Comparative Study on the Reactivity of 6-Haloimidazo[1,2-*a*]pyridine Derivatives towards *Negishi*- and *Stille*-Coupling Reactions

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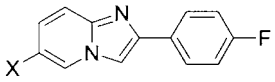
The scope of the *Suzuki*-cross-coupling reaction of 6-haloimidazo[1,2-*a*]pyridines is dependent on the availability of the (hetero)arylboronic acids. Thus, with the aim to develop expanded applications of (hetero)arylations of imidazo[1,2-*a*]pyridines, we investigated the *Negishi*- and *Stille*-cross-coupling reactions at the 6-position. Remarkably, attempts to apply the *Negishi*-cross-coupling conditions to the organozinc derivative prepared from 6-haloimidazo[1,2-*a*]pyridine *via* a lithium–zinc exchange led to the 5-phenyl compound **3** in 54% yield instead of the desired 6-phenyl isomer (*Scheme 1*). In contrast, various commercially available halogenated five- or six-membered-ring heterocycles were efficiently coupled to the 6-(trialkylstannyl)imidazo[1,2-*a*]pyridine under *Stille* conditions (*Table 2*).

Introduction. – The imidazo[1,2-*a*]pyridine scaffold has demonstrated significant and potential biological activities in medicinal chemistry (*e.g.*, as benzodiazepine-receptor ligands (*Ambien*) [1a], antiviral molecules [1b–d], inhibitors of p38 MAP kinase [1e], and ligands for detecting β-amyloid plaques in the brain [1f]). However, despite the intensive research in the imidazo[1,2-*a*]pyridine series, efficient routes that allow rapid access to a variety of analogues with different substituents at the pyridine moiety are still needed to conduct detailed structure–activity-relationship studies. In this area, we have developed new rapid pharmacomodulation methods for these series [2]. Among them, we previously reported *Suzuki*-cross-coupling processes with 6-haloimidazo[1,2-*a*]pyridines and demonstrated the influence of the substituent present at C(2) on the reactivity of the 6-position. The best coupling results were obtained with the 2-aryl derivative [3]. Both aryl- or heteroarylboronic acids were efficiently coupled to 6-haloimidazo[1,2-*a*]pyridines, but this protocol still presents limitations depending on the commercially available boronic acids.

With the aim to develop expanded applications of (hetero)arylations of imidazo[1,2-*a*]pyridines, we now developed new functionalization methods and investigated and compared *Negishi*- and *Stille*-cross-coupling reactions.

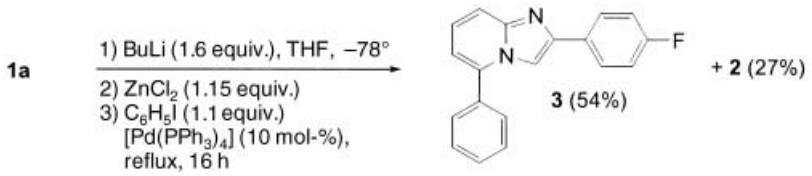
Results and Discussion. – The first part of this study was devoted to the investigation of the applicability of the *Negishi* reaction to the 2-(4-fluorophenyl)-6-haloimidazo[1,2-*a*]pyridines **1a**,**b** [2a][3]. Indeed, consistent with our previous studies in these series, compounds **1a**,**b** are convenient starting materials as they are easily obtained and more stable and reactive than the corresponding 2-alkyl derivatives under *Suzuki* conditions. To the best of our knowledge, no *Negishi* coupling in the imidazo[1,2-*a*]pyridine series has been described in the literature. In a first approach, compound **1b** was reacted with phenylzinc chloride (1.1 equiv.) in the presence of



1a X = Br
b X = I
2 X = H

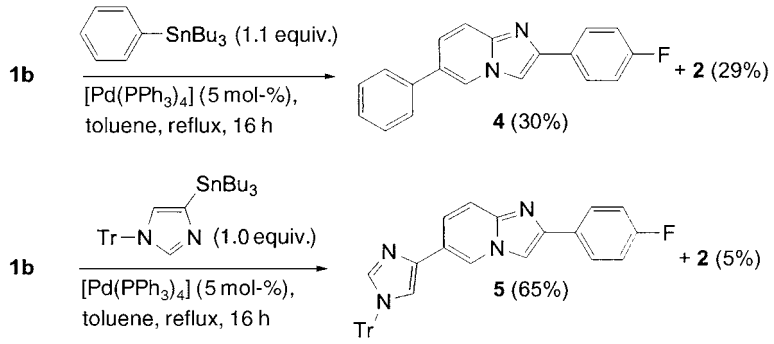
$[Pd(PPh_3)_4]$ (10 mol-%) as catalyst according to the procedure of *Gmeiner* and co-workers [4]. After refluxing for 16 h in THF, only 10% of **2**, *i.e.*, reduced **1b**, was obtained, besides starting material. Thus, we decided to prepare the organozinc derivative of imidazo[1,2-*a*]pyridine. We attempted its formation by Mg–Zn exchange; unfortunately, only 13% of **2** was recovered from the product mixture (data not shown). Finally, we tried to synthesize the organozinc derivative by Li–Zn exchange. For this purpose, compound **1a** was treated with BuLi (1.6 equiv.) and then with $ZnCl_2$ (1.15 equiv.) in THF at $-78°$, and finally overnight with iodobenzene (1.1 equiv.) in the presence of $[Pd(PPh_3)_4]$ (10 mol-%) in refluxing THF. Besides compound **2** obtained in 27% yield, the 5-phenyl derivative **3** was obtained in 54% yield (*Scheme 1*), and not the desired 6-phenyl compound **4**. The structure of **3** as 2-(4-fluorophenyl)-5-phenylimidazo[1,2-*a*]pyridine was established by ^{1}H- and ^{13}C-NMR spectroscopy. We have already reported *cine*-substitutions with compound **1a** [2b] and the interest they present in the direct preparation of 5-functionalized 2-arylimidazo[1,2-*a*]pyridine derivatives. As we have already pointed out, our attempts to form 5-halo-2-phenylimidazo[1,2-*a*]pyridine failed to give the convenient starting material for *Suzuki*-coupling reactions.

Scheme 1



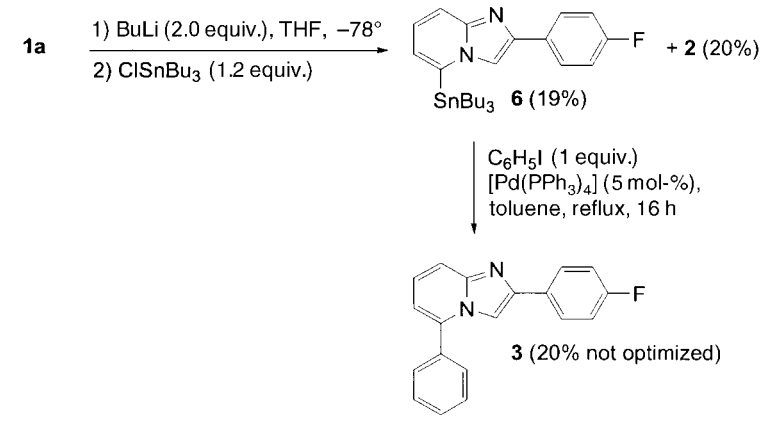
In a second approach, we investigated the *Stille*-cross-coupling reaction. Only two examples of *Stille* reaction have been described in these series [5]. Following the same strategy, we first studied the reaction of **1b** with tributylphenylstannane (1.1 equiv.) in the presence of $[Pd(PPh_3)_4]$ (5 mol-%) as catalyst in refluxing toluene. Under these conditions, the 6-phenyl derivative **4** was obtained in 30% yield besides **2** (29% yield) (*Scheme 2*). As an example of a heteroaryl coupling reaction that can not be performed *via* the *Suzuki* method, we then tried to introduce the 1-trityl-1*H*-imidazol-4-yl moiety. Thus, 4-(tributylstannyl)-1-trityl-1*H*-imidazole [6] (1.1 equiv.) was allowed to react with **1b** according to the same procedure to give the target compound **5** in 65% yield, together with only 5% of **2**.

Scheme 2



Since only few aryl- or heteroarylstannyl derivatives are commercially available, we turned our attention to the preparation of 6-(trialkylstannyl)imidazo[1,2-*a*]pyridines. In a first attempt, we tried to prepare the 2-(4-fluorophenyl)-6-(tributylstannyl)imidazo[1,2-*a*]pyridine from **1a** *via* a Li–Sn exchange. After treatment with BuLi (2 equiv.) in THF at −78°, reaction with tributyl chlorostannane (1.2 equiv.) afforded compound **2** in 20% yield, admixed with 19% of the 5-tributylstannyl compound **6** (*Scheme 3*). The structure of **6** was established by ^{1}H- and ^{13}C-NMR, and by mass spectroscopy. Further confirmation was obtained from the coupling of iodobenzene with **6**, leading to the previously described 5-phenyl derivative **3** in 20% yield (not optimized).

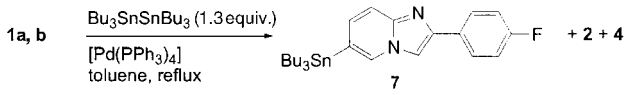
Scheme 3



Then we tried to obtain the 6-(tributylstannyl) derivative using a Mg–Sn exchange. Compound **1a** was treated with ethylmagnesium bromide (3 equiv.) in refluxing THF according to the procedure of *Yamanaka et al.* [7], and the obtained magnesium derivative was exposed to tributylchlorostannane (1.25 equiv.) at room temperature for 18 h; however, after treatment with NH_4Cl, only 49% of **2** were isolated.

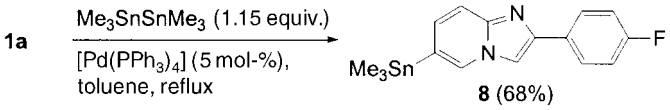
Based on previously reported methods [1f][5a][5b], we then attempted to prepare the organotin compound using a Pd-catalyzed process. Compound **1a** was allowed to react with hexabutyldistannane (2 equiv.) in the presence of $[Pd(PPh_3)_4]$ (8 mol-%) in refluxing toluene according to the procedure of *Katsifis et al.* (*Table 1*) [8]. Under these conditions, the 6-(tributylstannyl) compound **7** was obtained in only 28% yield due to difficulties encountered during its isolation, besides **2** (5%) and the 6-phenyl derivative **4** (5%). Formation of **4** has already been reported in the literature; its phenyl group is provided by an exchange with the triphenylphosphine ligand before the transmetallation step [9]. To optimize the reaction conditions, we decided to use compound **1b** as starting material and to modify the catalyst loading. The best result was obtained with 5 mol-% of $[Pd(PPh_3)_4]$, starting from compound **1b**, leading to **7** in 56% yield (*Table 1*). To overcome the purification problems, we changed to hexamethyldistannane as reactant. Thus, the 6-(trimethylstannyl) compound **8** was obtained from **1a** in 68% yield after an easier purification step than that for compound **7** (*Scheme 4*).

Table 1. *Palladium-Catalyzed Synthesis of 2-(4-Fluorophenyl)-6-(tributylstannyl)imidazo[1,2-a]pyridine* **7**



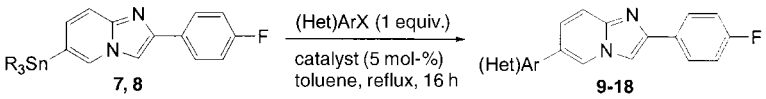
	X	Catalyst loading	Time [h]	Yield [%] of		
			2	**4**	**7**	
1a	Br	8 mol-%	5.5	5	5	28
1b	I	8 mol-%	3	8	8	43
	I	5 mol-%	2.25	5	5	56

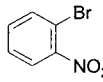
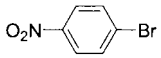
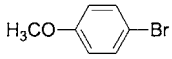
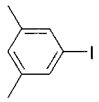
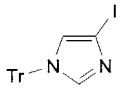
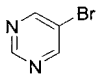
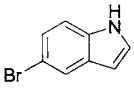
Scheme 4



The *Stille* coupling was then applied to the (trialkylstannyl)imidazo[1,2-*a*]pyridines **7** and **8** and different aryl and heteroarylhalides in the presence of $[Pd(PPh_3)_4]$ as catalyst (*Table 2*). After refluxing overnight in toluene, the desired compounds **9**–**12** were obtained from differently substituted phenyl halides in moderate to good yields (32–77%), the 2- or 4-nitrophenyl compounds **9** and **10**, respectively, being isolated in *ca*. 76% yield. The steric hindrance of the halogenated benzene did not perturb the reactivity. Moreover, the nature of the trialkylstannyl substituent in the starting material did not influence the coupling efficiency of the 4-nitrophenyl bromide (76% yield starting from **7**; 77% yield from **8**). In the cases of compounds **11** and **12**, obtained in *ca*. 40% yield, the 6-phenylimidazo[1,2-*a*]pyridine **4** (*ca*. 30%) was also observed as by-product, but difficult to separate from the target products. Thus, the electron-withdrawing NO_2 group seemed to largely improve the benzene-coupling efficiency compared to electron-donating groups such as MeO or Me. Similarly, different

Table 2. Stille *Cross-Coupling Reaction of (Hetero)arylhalides* ((Het)ArX) *with* **7** *and* **8**



	(Het)ArX	Catalyst	Yield [%]	
			R = Me	R = Bu
9		[Pd(PPh$_3$)$_4$]	75	
10		[Pd(PPh$_3$)$_4$]	77	76
11		[Pd(PPh$_3$)$_4$]	46	43
12		[Pd(PPh$_3$)$_4$]	40	32
5		[Pd(PPh$_3$)$_4$]	traces	
13		[Pd(PPh$_3$)$_4$]		82
14		[Pd(PPh$_3$)$_4$] [PdCl$_2$(MeCN)$_2$]	47 12	36
15		[Pd(PPh$_3$)$_4$]	65	
16		[Pd(PPh$_3$)$_4$]	61	
17		[Pd(PPh$_3$)$_4$]	45	
18		[Pd(PPh$_3$)$_4$] [Pd(PPh$_3$)$_4$] [Pd(Cl$_2$(dppf)] [PdCl$_2$(MeCN)$_2$]	11 6[a]) 12 22	

[a]) Reaction was run for 48 h.

commercially available five- or six-membered-ring heterocycles were introduced at the 6-position of the imidazo[1,2-*a*]pyridine; *e.g.*, the 2-iodothiophene was combined very efficiently with **7** to give **13** in 82% yield. In contrast, only moderate yields were obtained with 3-bromofuran and 5-bromo-1*H*-indole as substrates (47% of **14** and 11% of **18**, resp.). Again, a significant amount of compound **4** was formed during the coupling reactions, making the purification step of the targets **14** and **18** more difficult. To improve the process and to overcome the formation of compound **4**, we decided to switch to bis(acetonitrile)dichloropalladium(II) as catalyst. Unfortunately, in both cases, the coupling rate was slower, and remaining starting material was present in larger amount at the end of the reaction. Also observed were 22% of compound **2** in the furan-coupling reaction. However, as far as compound **18** is concerned, the absence of **4** led to a slight increase of the yield (22%) and largely facilitated the purification. Finally, the reaction with 5-bromopyrimidine, 3-bromopyridine, and 2-bromopyridine provided the desired products **15**–**17** in good yields (45–65%) considering the very easy applicability of this procedure.

Conclusions. – The *Stille* procedure can serve as a valuable tool for the functionalization of C(6) in the imidazo[1,2-*a*]pyridine series. 4-(Tributylstannyl)-1-trityl-1*H*-imidazole could be introduced into 6-iodoimidazo[1,2-*a*]pyridine (**1b**) in 65% yield. To the best of our knowledge, no imidazolylboronic acid synthesis was reported in the literature. The *Stille*-cross-coupling reaction is, thus, a new convenient synthetic approach that allows the introduction of the imidazolyl moiety at C(6). In contrast, the 6-(trimethylstannyl)imidazo[1,2-*a*]pyridine was not reactive in the presence of 4-iodo-1-trityl-1*H*-imidazole. Nevertheless, different halogenated five- or six-membered-ring heterocycles (thiophene, furan, pyrimidine, and pyridine) could be efficiently coupled to 6-(trialkylstannyl)imidazo[1,2-*a*]pyridines. The two steps of this synthetic approach, obtention of the trialkylstannyl derivative and *Stille*-cross-coupling reaction, required a very simple reaction procedure.

Experimental Part

General. Commercial reagents were used as received without additional purification. The compounds tetrakis(triphenylphosphine)palladium(0) [10], 6-bromo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine (**1a**) [3], and 6-iodo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine (**1b**) [2a] were prepared according to literature procedures. All metallation reactions were carried out in a flame-dried glass apparatus under N_2, and reagents were handled with syringes through septa. CC = Column chromatography. M.p.: *Kofler* bench; uncorrected. IR Spectra: in cm^{-1}. NMR Spectra: *Bruker-DPX-200* or *AM-400-WB* instruments; chemical shifts δ in ppm from residual $CHCl_3$ (δ 7.3 (^1H)) and the central resonance of $CDCl_3$ (δ 77.1 (^{13}C)); * means that assigments may be interchanged. EI- and CI-MS: *HP-5989A-GC-MS* spectrometer. Elemental analyses were performed at the University of Rouen (Institut de recherche en Chimie Organique Fine), France.

*2-(4-Fluorophenyl)-5-phenylimidazo[1,2-*a*]pyridine* (**3**): Negishi *Procedure.* At $-78°$, 2.6M BuLi in hexane (0.6 ml, 1.56 mmol) was added to a soln. of **1a** (300 mg, 1.03 mmol) in THF (4.6 ml). After stirring for 1 h, a soln. of freshly fused $ZnCl_2$ (165 mg, 1.21 mmol) in THF (4.6 ml) was added dropwise. After stirring for 1 h at $-78°$, [$Pd(PPh_3)_4$] (119 mg, 10 mol-%) and iodobenzene (231 mg, 1.13 mmol) were added, and the mixture was refluxed for 16 h. After cooling and dilution with sat. aq. NH_4Cl soln., the aq. phase was extracted with CH_2Cl_2, the combined org. layer dried ($CaCl_2$) and evaporated, and the residue purified by CC (silica gel, Et_2O; then neutral alumina, Et_2O/petroleum ether 1:1): **3** (54%). White solid. M.p. 130°. ^1H-NMR ($CDCl_3$): 7.92 (*dd*, *J* = 8.7, 5.4, H–C(2), H–C(6) of C_6H_4); 7.89 (*s*, H–C(3)); 7.58–7.72 (*m*, H–C(8), 5 H of Ph); 7.30 (*dd*, *J* = 9, 6.9, H–C(7)); 7.12 (*t*, *J* = 8.7, H–C(3), H–C(5) of C_6H_4); 6.77 (*dd*, *J* = 6.9, 1.1, H–C(6)). ^{13}C-NMR ($CDCl_3$): 163.1

($J = 245$, C(4) of C_6H_4); 146.9 (C(8a)*); 145.1 (C(2)*); 138.6 (C(5)); 134.9 (C(1) of Ph); 130.5 ($J = 3.5$, C(1) of C_6H_4); 130.2 (C(4) of Ph); 129.7 (C(3), C(5) of Ph); 128.7 (C(2), C(6) of Ph); 128.1 ($J = 8.5$, C(2), C(6) of C_6H_4); 125.6 (C(7)); 116.6 (C(8)); 116.0 ($J = 21.5$, C(3), C(5) of C_6H_4); 113.2 (C(6)); 106.8 (C(3)).

*2-(4-Fluorophenyl)-6-phenylimidazo[1,2-*a*]pyridine* (**4**). Stille *Procedure.* A mixture of **1b** (300 mg, 0.89 mmol), tributylphenylstannane (359 mg, 0.98 mmol), and $[Pd(PPh_3)_4]$ (51.4 mg, 5 mol-%) in toluene (15 ml) was refluxed for 16 h. After cooling, the mixture was diluted with 10% aq. KF soln. and extracted with CH_2Cl_2. The extract was dried ($CaCl_2$) and evaporated, and the residue was purified by CC (silica gel, Et_2O): **4** (30%). White solid. M.p. 191° ([3]: 191°).

*2-(4-Fluorophenyl)-6-[1-(triphenylmethyl)-1*H*-imidazol-4-y]imidazo[1,2-*a*]pyridine* (**5**): Stille *Procedure.* As described for **4**, with **1b** (300 mg, 0.89 mmol), 4-(tributylstannyl)-1-(triphenylmethyl)-1*H*-imidazole (533 mg, 0.89 mmol), $[Pd(PPh_3)_4]$ (51.4 mg, 5 mol-%), and toluene (15 ml): **5** (65%). White solid. M.p. 252°. ^{1}H-NMR ($CDCl_3$): 8.71 (*s*, H–C(5)); 7.95 (*dd*, $J = 8.9$, 5.4, H–C(2), H–C(6) of C_6H_4); 7.83 (*s*, H–C(3)); 7.58 (*d*, $J = 9.7$, H–C(8)); 7.56 (*d*, $J = 1.2$, H–C(5) of Im); 7.43–7.37 (*m*, H–C(7), 9 H of Tr); 7.26–7.10 (*m*, H–C(3), H–C(5) of C_6H_4, H–C(2) of Im, 6 H of Tr). ^{13}C-NMR ($CDCl_3$): 163.1 ($J = 245$, C(4) of C_6H_4); 145.4 (C(2)*); 142.6 (C(1) of Tr); 140.0 (C(2) of Im); 137.9 (C(8a)*); 130.5 ($J = 3$, C(1) of C_6H_4); 130.2 (C(3), C(6) of Tr); 128.7 (C(4) of Tr); 128.6 (C(3), C(5) of Tr); 128.5 (C(4) of Im); 128.0 ($J = 8$, C(2), C(6) of C_6H_4); 124.0 (C(7)); 121.7 (C(5)); 120.7 (C(6)); 118.0 (C(5) of Im); 117.3 (C(8)); 116.0 ($J = 21.5$, C(3), C(5), of C_6H_4); 108.7 (C(3)); 76.1 (C of Tr). Anal. calc. for $C_{35}H_{25}FN_4$: C 80.75, H 4.84, N 10.76; found: C 80.84, H 4.86, N 10.73.

*2-(4-Fluorophenyl)-5-(tributylstannyl)imidazo[1,2-*a*]pyridine* (**6**). To **1a** (300 mg, 1.03 mmol) and THF (5 ml) at −78°, 2.6M BuLi in hexane (1.25 ml, 2.06 mmol) was added. The mixture was stirred at −78° for 1 h, then tributylchlorostannane (402 mg, 1.24 mmol) was added. The soln. was stirred at −78° for 1 h and then at 20° for 2 h. The mixture was diluted with 10% aq. KF soln. and extracted with AcOEt, the combined org. layer was dried ($MgSO_4$) and evaporated, and the residue was purified by CC (silica gel, Et_2O/petroleum ether 3:7): **6** (19%). Colorless oil. ^{1}H-NMR ($CDCl_3$): 7.94 (*dd*, $J = 8.9$, 5.4, H–C(2), H–C(6) of C_6H_4); 7.71 (*s*, H–C(3)); 7.58 (*d*, $J = 9$, H–C(8)); 7.15 (*m*, H–C(7), H–C(3), H–C(5) of C_6H_4); 6.82 (*dd*, $J = 6.4$, 1.2, H–C(6)); 1.67–1.56 (*m*, 3 CH_2); 1.48–1.31 (*m*, 6 CH_2); 1.28–0.89 (*m*, 3 Me). ^{13}C-NMR ($CDCl_3$): 163.0 ($J = 245$, C(4) of C_6H_4); 146.1 (C(8a)*); 144.7 (C(2)*); 143.8 (C(5)); 130.7 ($J = 3$, C(1) of C_6H_4); 128.0 ($J = 8$, C(2), C(6) of C_6H_4); 124.7 (C(7)); 122.6 (C(6)); 117.2 (C(8)); 116.1 ($J = 21.5$, C(3), C(5) of C_6H_4); 110.1 (C(3)); 29.4 (3 CH_2–Sn); 27.7 (3 CH_2); 14.1 (3 Me); 10.6 (3 CH_2). EI-MS: 502 (M^+). Anal. calc. for $C_{25}H_{35}FN_2Sn$: C 59.90, H 7.04, N 5.59; found: C 59.85, H 6.92, N 5.49.

*2-(4-Fluorophenyl)-6-(tributylstannyl)imidazo[1,2-*a*]pyridine* (**7**). A mixture of **1b** (300 mg, 0.89 mmol), hexabutyldistannane (678 mg, 1.16 mmol), and $[Pd(PPh_3)_4]$ (51 mg, 5 mol-%) in toluene (15 ml) was refluxed for 2.25 h. After cooling, the mixture was diluted with 10% aq. KF soln. and then extracted with AcOEt. The combined org. layer was dried ($MgSO_4$) and evaporated, and the residue was purified by CC (alumina, petroleum ether/Et_3N 99:1, then CH_2Cl_2/petroleum ether/Et_3N 50:49:1): **7** (56%). Colorless oil. ^{1}H-NMR ($CDCl_3$): 8.01 (*s*, H–C(5)); 7.95 (*dd*, $J = 8.6$, 5.4, H–C(2), H–C(6) of C_6H_4); 7.80 (*s*, H–C(3)); 7.62 (*d*, $J = 8.8$, H–C(8)); 7.19 (*d*, $J = 8.8$, H–C(7)); 7.13 (*t*, $J = 8.6$, H–C(3), H–C(5) of C_6H_4); 1.68–1.53 (*m*, 3 CH_2–Sn); 1.44–1.15 (*m*, 6 CH_2); 1.11–0.90 (*m*, 3 Me). ^{13}C-NMR ($CDCl_3$): 163.0 ($J = 245$, C(4) of C_6H_4); 146.1 (C(8a)*); 144.7 (C(2)*); 131.8 (C(7)); 130.7 ($J = 3$, C(1) of C_6H_4); 130.5 (C(5)); 128.1 ($J = 8$, C(2), C(6) of C_6H_4); 122.6 (C(6)); 117.4 (C(8)); 116.0 ($J = 21.5$, C(3), C(5) of C_6H_4); 107.3 (C(3)); 29.2 (3 CH_2–Sn); 27.7 (3 CH_2); 14.1 (3 Me); 10.2 (3 CH_2). EI-MS: 502 (M^+). Anal. calc. for $C_{25}H_{35}FN_2Sn$: C 59.90, H 7.04, N 5.59; found: C 59.96, H 7.01, N 5.46.

*2-(4-Fluorophenyl)-6-(trimethylstannyl)-1*H*-imidazo[1,2-*a*]pyridine* (**8**). As described for **7**, with **1a** (807 mg, 2.77 mmol), hexamethyldistannane (1 g, 3.05 mmol), $[Pd(PPh_3)_4]$ (160 mg, 5 mol-%), and toluene (25 ml) for 45 min: **8** (68%). White solid. M.p. 137°. ^{1}H-NMR ($CDCl_3$): 8.03 (*d*, $J = 0.9$, H–C(5)); 7.94 (*dd*, $J = 8.7$, 5.4, H–C(2), H–C(6) of C_6H_4); 7.78 (*s*, H–C(3)); 7.62 (*d*, $J = 8.9$, H–C(8)); 7.21 (*dd*, $J = 8.9$, 0.9, H–C(7)); 7.14 (*t*, $J = 8.7$, H–C(3), H–C(5) of C_6H_4); 0.40 (*s*, 3 Me). ^{13}C-NMR ($CDCl_3$): 163.0 ($J = 245$, C(4) of C_6H_4); 146.1 (C(8a)*); 144.7 (C(2)*); 131.4 (C(7)); 130.1 ($J = 3$, C(1) of C_6H_4); 129.8 (C(5)); 128.0 ($J = 8$, C(2), C(6) of C_6H_4); 122.8 (C(6)); 117.1 (C(8)); 115.9 ($J = 21.5$, C(3), C(5) of C_6H_4); 107.3 (C(3)); −8.95 (3 Me). EI-MS: 361 ([M − 15]$^+$), 331. CI-MS: 376 (M^+). Anal. calc. for $C_{16}H_{17}FN_2Sn$: C 51.25, H 4.57, N 7.47; found: C 51.18, H 4.50, N 7.42.

Stille-*Cross-Coupling Reaction: General Procedure.* To a soln. of 2-(4-fluorophenyl)-(6-trialkylstannyl)-1*H*-imidazo[1,2-*a*]pyridine (0.80 mmol) in toluene (15 ml) were added the aryl or heteroaryl halide (1 equiv.) and $[Pd(PPh_3)_4]$ (46 mg, 5 mol-%). The mixture was refluxed for 16 h. After cooling, the mixture was diluted with a 10% aq. KF soln. The aq. layer was extracted with CH_2Cl_2, the combined org. phase was dried ($CaCl_2$) and evaporated, and the residue was purified by CC.

*2-(4-Fluorophenyl)-6-(2-nitrophenyl)imidazo[1,2-*a*]pyridine* (**9**): CC (alumina, CH_2Cl_2). M.p. 181°. ^{1}H-NMR ($CDCl_3$): 8.15 (*m*, H–C(5)); 8.01 (*dd*, $J = 7.7$, 1.5, H–C(3) of NO_2–C_6H_4); 7.97 (*dd*, $J = 8.8$, 5.3,

H–C(2), H–C(6) of F–C_6H_4); 7.87 (*s*, H–C(3)); 7.73 (*td*, *J* = 7.7, 1.5, H–C(5) of NO_2–C_6H_4); 7.68 (*d*, *J* = 9.3, H–C(8)); 7.64 (*dd*, *J* = 7.7, 1.8, H–C(6) of NO_2–C_6H_4); 7.55 (*td*, *J* = 7.7, 1.8, H–C(4) of NO_2–C_6H_4); 7.17 (*t*, *J* = 8.8, H–C(3), H–C(5) of F–C_6H_4); 7.14 (*dd*, *J* = 9.3, 1.8, H–C(7)). ^{13}C-NMR ($CDCl_3$): 162.9 (*J* = 246, C(4) of F–C_6H_4); 149.6 (C(2) of NO_2–C_6H_4); 146.2 (C(2)*); 145.2 (C(8a)*); 133.3 (C(5) of NO_2–C_6H_4); 132.6 (C(4) of NO_2–C_6H_4); 130.2 (*J* = 3.5, C(1) of F–C_6H_4); 129.6 (C(6) of NO_2–C_6H_4); 128.2 (*J* = 8, C(2), C(6) of F–C_6H_4); 126.2 (C(7)); 125.0 (C(3) of NO_2–C_6H_4); 124.2 (C(5)); 123.8 (C(1) of NO_2–C_6H_4); 117.6 (C(8)); 116.1 (*J* = 21.5, C(3), C(5) of F–C_6H_4); 108.8 (C(3)); C(6) not found. Anal. calc. for $C_{19}H_{12}FN_3O_2$: C 68.47, H 3.63, N 12.61; found: C 68.54, H 3.92, N 12.86.

*2-(4-Fluorophenyl)-6-(4-nitrophenyl)imidazo[1,2-*a*]pyridine* (**10**): CC (alumina, CH_2Cl_2). M.p. 238°. ^{1}H-NMR ((D$_6$)DMSO): 8.44 (*m*, H–C(5)); 8.39 (*d*, *J* = 8.5, H–C(3), H–C(5) of NO_2–C_6H_4); 7.99 (*dd*, *J* = 8.4, 5.4, H–C(2), H–C(6) of F–C_6H_4); 7.95 (*s*, H–C(3)); 7.79 (*m*, H–C(2), H–C(6) of NO_2–C_6H_4, H–C(8)); 7.50 (*dd*, *J* = 9.4, 1.9, H–C(7)); 7.19 (*t*, *J* = 8.4, H–C(3), H–C(5) of F–C_6H_4). ^{13}C-NMR ($CDCl_3$): 162.0 (*J* = 248, C(4) of F–C_6H_4); 146.6 (C(8a)*); 144.5 (C(2)*); 144.2 (C(4)* of NO_2–C_6H_4); 143.2 (C(1)* of NO_2–C_6H_4); 260.2 (*J* = 2.8, C(1) of F–C_6H_4); 127.6 (*J* = 9, C(2), C(6) of F–C_6H_4); 127.4 (C(3), C(5) of NO_2–C_6H_4); 125.6 (C(5)); 124.4 (C(7)); 124.1 (C(2), C(6) of NO_2–C_6H_4); 122.9 (C(6)); 116.8 (C(8)); 115.6 (*J* = 21.5, C(3), C(5) of F–C_6H_4); 109.6 (C(3)). Anal. calc. for $C_{19}H_{12}FN_3O_2$: C 68.47, H 3.63, N 12.61; found: C 68.77, H 3.46, N 12.65.

*2-(4-Fluorophenyl)-6-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine* (**11**): CC (silica gel, petroleum ether, then petroleum ether/Et_2O 1:1). M.p. 171°. ^{1}H-NMR ($CDCl_3$): 8.27 (*m*, H–C(5)); 7.97 (*dd*, *J* = 8.7, 5.5, H–C(2), H–C(6) of F–C_6H_4); 7.88 (*s*, H–C(3)); 7.69 (*d*, *J* = 9.3, H–C(8)); 7.53 (*d*, *J* = 8.6, H–C(2), H–C(6) of MeO–C_6H_4); 7.45 (*dd*, *J* = 9.3, 1.8, H–C(7)); 7.17 (*t*, *J* = 8.7, H–C(3), H–C(5) of F–C_6H_4); 7.05 (*d*, *J* = 8.6, H–C(3), H–C(5) of MeO–C_6H_4); 3.91 (*s*, MeO). ^{13}C-NMR ($CDCl_3$): 163.1 (*J* = 245, C(4) of F–C_6H_4); 160.0 (C(4) of MeO–C_6H_4); 145.7 (C(2)*); 145.3 (C(8a)*); 130.4 (*J* = 3, C(1) of F–C_6H_4); 130.0 (C(1) of MeO–C_6H_4); 128.4 (C(2), C(6) of MeO–C_6H_4); 128.1 (*J* = 8, C(2), C(6) of F–C_6H_4); 127.1 (C(6)); 126.0 (C(7)); 122.6 (C(5)); 117.6 (C(8)); 116.1 (*J* = 21.5, C(3), C(5) of F–C_6H_4); 115.0 (C(3), C(5) of MeO–C_6H_4); 108.5 (C(3)); 55.8 (MeO). Anal. calc. for $C_{20}H_{15}FN_2O$: C 75.46, H 4.75, N 8.80; found: C 75.68, H 4.49, N 8.77.

*6-(3,5-Dimethylphenyl)-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine* (**12**): CC (silica gel, AcOEt/petroleum ether 1:1; then neutral alumina, CH_2Cl_2). M.p. 134°. ^{1}H-NMR ($CDCl_3$): 8.31 (*dd*, *J* = 1.6, 0.8, H–C(5)); 7.98 (*dd*, *J* = 9, 5.4, H–C(2), H–C(6) of C_6H_4); 7.88 (*s*, H–C(3)); 7.72 (*dd*, *J* = 9.2, 0.8, H–C(8)); 7.47 (*dd*, *J* = 9.2, 1.6, H–C(7)); 7.22 (*m*, H–C(2), H–C(6) of C_6H_3); 7.17 (*t*, *J* = 9, H–C(3), H–C(5) of C_6H_4); 7.09 (*m*, H–C(4) of C_6H_3); 2.44 (*s*, 2 Me). ^{13}C-NMR ($CDCl_3$): 164.1 (*J* = 245.3, C(4) of C_6H_4); 145.7 (C(8a)*); 145.5 (C(2)*); 139.1 (C(3), C(5) of C_6H_3); 137.5 (C(1) of C_6H_3); 130.4 (*J* = 3, C(1) of C_6H_4); 130.0 (C(4) of C_6H_3); 128.0 (*J* = 8, C(2), C(6) of C_6H_4); 127.6 (C(6)); 126.1 (C(7)); 125.1 (C(2), C(6) of C_6H_3); 123.1 (C(5)); 117.5 (C(8)); 116.0 (*J* = 21.5, C(3), C(5) of C_6H_4); 108.5 (C(3)); 21.8 (2 Me). Anal. calc. for $C_{21}H_{17}FN_2$: C 79.72, H 5.42, N 8.85; found: C 79.74, H 5.36, N 8.91.

*2-(4-Fluorophenyl)-6-(2-thienyl)imidazo[1,2-*a*]pyridine* (**13**): CC (silica gel, CH_2Cl_2; then silica gel, Et_2O). M.p. 174°. ^{1}H-NMR ($CDCl_3$): 8.33 (*dd*, *J* = 1.8, 0.9, H–C(5)); 7.94 (*dd*, *J* = 8.9, 5.4, H–C(2), H–C(6) of C_6H_4); 7.81 (*s*, H–C(3)); 7.64 (*dd*, *J* = 9.4, 0.9, H–C(8)); 7.44 (*dd*, *J* = 9.4, 1.8, H–C(7)); 7.34 (*dd*, *J* = 5.1, 1.2, H–C(5) of Th); 7.29 (*dd*, *J* = 3.6, 1.2, H–C(3) of Th); 7.15 (*t*, *J* = 8.9, H–C(3), H–C(5) of C_6H_4); 7.13 (*dd*, *J* = 5.1, 3.6, H–C(4) of Th). ^{13}C-NMR ($CDCl_3$): 163.2 (*J* = 245.5, C(4) of C_6H_4); 145.9 (C(8a)*); 145.2 (C(2)*); 140.2 (C(2) of Th); 130.2 (*J* = 3.5, C(1) of C_6H_4); 128.6 (C(4) of Th); 128.1 (*J* = 8, C(2), C(6) of C_6H_4); 125.6 (C(5) of Th); 125.2 (C(7)); 124.3 (C(3) of Th); 122.0 (C(5)); 121.3 (C(6)); 117.7 (C(8)); 116.1 (*J* = 21.5, C(3), C(5) of C_6H_4); 108.6 (C(3)). Anal. calc. for $C_{17}H_{11}FN_2S$: C 69.37, H 3.77, N 9.52; found: C 69.39, H 3.70, N 9.48.

*2-(4-Fluorophenyl)-6-(furan-3-yl)imidazo[1,2-*a*]pyridine* (**14**): CC (silica gel, Et_2O/petroleum ether 1:1). M.p. 193°. ^{1}H-NMR ($CDCl_3$): 8.22 (*dd*, *J* = 1.7, 1, H–C(5)); 7.95 (*dd*, *J* = 8.9, 5.4, H–C(2), H–C(6) of C_6H_4); 7.82 (*s*, H–C(3)); 7.76 (*dd*, *J* = 1.6, 0.9, H–C(2) of Fur); 7.65 (*d*, *J* = 9.3, H–C(8)); 7.56 (*dd*, *J* = 1.9, 1.6, H–C(5) of Fur); 7.34 (*dd*, *J* = 9.3, 1.7, H–C(7)); 7.15 (*t*, *J* = 8.9, H–C(3), H–C(5) of C_6H_4); 6.69 (*dd*, *J* = 1.9, 0.9, H–C(4) of Fur). ^{13}C-NMR ($CDCl_3$): 163.2 (*J* = 245, C(4) of C_6H_4); 145.6 (C(8a)*); 145.3 (C(2)*); 144.6 (C(5) of Fur); 139.1 (C(2) of Fur); 130.3 (*J* = 3, C(1) of C_6H_4); 128.1 (*J* = 8, C(2), C(6) of C_6H_4); 125.0 (C(7)); 123.1 (C(3) of Fur); 121.8 (C(5)); 118.9 (C(6)); 117.9 (C(8)); 116.1 (*J* = 21.5, C(3), C(5) of C_6H_4); 108.7 (C(4) of Fur); 108.5 (C(3)). Anal. calc. for $C_{17}H_{11}FN_2O$: C 73.37, H 3.98, N 10.07; found: C 73.15, H 3.76, N 9.96.

*2-(4-Fluorophenyl)-6-(pyrimidin-5-yl)imidazo[1,2-*a*]pyridine* (**15**): Upon cooling, the coupling product precipitated and was filtered off and washed with Et_2O. M.p. >260°. ^{1}H-NMR ((D$_6$)DMSO): 9.24 (*s*, H–C(4), H–C(6) of Py); 9.23 (*s*, H–C(2) of Py); 9.11 (*m*, H–C(5)); 8.45 (*s*, H–C(3)); 8.08 (*dd*, *J* = 8.6, 5.6, H–C(2), H–C(6) of C_6H_4); 7.76 (*m*, H–C(7), H–C(8)); 7.31 (*t*, *J* = 8.6, H–C(3), H–C(5) of C_6H_4). ^{13}C-NMR ((D$_6$)DMSO): 162.9 (*J* = 243, C(4) of C_6H_4); 158.3 (C(2) of Py); 155.5 (C(4), C(6) of Py); 145.3 (C(8a)*); 145.1 (C(2)*); 131.3 (C(5) of Py); 131.0 (*J* = 3, C(1) of C_6H_4); 128.6 (*J* = 8, C(2), C(6) of C_6H_4); 126.0 (C(5)); 125.1

(C(7)); 120.1 (C(6)); 117.9 (C(8)); 116.5 (J = 21, C(3), C(5) of C_6H_4); 110.5 (C(3)). Anal. calc. for $C_{17}H_{11}FN_4$: C 70.34, H 3.82, N 19.30; found: C 70.32, H 3.31, N 19.22.

*2-(4-Fluorophenyl)-6-(pyridin-3-yl)imidazo[1,2-*a*]pyridine* (**16**): CC (silica gel, AcOEt/petroleum ether 1:1; then silica gel, AcOEt). M.p. 173–174°. ^{1}H-NMR ($CDCl_3$): 8.88 (*d*, J = 2.3, H–C(2) of Py); 8.69 (*dd*, J = 4.8, 1.6, H–C(6) of Py); 8.34 (*dd*, J = 1.7, 0.9, H–C(5)); 7.97 (*dd*, J = 8.8, 5.4, H–C(2), H–C(6) of C_6H_4); 7.91 (*s*, H–C(3)); 7.88 (*dd*, J = 8, 2.3, H–C(4) of Py); 7.75 (*dd*, J = 9.3, 0.9, H–C(8)); 7.46 (*dd*, J = 8, 4.8, H–C(5) of Py); 7.43 (*dd*, J = 9.3, 1.7, H–C(7)); 7.17 (*t*, J = 8.8, H–C(3), H–C(5) of C_6H_4). ^{13}C-NMR ($CDCl_3$): 163.2 (J = 245.5, C(4) of C_6H_4); 149.6 (C(6) of Py); 148.3 (C(2) of Py); 146.3 (C(8a)*); 145.4 (C(2)*); 134.6 (C(4) of Py); 133.4 (C(3) of Py); 130.2 (J = 3, C(1) of C_6H_4); 128.2 (J = 8, C(2), C(6) of C_6H_4); 125.2 (C(7)); 124.2 (C(5) of Py); 124.1 (C(6)); 123.5 (C(5)); 118.2 (C(8)); 115.9 (J = 21.5, C(3), C(5) of C_6H_4); 108.7 (C(3)). Anal. calc. for $C_{18}H_{12}FN_3$: C 74.73, H 4.18, N 14.52; found: C 74.20, H 4.12, N 14.49.

*2-(4-Fluorophenyl)-6-(pyridin-2-yl)imidazo[1,2-*a*]pyridine* (**17**): CC (silica gel, AcOEt/petroleum ether 1:1; then neutral alumina, CH_2Cl_2). M.p. 183–184°. ^{1}H-NMR ($CDCl_3$): 8.89 (*dd*, J = 1.6, 1, H–C(5)); 8.69 (*dd*, J = 4.8, 0.8, H–C(6) of Py); 7.95 (*dd*, J = 8.6, 5.4, H–C(2), H–C(6) of C_6H_4); 7.84 (*s*, H–C(3)); 7.83–7.70 (*m*, H–C(8), H–C(3), H–C(4) of Py); 7.67 (*dd*, J = 9.1, 1.6, H–C(7)); 7.27 (*dd*, J = 7.3, 4.8, H–C(5) of Py); 7.14 (*t*, J = 8.6, H–C(3), H–C(5) of C_6H_4). ^{13}C-NMR ($CDCl_3$): 163.2 (J = 245.5, C(4) of C_6H_4); 154.3 (C(2) of Py); 150.3 (C(6) of Py); 146.1 (C(2)*); 145.9 (C(8a)*); 137.5 (C(3) of Py); 130.2 (J = 3, C(1) of C_6H_4); 128.1 (J = 8, C(2), C(6) of C_6H_4); 125.4 (C(6)); 124.9 (C(5)); 124.2 (C(4) of Py); 123.0 (C(5) of Py); 120.2 (C(7)); 117.4 (C(8)); 116.1 (J = 21.5, C(3), C(5) of C_6H_4); 108.9 (C(3)). Anal. calc. for $C_{18}H_{12}FN_3$: C 74.73, H 4.18, N 14.52; found: C 74.36, H 4.09, N 14.45.

*6-(1*H*-Indol-5-yl)-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine* (**18**): CC (silica gel, Et_2O), then recristallization from MeOH. M.p. 246–247°. IR (neat): 3132. ^{1}H-NMR ((D$_6$)DMSO): 11.26 (br. *s*, NH); 8.83 (*s*, H–C(5)); 8.39 (*s*, H–C(3)); 8.04 (*dd*, J = 8.4, 5.4, H–C(2), H–C(6) of C_6H_4); 7.90 (*s*, H–C(4) of Ind); 7.66 (*m*, H–C(7), H–C(8)); 7.56–7.43 (*m*, H–C(2), H–C(6), H–C(7) of Ind); 7.30 (*t*, J = 8.4, H–C(3), H–C(5) of C_6H_4); 6.53 (br. *s*, H–C(3) of Ind). ^{13}C-NMR ((D$_6$)DMSO): 162.7 (J = 243, C(4) of C_6H_4); 144.9 (C(8a)*); 144.6 (C(2)*); 136.4 (C(7a) of Ind); 131.4 (J = 3, C(1) of C_6H_4); 129.2 (C(3a) of Ind); 128.4 (C(5)* of Ind); 128.3 (J = 8, C(2), C(6) of C_6H_4); 127.9 (C(2) of Ind); 127.2 (C(7)); 126.7 (C(6)*); 124.0 (C(5)); 120.9 (C(6) of Ind); 119.0 (C(4) of Ind); 117.3 (C(8)); 116.5 (J = 21.5, C(3), C(5) of C_6H_4); 112.9 (C(7) of Ind); 110.1 (C(3)); 102.4 (C(3) of Ind). Anal. calc. for $C_{21}H_{14}FN_3$: C 77.05, H 4.31, N 12.84; found: C 77.10, H 4.25, N 12.78.

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