Synthesis of new pentacyclic chromophores through a highly regio- and diastereoselective cascade process†‡

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A new family of pentacyclic compounds incorporating a central 1,2-dihydropyridine core is obtained through a pseudo three-component reaction. Four new bonds and two stereocenters with *trans* relationship are produced during the cascade process under palladium catalysis.

Aza-polycyclic compounds containing the pyridine core or its polyhydro derivatives constitute a great family of natural products with diverse biological activities[1] and have found numerous applications in material science.[2] Thus, Haouamine A **1** with an unusual indeno-tetrahydropyridine ring system was shown to possess a selective anticancer activity in human colon carcinoma cells ($IC_{50} = 0.1\ \mu g\ mL^{-1}$)[3] and indolizino[3,4,5-*ab*]isoindoles **2** were described as highly fluorescent heterocyclic systems[4] (Fig. 1).

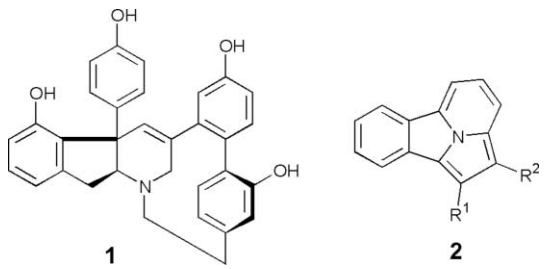
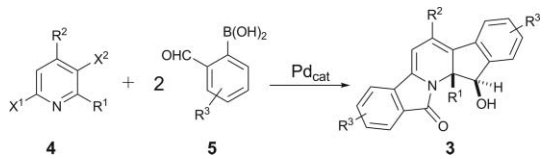


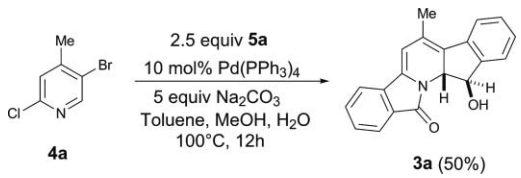
Fig. 1 Aza-polycycles with interesting properties.

Our interest in the synthesis of polyheterocyclic compounds with potential use in material science[5] or in biological chemistry[6] led us to develop new cascade reactions. Indeed the development of new chemical processes designed to produce elaborate heterocyclic structures in rapid, environmentally friendly way has become an important area of research in organic chemistry.[7] We have recently described a palladium-catalyzed reaction that allowed the one-pot formation of pyrido[2,1-*a*]isoindolones starting from 2-halopyridines and 2-formylphenylboronic acid.[8] We report herein a new cascade process that led after four bonds formation to a new π-conjugated pentacyclic structure **3**. In addition to the exceptional increase in molecular complexity, this reaction between 2,5-dihalopyridines **4** and two-fold of 2-formylphenylboronic acids **5** was found to be diastereoselective since two contiguous stereocenters with *trans* configuration between R^1 and H were formed. Structurally, **3** can be seen as two distinct substructures incorporating the central dihydropyridine core, the indeno-dihydropyridine system in the right and the pyrido[2,1- *a*]isoindolone in the left (Scheme 1).



Scheme 1 "One-pot" synthesis of pentacycles **3**.

During our work on the synthesis of benzo-(iso)quinoline derivatives,[6a] we were interested in the reaction of pyridine **4a** with 2-formylphenylboronic acid **5a** (R^3 = H) (1.2 equiv). Under classical Suzuki conditions[9] (5% $Pd(PPh_3)_4$, 2 equiv Na_2CO_3 1M in H_2O, toluene, methanol, 100 °C, 12 h), the desired cross-coupling product was accompanied with a small amount of a fluorescent by-product.[10] Increasing amounts of **5a** (2.5 equiv), base (5 equiv) and catalyst loading (10 mol%) led to the formation in 50% yield of **3a**, structure of which was assigned on the basis of its NMR spectra and X-ray crystal structure[11] (Scheme 2 and Fig. 2). Interestingly, only the *trans* product was formed and C4-addition was not observed.



Scheme 2 Regioselective and diastereoselective cascade reaction.

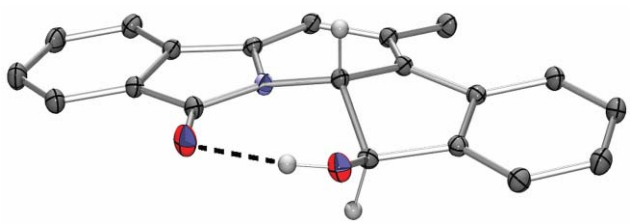


Fig. 2 ORTEP plot of **3a** (hydrogen atoms, except those in *trans* relationship and involved in the hydrogen bond, are omitted for clarity); thermal ellipsoids set at 50% probability. Intramolecular hydrogen bond (shown as a broken line) distances and angles: H···O = 2.00 Å, O···H···O = 149°.

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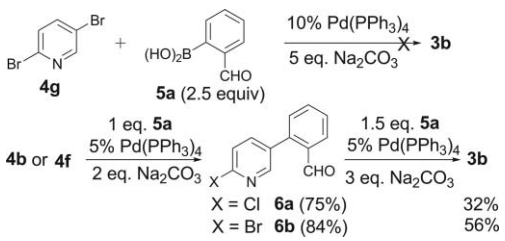
† Electronic supplementary information (ESI) available: General and experimental procedures, spectral data, copy of ^1H and ^{13}C NMR spectra, CIF files for **3a**, **3c** and **3f**, theoretical calculations data. CCDC reference numbers 734891–734893. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00390e

‡ Dedicated to Prof. Henri Kagan on the occasion of his 80th birthday.

Next, the substrate scope was studied by changing both the pyridine and the boronic acid (Scheme 1 and Table 1). It appeared that the C6 regioselectivity was not dependant on the pyridine substitution since pyridine **4b** with no methyl group in C4 reacted only at C6 with formation of compound **3b** in 57% yield (entry 1).[12] Similarly, pyridine **4c** with a methyl group in C6 reacted again at the same position to give **3c** bearing a quaternary center in a good yield of 59% (entry 2).

4,6-Dimethylsubstituted pyridine **4d** afforded the expected pentacycle **3d** in a lower yield of 36% (entry 3) whereas the 4-phenylsubsituted pyridine **4e** generated compound **3e** with a good yield of 60% (entry 4). The reaction of the *p*-MeO-substituted boronic acid **5b** with pyridine **4b** resulted in the formation of **3f** in a low yield of 17% (entry 5). However, the yield of **3f** was increased to 55% by employing the more reactive 2-bromo-5-iodopyridine **4f** (entry 6). Analogously, compound **3g** was produced in a moderate yield of 31% (entry 7) by using boronic acid **5c**. Boronic acid **5d** did not react well yielding the dimethylamino-substituted product **3h** in a poor yield of 12% (entry 8). The low yields of **3g** and **3h** can be explained by the fact that donating groups such as MeO (in *para* to CHO) and NMe_2 rendered the second cyclization more difficult (*vide supra*). Finally fluorinated pentacycle **3i** was formed starting from boronic acid **5e**[13] in a good yield of 51% (entry 9). For all compounds, the same *trans* stereochemistry was obtained as evidenced by X-ray diffraction analysis (**3c** and **3f**) or by ^{1}H NMR by comparison with compound **3a**.

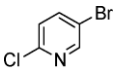
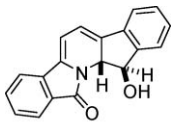
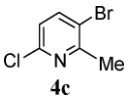
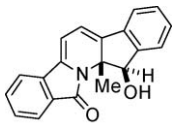
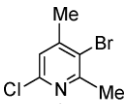
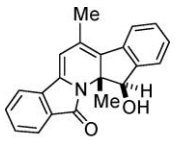
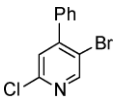
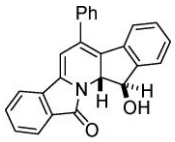
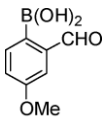
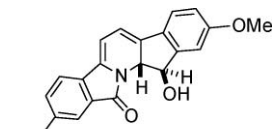
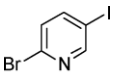
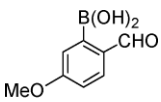
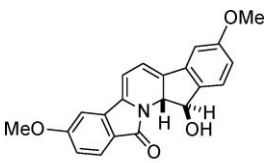
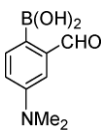
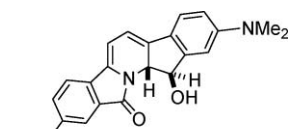
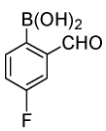
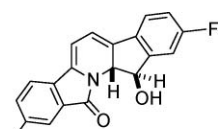
In order to have some insight about the mechanism, different experiments have been conducted. It appeared that the C5 then C2 order of reactivity toward palladium was crucial since 2,5-dibromopyridine **4g** having the reverse order of reactivity[14] failed to give the desired product **3b**. Therefore, C5 functionalised compounds **6a, b** were prepared by coupling pyridines **4b** and **4f** with one equivalent of **5a**. These compounds were then used in the cascade reaction with boronic acid **5a** to give **3b** in 32% and 56% yields respectively (Scheme 3). In both cases, compound **3b** was obtained with the same regio- and stereoselectivity.



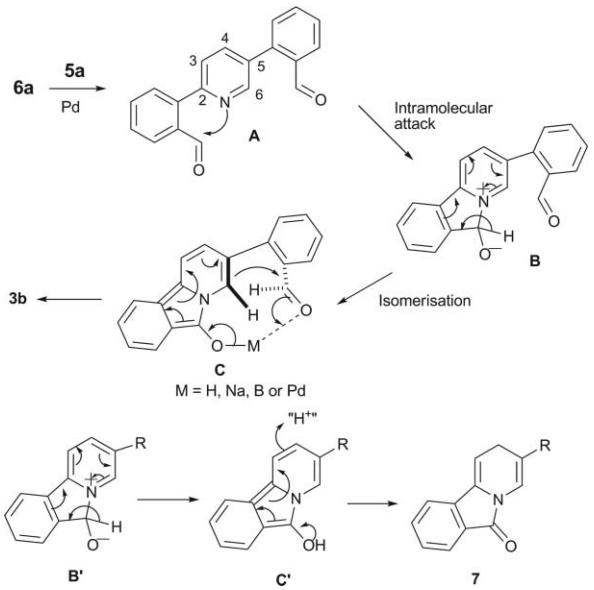
Scheme 3 Prior C5-functionalisation of dihalopyridines.

Considering that aldehyde **6a** is the first intermediate in the cascade process, we assume that a second coupling in 2-position would deliver bis-aldehyde **A** (Scheme 4). Until now, our efforts to isolate this intermediate failed. Intermediate **A** seems to be very reactive, suffering an intramolecular attack of the carboxaldehyde by the pyridine nitrogen to give intermediate **B**. The involvement of a similar intermediate **B′** was already proposed in the synthesis of pyrido[2,1-*a*]isoindolones **7**.[8,15] Indeed, the 1,4-dihydropyridine system was obtained after isomerisation to give **C′** following by proton trapping from the reaction mixture. In the present case, after isomerisation of **B** to **C**, the second carboxadehyde serves as the electrophilic trapping group resulting in the formation of

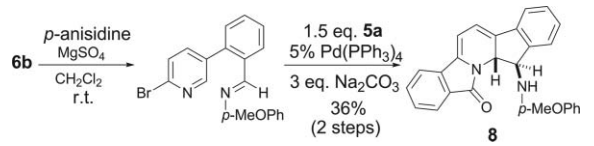
Table 1 Scope of the reaction[a]

Entry	Boronic acid **5**	Pyridine **4**	Pentacycle **3** (Yield)
1	**5a**	 **4b**	 **3b** (57%)
2	**5a**	 **4c**	 **3c** (59%)
3	**5a**	 **4d**	 **3d** (36%)
4	**5a**	 **4e**	 **3e** (60%)
5	 **5b**	**4b**	 **3f** (17%)
6	**5b**	 **4f**	**3f**[c] (55%)
7[b]	 **5c**	**4f**	 **3g** (31%)
8[b]	 **5d**	**4f**	 **3h** (12%)
9[b]	 **5e**	**4f**	 **3i** (51%)

[a] Reaction conditions: **4** (0.5 mmol), **5** (0.5 M in MeOH, 2.5 equiv, 1.25 mmol), $Pd(PPh_3)_4$ (10 mol%, 0.05 mmol), Na_2CO_3 (1M in H_2O, 5 equiv, 2.5 mmol), toluene (5 mL), 100 °C, 12 h. [b] 3 equiv of **5** and 6 equiv of Na_2CO_3 were used. [c] Crystal structure given in the ESI.†



Scheme 4 Proposed mechanism for the cascade process.



Scheme 5 Involvement of an imine in the cascade process.

pentacycle **3b**.[16] Interestingly, changing the electrophile to an imine resulted in the regio- and diastereoselective formation of the new pentacyclic amine **8**[17] in 36% overall yield starting from aldehyde **6b** (Scheme 5).

The observed C6-regioselectivity for compounds **3** and **8** is probably the result of an internal chelation between the two oxygen atoms of intermediate **C**. Indeed, several components of the reaction mixture can be drawn to assist the internal chelation including hydrogen, sodium, boron and palladium. In order to have some insight about the regioselectivity and diastereoselectivity of the reaction, we performed density functional theory (DFT) calculations (at the B3LYP 6-311+G(d,p) level of theory) about the last cyclization step taking the hydrogen as the simplest chelating group leading directly, by hydrogen transfer, to compound **3b** which displays in the crystalline state an intramolecular hydrogen bond between the keto and hydroxyl functions. All the possible conformations of **C** have been considered (**C-3b**, **C-C6cis**, **C-C4trans** and **C-C4cis**) leading respectively to **3b**, the hypothetical product cyclized at C6 with *cis* configuration (**C6cis**) and hypothetical products cyclized at C4 with both configurations (**C4trans** and **C4cis**) (Fig. 3). As shown by DFT calculations, the cyclization at C6 proceeds in the gas phase through an intra-molecular proton transfer from the hydroxyl group to the carboxaldehyde in **C** (**C-3b** and **C-C6cis**), passing through transition states characterized by a strong hydrogen bond between the alcohol and aldehyde oxygen atoms. Both the larger stability of the final *trans* product **3b** over the *cis* form **C6cis** ($\Delta G^{373\,K}$ = 3.48 kcal mol^{-1}) and the smaller activation energy in the case of *trans* configuration compared to the *cis* configuration ($\Delta\Delta^{\ddagger} G^{373\,K}$ = 8.20 kcal mol^{-1}) tend to favor the observed diastereoselectivity. Moreover, the impossibility of the

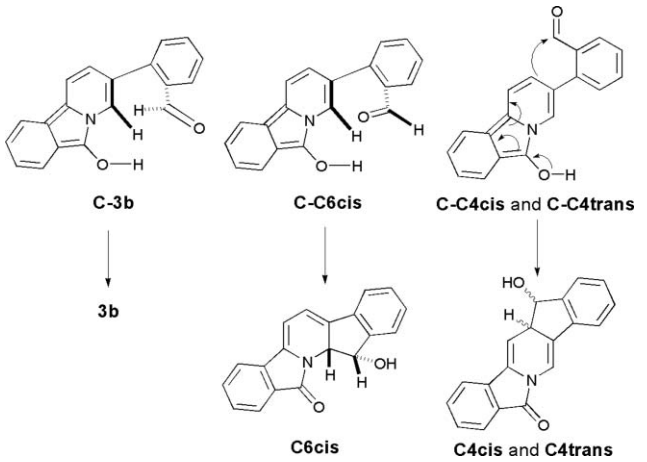


Fig. 3 Structures of compounds considered in the DFT calculations.

intramolecular proton transfer when the cyclization is attempted at C4 (*i.e.* no reaction pathway found between **C-C4cis(*trans*)** and **C4cis(*trans*)**), together with the fact that **C4cis** and **C4trans** are 5.56 and 4.82 kcal mol^{-1} respectively less stable than the experimentally observed structure **3b** also account the obtained regioselectivity (Fig. 4).

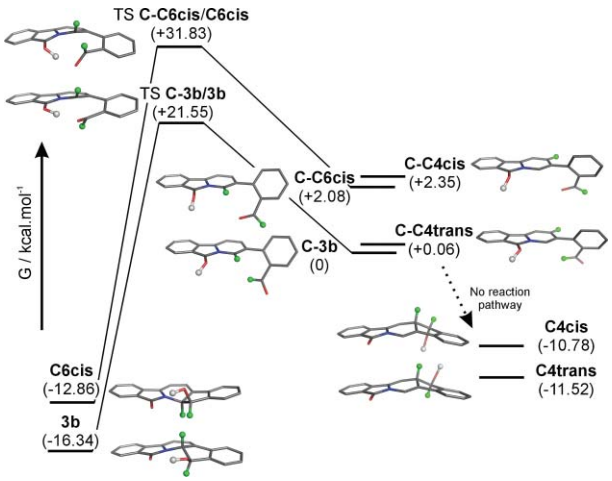


Fig. 4 Energetic profile for the last cyclization step displaying the products of cyclization at C6 and C4, together with the corresponding **C**- intermediates and the associated transitions states structures (TS). Free energies (at 373 K) are given in kcal mol^{-1}. Hydrogen atoms, except those involved in *trans* relationship (in green) and in the intramolecular hydrogen bond are omitted for clarity. All the calculations were performed at the B3LYP 6-311+G(d,p) level of theory.

In summary, we have developed a new cascade reaction that allowed the one-pot synthesis of diversely substituted pentacyclic compounds. The cascade process was initiated by a palladium-catalyzed cross-coupling reaction and was followed by two successive nucleophilic cyclizations; the first cyclization performed on the pyridine nitrogen and the second occurred regioselectively on the adjacent carbon atom. The overall process led to the creation of four chemical bonds with complete regioselective and diastereoselective control interpreted by Density Functional Theory calculations which evidenced the occurrence of an internal chelation in the transition state. In regard to their original

pentacyclic structure and to the strong fluorescence emission observed for **3a**, these new compounds would found important applications in material science and biology.

Acknowledgements

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9 N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457.
10 Compound **3a** fluoresces between 481 and 506 nm with a high quantum yield (91% in CH_2Cl_2). Fluorescein ($\Phi = 95\%$ in 0.1 M NaOH) was used as a reference for the measurement.
11 **3a**: $C_{20}H_{15}NO_2$, $M_r = 301.33$, crystal dimensions: 0.31*0.28*0.10 mm, orthorhombic, space group $P2_12_12_1$, $a = 4.03310(7)$ Å, $b = 15.7754(2)$ Å, $c = 22.1253(3)$ Å, $V = 1407.69(4)$ Å^3, $T = 110(2)$ K, $Z = 4$, $\rho_c = 1.422$ g cm^{-3}, $\mu = 0.09$ mm^{-1}, 23052 reflections collected, 3499 unique reflections, $R_{int} = 0.022$, $2\theta_{max_2} = 69.28°$, 210 parameters, $R_1 = 0.050$, w$R_2 = 0.125$, $\Delta\rho_{min} = -0.308$e.Å^{-3}, $\Delta\rho_{max} = 0.512$e.Å^{-3}. CCDC734892 **3a** contain the detailed crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.ik/data_request/cif.
12 The ^{1}H NMR spectrum of the crude mixture indicated the presence of only one regioisomer. See spectrum in Supporting Information.
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16 For the electrophilic substitution of the pyrido[2,1-*a*]isoindole system, see: C. K. Bradsher and C. F. Voigt, *J. Org. Chem.*, 1971, **36**, 1603.
17 The stereochemistry of **8** was determined by analogy to compound **3a** (J_{Ha-Hb} around 5–6 Hz for **3a** and **8**).

