the one-pot synthesis of 9-aminofluorenes **9**.



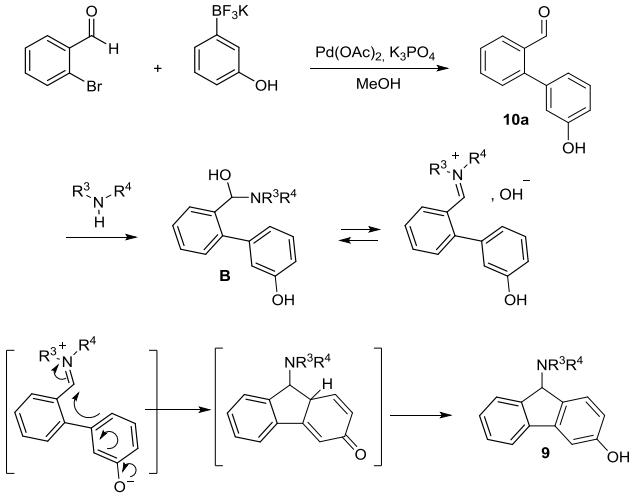


[a] Yields of pure isolated regioisomers purified by column chromatography on silica gel.
[b] Ratio of regioisomers (3-OH/1-OH) determined by ^{1}H NMR on the crude material.
[c] Presence of the bisadduct : 2 fluorenyl moieties / 1 benzylamine (**9f**/**9f'**/bisadduct = 2.6/1/0.5).

This approach is not restricted to secondary amines and *N*-benzyl 1-hydroxy- and 3-hydroxy-9*H*-fluoren- 9-amines **9f** and **9'f** were obtained from potassium (2-hydroxyphenyl) trifluoroborate and benzylamine as a 2.6/1 separable mixture in a cumulated 72% yield. Electron withdrawing and donating groups either on the starting aldehyde or the potassium aryltrifluoroborate were also well tolerated.

Based on these experimental results and literature data, a tentative mechanism for this sequence is proposed in Scheme 4. The process starts with the formation of the key intermediate **10** resulting from a Suzuki coupling. The addition of the amine leads to the hemiaminal **B** in equilibrium with the corresponding iminium, [33] which is then trapped by the phenolate according to a Mannich-type condensation. The formation of the regioisomer **9'** results from the attack via the *ortho* position, as previously observed for the 9-hydroxyfluorenes **8'**.

Single-crystal X-ray diffraction analysis of **9'a** and **9'e** indicates that they crystallized in a monoclinic centrosymmetric space group P21/n.[31] The favorable geometry is responsible of the presence of intra-



Scheme 4. Proposed mechanism for the synthesis of 9-aminofluorenes **9**.

molecular hydrogen bonds formed between the hydroxyl group and the nitrogen atom, with H···N distances of 2.058 and 2.052 Å and O–H···N angles of 143 and 148°, respectively. These characteristics are typically observed for Betti base analogs,[33] which are valuable model systems for the investigation of proton-coupled electron transfer reactions.[34]

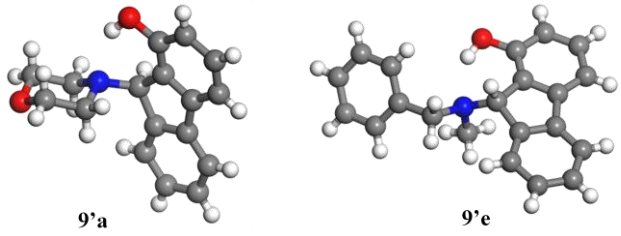


Figure 2. X-ray crystallographic structures of **9'a** and **9'e**.

The ^{1}H and ^{13}C NMR spectra of **9'**, recorded at ambient temperature in $CDCl_3$, showed significantly broadened peaks, thus suggesting an intramolecular dynamic process of phenolic proton exchange.[33c,35] Recording the NMR spectra of **9'e** at low temperature greatly improves the resolution (Figure 3) and allows the observation at 223°K of a 6/4 mixture of diastereomers due to the presence of a stereogenic nitrogen atom.

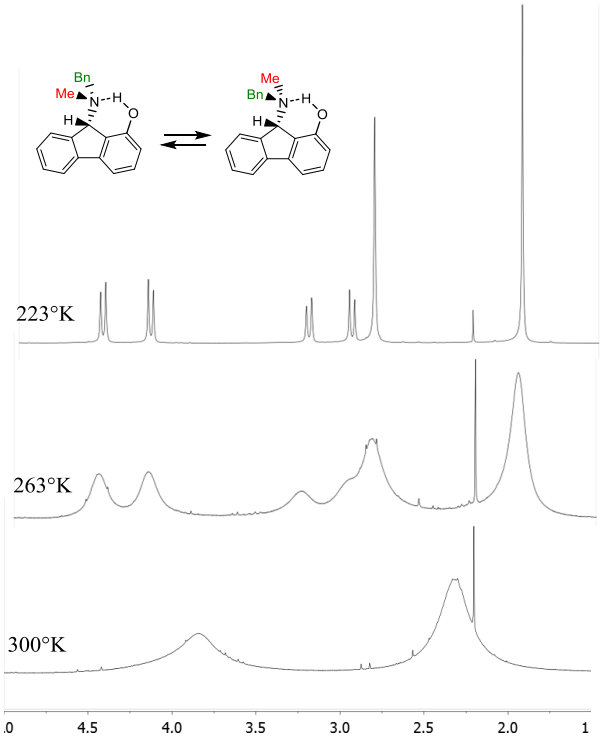
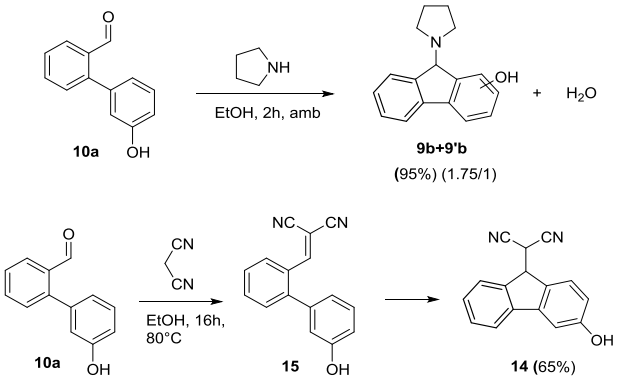


Figure 3. ^{1}H NMR spectra of **9'e** at various temperatures.

If this one-pot approach provided the desired compounds in good yield, as expected and in agreement with the proposed mechanism, it is also possible to use **10** as a precursor of 9-aminofluorenes. It allows the direct introduction of a fluorenyl moiety on amino functionalized molecules under mild conditions, without metal species, and only with generation of water as by product (Scheme 5). It also worthy to note that, via a related condensation/pseudo Michael process, malonitrile reacted with **10a** with no additive to give the fluorene derivative **14** as major regioisomer.[36,37]



Scheme 5. 10 as precursor of 9-aminofluorenes **9b+9'b** and 2-(3-hydroxy-9H-fluoren-9-yl)malononitrile **14**.

In summary, a palladium-catalyzed cross-coupling/ intramolecular phenolic aldol condensation sequence was developed to access 9-hydroxyfluorenes **8** in

good to moderate yields. Addition of an amine component as additional partner has been also exploited to synthesize 9-aminofluorenes **9** via an efficient three-component process. Mechanistic hypotheses have been proposed to rationalize experimental results. Current efforts in our group are now devoted to expand the scope of these reactions to other substrates and to use this fluorene derivatives as precursors of the corresponding *o*-quinone methides, which are versatile reactive intermediates in organic synthesis.[38,39]

Experimental Section

General procedure for the synthesis of 9-hydroxyfluorenes 8 and 8'.

In a flame-dried Schlenk flask, were sequentially added potassium phosphate tribasic monohydrate (1.60 mmol), potassium 3-hydroxyphenyltrifluoroborate (0.50 mmol), 2-bromo-benzaldehyde (0.50 mmol) and methanol (5 mL). The resulting mixture was degassed under slow bubbling of argon for 5 min. Palladium acetate (1.35 mL of a freshly prepared 2.10^{-3} M solution in methanol, 2.7 10^{-3} mmol) was then introduced. The mixture was heated to reflux for 5 hours. After cooling, ethyl acetate (20 mL) and water (2 mL) were added. Phases were separated, and the aqueous one was neutralized with aqueous 1N HCl and extracted with ethyl acetate (3x10 mL). Organic phases were combined, dried with anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel chromatography on silica gel(cyclohexane/ethyl acetate).

General procedure for the synthesis of 9-aminofluorenes 9 and 9'.

In a flame-dried Schlenk flask under argon, were introduced potassium 3-hydroxyphenyltrifluoroborate (1 mmol) and methanol (4 mL). The mixture was degassed by slow bubbling of argon for 15 minutes. Tribasic potassium phosphate (637 mg, 3 mmol), 2-bromobenzaldehyde (1 mmol), palladium acetate (11.2 mg, 0.05 mmol) and amine (1 mmol) were then added. The solution was refluxed for 1 hour. After cooling under argon, potassium 3-hydroxyphenyltrifluoroborate (0.5 mmol) was re-added and the mixture was refluxed for 2 additional hours. 5 mL of saturated NH_4Cl solution and 20 mL of dichloromethane were added to the reaction mixture previously cooled to room temperature. After extraction of the aqueous phase with dichloromethane (3×10 mL), the organic phases were combined and dried over $MgSO_4$. The residue was purified by chromatography on silica gel.

All procedures and characterisation data are presented in the Supporting information.

Acknowledgements

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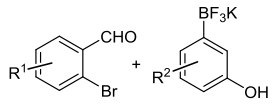

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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