Regiocontrolled Microwave Assisted Bifunctionalization of 7,8-Dihalogenated Imidazo[1,2-\textit{a}]pyridines: A One Pot Double-Coupling Approach

Emilie Marie, Sébastien Bouclé, Cécile Enguehard-Gueiffier * and Alain Gueiffier

Recherche et Innovation en Chimie Médicinale, UMR INRA 1282 Infectiologie et Santé Publique, Université F. Rabelais, 31 avenue Monge, F-37200 Tours, France;
E-Mails: emilie.marie-2@etu.univ-tours.fr (E.M.); s.boucle@hotmail.fr (S.B.); alain.gueiffier@univ-tours.fr (A.G.)

* Author to whom correspondence should be addressed;
E-Mail: cecile.enguehard-gueiffier@univ-tours.fr; Tel.: +33-247-367-172; Fax: +33-247-367-288.

Received: 27 July 2012; in revised form: 31 August 2012 / Accepted: 3 September 2012 / Published: 6 September 2012

Abstract: The reactivity of the 7-chloro-8-iodo- and 8-chloro-7-iodoimidazo[1,2-\textit{a}]pyridines 1a–e diversely substituted on the 2 position, towards Suzuki-Miyaura, Sonogashira, and Buchwald-Hartwig cross-coupling reactions as well as cyanation was evaluated. Various methodologies are proposed to introduce aryl, heteroaryl, alkyne, amine or cyano groups in the two positions depending on the nature of the substituent present in position 2. In both series, the substitution of the iodine atom was totally regioselective and the difficulty was to substitute the chlorine atom in a second step. Until now, only hetero(aryl) groups could be introduced though Suzuki-Miyaura cross-coupling. We overcame this problem evaluating both regioisomers in parallel. The double coupling approach was also studied allowing the one pot Suzuki/Suzuki, cyanation/Sonogashira and cyanation/Buchwald reactions leading to polyfunctionnalized imidazo[1,2-\textit{a}]pyridines.

Keywords: imidazo[1,2-\textit{a}]pyridine; metallo-catalyzed cross-coupling reaction; microwave irradiation; Suzuki-Miyaura cross-coupling; Sonogashira cross-coupling; cyanation; Buchwald-Hartwig cross-coupling
1. Introduction

Over the last decades, the imidazo[1,2-\(a\)]pyridine ring has been considered an important scaffold for biomolecules in medicinal chemistry, with a broad spectrum of potential therapeutic properties such as, for example, antibacterial [1], HIV inhibitory [2], anti-inflammatory [3] and anticancer [4] properties. Moreover, several drug formulations containing imidazo[1,2-\(a\)]pyridine derivatives, are marketed in the anxiolytic/hypnotic area (zolpidem, alpidem) and GDR/peptic ulcer therapy (zolimidine). Therefore, convergent, rapid, and easy to implement functionalization routes are still needed to introduce various modulations on this skeleton, in order to complete the putative biological activities evaluation of these series of compounds.

In the course of our work evaluating the chemical and pharmacological properties of the imidazo[1,2-\(a\)]pyridine series, we further pursued investigations on methods of functionalization which would allow the rapid preparation of a number of structural variants. We thus became interested in the regiocontrolled substitution of 7,8-dihalogenated imidazo[1,2-\(a\)]pyridine derivatives. The introduction of various substituents such as aryl, heteroaryl, cyano and amino groups was studied and our results in this area are the subject of this manuscript. Analogous works on double-coupling approach in positions 3 and 6, or positions 6 and 8 of this scaffold were already presented by other groups [5,6].

Recently in the literature, a few pharmacomodulation studies of the imidazo[1,2-\(a\)]pyridine scaffold required this type of 7,8-disubstitution pattern for their purposes. Kettle et al. described a two-step introduction of aryl groups in these 7 and 8 positions [7]. In our work, we propose an alternative one-step procedure. Moreover, Trabanco et al. synthesized 7-aryl-8-cyano or 7-aryl-8-chloroimidazo[1,2-\(a\)]pyridine derivatives starting from the convenient 7,8-dihalogenated starting material [8]. Concerning older publications [9–11], authors usually introduced the cyano group on the pyridine ring before cyclisation, increasing the number of synthetic steps.

2. Results and Discussion

In order to control the regioselectivity of the dissubstitution pattern in positions 7 and 8 of the imidazo[1,2-\(a\)]pyridine scaffold, we chosen as starting materials the 7-chloro-8-ido- and 8-chloro-7-iodoimidazo[1,2-\(a\)]pyridines \(1a\)–\(e\) diversely substituted on the 2 position. Both series were studied concomitantly in order to offer the largest scope of functionalization. To our knowledge, the analogous 7-bromo-8-ido- and 8-bromo-7-iodoimidazo[1,2-\(a\)]pyridines are still not described in the literature.

Compounds \(1a\)–\(e\) were obtained in 71–100\% yields by condensation of 2-amino-3-chloro-4-iodopyridine or 2-amino-4-chloro-3-iodopyridine, with the corresponding \(\alpha\)-halogenoketones. Different groups (phenyl, ethyl carboxylate, methyl) were considered in position 2 to overview the influence of this position on the reactivity of the 7 and 8 positions of the imidazo[1,2-\(a\)]pyridine series towards various cross-coupling reactions. Indeed, such an influence of the 2-substituent on the reactivity of not only position 3 [12], but also of position 6 [13], was previously noticed by our group.
2.1. Regioselective Substitution of the Iodine Atom of Compounds 1a–e

Initial work focused on the regioselective substitution of iodine atom of compounds 1a–e. Three classical cross-coupling reactions were studied: Suzuki-Miyaura, Sonogashira and Buchwald-Hartwig reactions, as well as cyanation reactions (Schemes 1–4).

2.1.1. Suzuki Cross-Coupling on Compounds 1a–c

Suzuki cross-coupling standard conditions were first applied to 1a–c using 4-fluorophenylboronic acid (2 equiv.), PdCl₂(dppf) (0.05 equiv.), Na₂CO₃ (3 equiv.) in a mixture of THF-H₂O at 75 °C overnight leading to compounds 2–4 in 87%–90% yields (Scheme 1). Total conversion and regioselectivity were observed. No influence of the 2 position was noticed.

**Scheme 1.** Suzuki cross-coupling reaction on position 7 of compounds 1a–c (isolated yields).

```
\begin{align*}
\text{F} & \text{Cl} \\
& \text{N} \text{R}_2 \\
\text{1a} \text{ R}_2 = \text{Phenyl} & \text{2} \text{ R}_2 = \text{Phenyl 90\%} \\
\text{1b} \text{ R}_2 = \text{CO}_2\text{Et} & \text{3} \text{ R}_2 = \text{CO}_2\text{Et 87\%} \\
\text{1c} \text{ R}_2 = \text{CH}_3 & \text{4} \text{ R}_2 = \text{CH}_3 89\% \\
\end{align*}
```

*Reaction conditions*: 4-fluorophenylboronic acid (2 equiv.), PdCl₂(dppf) (0.05 equiv.), Na₂CO₃ (3 equiv.), THF/H₂O, 75 °C, overnight, sealed tube.

2.1.2. Sonogashira Cross-Coupling on Compounds 1a–e

Optimization of Sonogashira cross-coupling conditions was conducted in position 8 of compound 1d using 4-ethynyltoluene (3 equiv.), PdCl₂(dppf) (0.05 equiv.), TEA (5 equiv.) and CuI (0.1 equiv.) in DMF at 90 °C for 1 h under microwave irradiation [14]. A partial conversion was observed (NMR yield of 29%) and a large amount of starting material was recovered, that could not be separated from the attempted product. A methodology developed in our laboratory using 4-ethynyltoluene (1.3 equiv.), Pd(PPh₃)₄ (0.1 equiv.), PCy₃HBF₄ (0.3 equiv.) in the presence of t-BuONa (3 equiv.) and CuI (0.4 equiv.) in DMF at 100 °C for 20 min under microwave irradiation was then tested. A total dehalogenation occurred in position 8. Thus, we decided to work at lower temperature (90 °C), to change the base to Et₃N (5 equiv.) and to lower the amount of CuI (0.2 equiv.). Under these conditions, a total conversion was observed allowing the purification of the attempted compounds 7 and 8 in moderate yields (60 and 50%, respectively) (Scheme 2). The position 7 appeared to be more reactive towards these Sonogashira conditions than position 8, leading to compounds 5 and 6 in 71% and 77% yields respectively (Scheme 2). The presence of N₁ in close vicinity of position 8 may explain its lower reactivity. Moreover, the 2-ester function seems to lower the reactivity of the 8 position towards the Sonogashira cross-coupling.
Scheme 2. Sonogashira cross-coupling reaction on compounds 1a, 1b, 1d, 1e (isolated yields).

Reaction conditions: 4-ethynyltoluene (1.3 equiv.), Pd(PPh₃)₄ (0.1 equiv.), PCy₃HBF₄ (0.3 equiv.), Et₃N (5 equiv.), CuI (0.2 equiv.), DMF, 90 °C, 30 min, MW.

2.1.3. Cyanation on Compounds 1a–e

Then, we considered the cyanation of compounds 1 (Scheme 3). According to a literature procedure, reaction of 1a with CuCN (1.6 equiv.) in acetonitrile at 160 °C for 30 min under microwaves irradiation led to 9 in 32% yield [8]. We then changed the solvent to DMF and reaction of 1a or 1b with CuCN (1.3 equiv.) at 200 °C for 15 min under microwave irradiation, afforded 9 and 10 in respective yields of 72 and 63%. Applying the same conditions to compounds 1d–e led to formation of dehalogenated compounds. The 8-cyano compounds 11 and 12 were obtained after reaction at 150 °C for 15 min in 69% and 46% yields, respectively. Again, the 2-ester function seems to lower the reactivity of the 8 position towards the cyanation reaction.

Scheme 3. Cyanation on compounds 1a, 1b, 1d, 1e (isolated yields).

Reaction conditions: CuCN (1.3 equiv.), 200 °C or 150 °C, 15 min, MW.
2.1.4. Buchwald-Hartwig Cross-Coupling on Compounds 1a–e

Finally, we carried out a short study of Buchwald-Hartwig amination to optimize the aniline cross-coupling conditions, depending on the substituent present in position 2 of the imidazo[1,2-a]pyridine ring (Scheme 4). A nucleophilic substitution was first attempted following the procedure described by Tresadern et al. for the coupling of alkylpiperazine to 7-iodo-8-cyanoimidazo[1,2-a]pyridine derivatives [9]. Treatment of 1a with N-methylpiperazine (3 equiv.), DIPEA (4 equiv.) in acetonitrile at 180 °C for 1 h under microwave irradiation led exclusively to a mixture of starting material and deiodinated compound. The 8-cyano group appears to greatly increase the reactivity of the adjacent position, allowing a nucleophilic substitution.

Scheme 4. Buchwald-Hartwig cross-coupling on compounds 1a, 1b, 1d, 1e (isolated yields).

| Scheme 4 | Buchwald-Hartwig cross-coupling on compounds 1a, 1b, 1d, 1e (isolated yields). |
|----------|-----------------------------------------------------------------------------|
| 1a R2 = Phenyl                                                                 |
| 1b R2 = CO2Et                                                                     |
| 1c                                                                                     |
| 1d R2 = Phenyl                                                                 |
| 1e R2 = CO2Et                                                                     |
| R2NH2                                | Cl | R2NH2                                | Cl |
| 13 R2 = R7 = Phenyl 48%a or 41%b                                                      |
| 14 R2 = CO2Et R7 = C6H11 40%c                                                        |
| 15 R2 = R8 = Phenyl 51%a                                                             |
| 16 R2 = CO2Et R8 = C6H11 66%c                                                        |

Reaction conditions: a aniline (3 equiv.), Pd(PPh3)4 (0.1 equiv.), rac-BINAP (0.3 equiv.), t-BuONa (3 equiv.), CuI (0.2 equiv.), DME, 85 °C, 45 min, MW; b aniline (1.1 equiv.), Pd2dba3 (0.05 equiv.), rac-BINAP (0.1 equiv.), t-BuONa (3 equiv.), dioxane, 80 °C, 30 min, MW; c cyclohexylamine (13 equiv.), Pd2dba3 (0.04 equiv.), Xantphos (0.12 equiv.), K2CO3 (15 equiv.), dioxane, 150 °C, 1 h 15 min, MW.

In view to study one-pot heterogeneous double-coupling of aryl and amine groups in positions 7 and 8, Pd(PPh3)4 was preferred as catalyst in a first attempt. Thus, the reaction was achieved using aniline (1 equiv.), Pd(PPh3)4 (0.1 equiv.), Xantphos (0.3 equiv.), t-BuONa (3 equiv.) in dioxane, but only starting material was recovered after 90 min at 100 °C under microwave irradiation. In the same way, only traces of the attempted compounds 13 were obtained using the following conditions: aniline (3 equiv.), Pd(PPh3)4 (0.1 equiv.), rac-BINAP (0.3 equiv.), t-BuONa (3 equiv.) in DME at 85 °C after 2 h 30 min under microwave irradiation. Therefore, we attempted these last conditions but with a catalytic amount of CuI (0.2 equiv.). We noticed that the reaction was completed after 45 min at 85 °C under microwaves and we obtained 13 in 48% yield. Under the same conditions, we synthesized 15 in 51% yield (Scheme 4).

Several metallo-catalyzed procedures commonly used for aminations were also applied to compound 1a. Only traces of the attempted compounds 13 were obtained using the following conditions: aniline (1 equiv.), Pd(OAc)2 (0.1 equiv.), rac-BINAP (0.3 equiv.), t-BuONa (3 equiv.) in toluene for 90 min at 90 °C under microwave irradiation. Nevertheless, compound 13 was afforded in
41% yield using aniline (1.1 equiv.), Pd2dba3 (0.05 equiv.), rac-BINAP (0.1 equiv.), t-BuONa (3 equiv.) in dioxane at 80 °C for 30 min in a microwave apparatus. Thus, amination in positions 7 and 8 may be achieved through different methodologies with similar yields of around 40%–50%.

The presence of the ester group in compounds 1b and 1e prevented us from using t-BuONa as base for the amination reaction. The different approaches evaluated to introduce the aniline were unsuccessful. We then decided to work with cyclohexylamine. The coupling reaction was first conducted on 1b using cyclohexylamine (2 equiv.), Pd(PPh3)4 (0.1 equiv.), Xantphos (0.2 equiv.), K2CO3 (15 equiv.) in DMF at 160 °C during 1 h under microwave irradiation. This reaction did not afford the expected product 14. The reaction was then attempted on 1e using cyclohexylamine (13 equiv.), Pd2dba3 (0.04 equiv.), Xantphos (0.12 equiv.), K2CO3 (15 equiv.) in dioxane for 1 h 15 min at 150 °C under microwaves, leading to 16 in 66% yield (Table 2). These last conditions applied to 1b led to 14 in 40% yield (Scheme 4).

2.2. Substitution of the Chlorine Atom in Position 8 of Compounds 2–6, 9–10, 14

In a second part, we focused on the substitution of the chlorine atom in position 8 of the 7-substituted imidazo[1,2-a]pyridines 2–6, 9–10, 14. The reactivity of this position was evaluated towards the Suzuki-Miyaura cross-coupling reaction (Table 1). In a first attempt, the reaction was performed on the ester compound 3 using 4-tolylboronic acid (1.8 equiv.), Pd(PPh3)4 (0.05 equiv.), Na2CO3 (1.5 equiv.), in DME/H2O at 75 °C in a sealed tube, leading to the target compound 17 in 53% yield. Nevertheless, a reaction time of 22 h was required, and addition of amounts of 4-tolylboronic acid to the reaction mixture until 2.5 equivalents of 4-tolylboronic acid were used. A higher temperature was incompatible with the ester group. These conditions were greatly improved using 4-tolylboronic acid (1.4 equiv.), Pd(PPh3)4 (0.1 equiv.), K2CO3 (2 equiv.) in dioxane/EtOH for 15 min at 150 °C under microwave irradiation, leading to 17 in 95% yield. In the same conditions, 18 was obtained in 76% yield. Starting from the 2-phenyl or 2-methyl compounds 2 or 4, compounds 19–20 and 21–22 were obtained using classical conditions (boronic acid (1.4 or 2 equiv.), Pd(PPh3)4 (0.05 equiv.), Na2CO3 (2 equiv.), DME/H2O at 120 °C under microwave irradiation) in good yields (80 to 90%). In these conditions, no influence of the nature of the 2-substituent was noticed on the reactivity of the 8 position.

Table 1. Functionalization in position 8 of compounds 2–4.
Table 1. Cont.

| S.M. | Product | Isolated Yield (%) | S.M. | Product | Isolated Yield (%) |
|------|---------|--------------------|------|---------|--------------------|
| 3    | ![Image](image1.png) | 95<sup>a</sup>     | 3    | ![Image](image2.png) | 76<sup>a</sup>     |
| 2    | ![Image](image3.png) | 90<sup>b</sup>     | 4    | ![Image](image4.png) | 84<sup>b</sup>     |
| 2    | ![Image](image5.png) | 82<sup>b</sup>     | 4    | ![Image](image6.png) | 80<sup>b</sup>     |

*Reaction conditions:*<sup>a</sup> RB(OH)₂ (1.4 equiv.), K₂CO₃ (2 equiv.), Pd(PPh₃)₄ (0.1 equiv.), dioxane/EtOH, 150 °C, MW or<sup>b</sup> RB(OH)₂ (1.4 or 2 equiv.), Na₂CO₃ (2 equiv.), Pd(PPh₃)₄ (0.05 equiv.), DME/H₂O, 120 °C, MW.

The Suzuki coupling reaction was then extended to the diversely 7-substituted imidazo[1,2-a]pyridines 5–6, 9–10, 14 (Table 2). As previously described, two synthetic routes were applied depending on the 2-substituent. Reaction of 5 or 9 with various (hetero)arylboronic acids (1.4 or 2 equiv.) in the presence of Pd(PPh₃)₄ (0.05 equiv.), Na₂CO₃ (2 equiv.) in DME/H₂O at 120 °C under microwaves irradiation gave 23 to 25 in moderate to good yields (19%–71%). Reaction of the ester compounds 6, 10, 14 with (hetero)arylboronic acids (1.4 or 2 equiv.) in the presence of Pd(PPh₃)₄ (0.1 equiv.), K₂CO₃ (2 equiv.) in dioxane/EtOH at 150 °C under microwave irradiation led to 27 to 35% of compounds 26–30.

Table 2. Functionalization in position 8 of compounds 5–6, 9–10, 14.
Due to the lower reactivity of the chlorine atom in position 8 of the imidazo[1,2-a]pyridines 2–6, 9–10, 14, only 8-(hetero)aryl-7-substituted compounds could be obtained through Suzuki cross-coupling reactions. No cyanation, Sonogashira or amination reaction could be achieved at this position. Nevertheless, the problem of chlorine reactivity could be solved starting from the regioisomers 7–8, 11, 15 iodinated in position 8.

### 2.3. Substitution of the Chlorine Atom in Position 7 of Compounds 7–8, 11, 15

Using the previously established experimental conditions, four examples of 7-arylimidazo[1,2-a]pyridines 31–34 were obtained presenting an alkyne, cyano or amino group in position 8 (44 to 69% yields) (Table 3). For compound 34, we noticed the formation of a dehalogenated compound during

#### Table 2. Cont.

| S.M. | Products          | Isolated Yield (%) | S.M. | Products          | Isolated Yield (%) |
|------|-------------------|--------------------|------|-------------------|--------------------|
| 5    | ![Image](image5)  | 19<sup>a</sup>     | 9    | ![Image](image9)  | 71<sup>a</sup>     |
|      | ![Image](image23) |                    |      | ![Image](image24) |                    |
| 9    | ![Image](image25) | 42<sup>a</sup>     | 14   | ![Image](image26) | 27<sup>b</sup>     |
|      | ![Image](image27) |                    |      | ![Image](image28) |                    |
| 6    | ![Image](image27) | 35<sup>b</sup>     | 10   | ![Image](image28) | 31<sup>b</sup>     |
|      | ![Image](image29) |                    |      | ![Image](image30) |                    |
| 10   | ![Image](image29) | 34<sup>b</sup>     | 14   | ![Image](image30) | 28<sup>b</sup>     |

*Reaction conditions:*  
<sup>a</sup> RB(OH)<sub>2</sub> (1.4 or 2 equiv.), Na<sub>2</sub>CO<sub>3</sub> (2 equiv.), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.05 equiv.), DME/H<sub>2</sub>O, 120 °C, MW;  
<sup>b</sup> RB(OH)<sub>2</sub> (1.4 or 2 equiv.), K<sub>2</sub>CO<sub>3</sub> (2 equiv.), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.1 equiv.), dioxane/EtOH, 150 °C, MW.
the Suzuki cross-coupling reaction, and a higher amount of boronic acid was then required to complete the reaction.

Table 3. Functionalization in position 7 of compounds 7–8, 11, 15.

| S.M. Products | Isolated Yield (%) | S.M. Products | Isolated Yield (%) |
|---------------|--------------------|---------------|--------------------|
| 7 | ![Image of 7](image1) | 56<sup>a</sup> | 8 | ![Image of 8](image2) | 69<sup>b</sup> |
| 11 | ![Image of 11](image3) | 61<sup>a</sup> | 15 | ![Image of 15](image4) | 44<sup>a</sup> |

Reaction conditions: <sup>a</sup> RB(OH)₂ (1.4 or 2 or 5 equiv.), Na₂CO₃ (2 equiv.), Pd(PPh₃)₄ (0.05 equiv.), DME/H₂O, 120 °C, MW; <sup>b</sup> RB(OH)₂ (1.4 equiv.), K₂CO₃ (2 equiv.), Pd(PPh₃)₄ (0.1 equiv.), dioxane/EtOH, 150 °C, MW.

2.4. Double Coupling Approach

Finally, the 7,8-diarylation of the imidazo[1,2-α]pyridine scaffold in a one-pot approach was evaluated (Table 4). Starting from compound 1a, optimization of the Suzuki double coupling led to the following conditions: first boronic acid (1 equiv.), Na₂CO₃ (3 equiv.), Pd(PPh₃)₄ (0.05 equiv.) in a mixture DME/H₂O for 30 min at 95 °C under microwave irradiation, then second boronic acid (1.4 equiv.), Pd(PPh₃)₄ (0.05 equiv.) for 30 min at 120 °C under microwave irradiation. Compounds 18, 35 and 36 were obtained in 43 to 72% yields. Starting from the regioisomer 1d, 2 equivalents of both boronic acids were required.

One pot cyanation/Sonogashira and cyanation/Buchwald double couplings could be performed starting from compounds 1d–e leading to compounds 38–41 in 32 to 67% yields. After optimization, the one pot cyanation/Sonogashira conditions required CuCN (1.2 equiv.) in DMF at 90 °C for 4 h under microwave irradiation, then 4-ethylnyltoluene (1.3 equiv.), Et₃N (5 equiv.), Pd(PPh₃)₄ (0.1 equiv.), PCy₃HBF₄ (0.3 equiv.), CuI (0.2 equiv.) at 130 °C for 1 h under microwave irradiation. The one pot
cyanation/Buchwald double coupling was performed using CuCN (1.2 equiv.) in DMF at 90 °C for 4 h under microwave irradiation, then DIPEA (2 equiv.), 4-fluorophenylpiperidine (2 equiv.) at 130 °C for 1 h under microwave irradiation. These results encouraged us to study other heterogeneous double couplings.

Table 4. One pot double-coupling approach applied to compounds 1a, 1d and 1e.

| S.M. Products | Isolated Yield (%) | S.M. Products | Isolated Yield (%) |
|---------------|--------------------|---------------|--------------------|
| 1a            | 72 a               | 1a            | 44 a               |
| 1b            | 43 a               | 1d            | 47 b               |
| 1c            | 32 c               | 1d            | 67 d               |
| 1d            | 43 c               | 1e            | 54 d               |

Reaction conditions: 

- a R,B(OH)_2 (1 equiv.), Na_2CO_3 (3 equiv.), Pd(PPh_3)_4 (0.05 equiv.), DME/H_2O, 95 °C, 30 min, MW then R_2B(OH)_2 (1.4 equiv.), Pd(PPh_3)_4 (0.05 equiv.), 120 °C, 30 min, MW;
- b R,B(OH)_2 (2 equiv.), Na_2CO_3 (3 equiv.), Pd(PPh_3)_4 (0.05 equiv.), DME/H_2O, 95 °C, 1 h 30 min, MW then R_2B(OH)_2 (2 equiv.), Pd(PPh_3)_4 (0.05 equiv.), 120 °C, 30 min, MW;
- c CuCN (1.2 equiv.), DMF, 90 °C, 4 h, MW then 4-ethynyltoluene (1.3 equiv.), Et_3N (5 equiv.), Pd(PPh_3)_4 (0.1 equiv.), PCy_3HBF_4 (0.3 equiv.), CuI (0.2 equiv.), 130 °C, 1 h, MW;
- d CuCN (1.2 equiv.), DMF, 90 °C, 4 h, MW then DIPEA (2 equiv.), 4-fluorophenylpiperidine (2 equiv.), 130 °C, 1 h, MW.
3. Experimental

3.1. General

Commercial reagents were used as received without additional purification. The microwave experiments were performed with a CEM Discover SP® equipped with an Explorer hybrid unit, only the set point temperature was adjusted (set point pressure: 17 bar, set point power: 200 W). The compounds were purified on a Flashsmart® flash chromatography system and columns from AIT® and Macherey-Nagel® were used. $^1$H and $^{13}$C-NMR spectra were recorded on a Bruker 300 MHz spectrometer in CDCl$_3$ or in DMSO-$d_6$. The possible inversion of two values in the NMR spectra is expressed by an asterisk. The melting points were determined in a capillary apparatus Stuart® SMP3 and are uncorrected.

3.2. Synthesis

3.2.1. Obtention of the Aminochloroiodopyridines

2,3-Dichloro-4-iodopyridine [8,15]. To a solution of $n$-butyllithium (27.6 mL, 69 mmol, 2.5 M in hexanes) in dry Et$_2$O (153 mL) cooled at $-78$ °C, was added dropwise 2,2,6,6-tetramethylpiperidine (11.64 mL, 69 mmol). The mixture was stirred at $-78$ °C for 10 min and a solution of 2,3-dichloropyridine (10 g, 67.57 mmol) in dry THF (75 mL) was added dropwise. The resulting mixture was stirred at $-78$ °C for 30 min and a solution of I$_2$ (25.38 g, 100 mmol) in dry THF (75 mL) was added. The reaction was cooled to room temperature overnight, quenched with a saturated aqueous solution of Na$_2$S$_2$O$_3$ and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with a saturated aqueous solution of NaHCO$_3$, dried with anhydrous MgSO$_4$ and evaporated in vacuo. The residue was purified on column chromatography [silica gel, cyclohexane/EtOAc (7:3)] to give a pale cream solid. M.p. = 110 °C (Ref. [8] 113 °C). 67% yield. $^1$H-NMR (CDCl$_3$) $\delta$ 7.89 (d, 1H, $J$ = 5.1 Hz, H-6), 7.73 (d, 1H, $J$ = 5.1 Hz, H-5). $^{13}$C-NMR (CDCl$_3$) $\delta$ 148.5, 146.6, 135.4, 134.0, 111.2.

2-Amino-3-chloro-4-iodopyridine [8]. A mixture of 2,3-dichloro-4-iodopyridine (4 g, 14.71 mmol) in NH$_4$OH 28% (75 mL) was heated in a Parr bomb at 129 °C for 16 h. The reaction was cooled to room temperature and CH$_2$Cl$_2$ (100 mL) was added. The mixture was extracted with CH$_2$Cl$_2$ (3 × 100 mL), dried with anhydrous MgSO$_4$ and evaporated in vacuo. The residue was purified by flash chromatography [silica gel, cyclohexane/EtOAc (7:3)] and a white solid was obtained. M.p. = 110 °C. 38% yield. $^1$H-NMR (CDCl$_3$) $\delta$ 7.54 (d, 1H, $J$ = 5.1 Hz, H-6), 7.08 (d, 1H, $J$ = 5.3 Hz, H-5), 5.32 (s, 2H, NH$_2$). $^{13}$C-NMR (CDCl$_3$) $\delta$ 154.6, 146.6, 135.4, 134.0, 119.4, 109.8.

t-Butyl-(4-chloropyridin-2-yl)carbamate [16,17]. To a solution of 2-amino-4-chloropyridine (3 g, 23.34 mmol) in t-BuOH (43 mL), di-t-butyl dicarbonate (5.6 g, 25.67 mmol) was added. The mixture was stirred at 30 °C overnight. A solid appeared and was filtered off, washed with $n$-hexane and diethyl ether to give a white solid. M.p. = 150 °C. 77% yield. $^1$H-NMR (DMSO-$d_6$) $\delta$ 10.14 (bs, 1H, NH), 8.22 (d, 1H, $J$ = 5.4 Hz, H-6), 7.88 (d, 1H, $J$ = 1.9 Hz, H-3), 7.14 (dd, 1H, $J$ = 5.4–1.9 Hz, H-5), 1.47 (s, 9H, CH$_3$). $^{13}$C-NMR (DMSO-$d_6$) $\delta$ 153.69, 152.66, 149.34, 143.84, 118.29, 111.65, 80.15, 27.95.
t-Butyl-(4-chloro-3-iodopyridin-2-yl)carbamate [17]. To a solution of t-butyl-(4-chloropyridin-2-yl)carbamate (9 g, 39.5 mmol) in anhydrous THF (250 mL), TMEDA (14.4 mL) was added under nitrogen atmosphere and cooled to −70 °C. To the mixture, 2.5 M in hexane n-BuLi (39.6 mL, 98 mmol) was added dropwise over a period of 30 min. The mixture was stirred at −70 °C for 1 h and then treated dropwise with a solution of I2 (50 g, 198 mmol) in anhydrous THF (30 mL) at −70 °C. After the addition was complete, the reaction was stirred at −70 °C for 30 min and then allowed to warm to room temperature. The mixture was treated with an aqueous saturated solution of Na2S2O3 and stirred for 30 min. The solution was extracted with EtOAc (3 × 200 mL). The combined organic layer was washed with brine, dried with anhydrous MgSO4 and evaporated under reduced pressure. The product was purified by flash chromatography [silica, cyclohexane/EtOAc (7:3)] to give a white solid. M.p. = 183 °C. 75% yield. 1H-NMR (DMSO-d6) δ 9.48 (s, 1H, NH), 8.30 (d, 1H, J = 5.1 Hz, H-6), 7.47 (d, 1H, J = 5.1 Hz, H-5), 1.45 (s, 9H, CH3). 13C-NMR (DMSO-d6) δ 154.9, 152.6, 149.0, 148.4, 122.0, 99.2, 79.4, 28.1.

2-Amino-4-chloro-3-iodopyridine [7,8,17]. A suspension of t-butyl-(4-chloro-3-iodopyridin-2-yl)carbamate (6 g, 23.5 mmol) in 48% hydrobromic acid (12 mL) was heated at 100 °C for 10 min to give a clear solution. The mixture was cooled, treated with ice and made basic with 10 M NaOH solution. The precipitated product was filtered off, washed with H2O to give a cream solid. M.p. = 111 °C. 97% yield. 1H-NMR (DMSO-d6) δ 7.84 (d, 1H, J = 5.2 Hz, H-6), 6.72 (d, 1H, J = 5.2 Hz, H-5), 6.44 (bs, 2H, NH2). 13C-NMR (DMSO-d6) δ 161.0, 148.4, 147.7, 113.0, 81.4.

3.2.2. General Procedure for Cyclization

8-Chloro-7-iodo-2-phenylimidazo[1,2-a]pyridine (1a). Method A. To a solution of 2-amino-3-chloro-4-iodopyridine (1 g, 3.94 mmol) in EtOH (10 mL), was added bromoacetophenone (1.56 g, 7.87 mmol). The mixture was stirred at 65 °C overnight. The solution was then evaporated to dryness in vacuo. The residue was dissolved in CH2Cl2 (50 mL) and the resulting solution made basic by the addition of a saturated aqueous solution of Na2CO3. The solution was extracted with CH2Cl2 (3 × 100 mL), the combined organic layers were dried with anhydrous MgSO4 and evaporated under reduced pressure. The crude product was purified by flash chromatography [silica gel, cyclohexane/EtOAc (7:3)]. M.p. = 101 °C. 97% yield. 1H-NMR (CDCl3) δ 7.96 (dd, 2H, J = 8.2–1.3 Hz, Ph-2,6), 7.88 (s, 1H, H-3), 7.80 (d, 1H, J = 7.0 Hz, H-5), 7.44 (m, 2H, Ph-3,5), 7.35 (m, 1H, Ph-4), 7.12 (d, 1H, J = 7.0 Hz, H-6). 13C-NMR (CDCl3) δ 146.8, 143.0, 132.8, 128.7, 128.5, 126.4, 123.9, 121.7, 110.0, 92.1(1C not found).

Ethyl 8-chloro-7-idoimidazo[1,2-a]pyridine-2-carboxylate (1b). Method B. To a solution of 2-amino-3-chloro-4-iodopyridine (1 g, 3.94 mmol) in DME (18 mL), was added ethyl bromopyruvate (1.16 g, 5.91 mmol). The mixture was stirred at room temperature overnight. The solution was evaporated in vacuo to dryness and EtOH (18 mL) was added. The mixture was stirred at 78 °C for 2 h. After cooling to room temperature, the solution was evaporated to dryness under vacuum. The residue was dissolved in CH2Cl2 (50 mL) and the resulting solution made basic by the addition of a saturated solution of Na2CO3. The solution was extracted with CH2Cl2 (3 × 100 mL), the combined organic layers were dried with anhydrous MgSO4 and evaporated under reduced pressure. The crude product was washed with diethyl ether and n-hexane to give a pale cream solid. M.p. = 249 °C. 95% yield.
$^1$H-NMR (CDCl$_3$) $\delta$ 8.66 (s, 1H, H-3), 8.33 (d, 1H, $J$ = 6.9 Hz, H-5), 7.41 (d, 1H, $J$ = 6.9 Hz, H-6), 4.32 (q, 2H, $J$ = 7.2 Hz, CH$_2$), 1.32 (t, 3H, $J$ = 7.2 Hz, CH$_3$). $^{13}$C-NMR (CDCl$_3$) $\delta$ 162.6, 142.3, 136.1, 127.1, 123.0, 120.8, 97.4, 61.0, 14.7 (1C not found).

8-Chloro-7-iodo-2-methylimidazo[1,2-a]pyridine (1c). Method A. 2-Amino-3-chloro-4-iodopyridine (1 g, 3.94 mmol) and chloroacetone (1.46 g, 15.75 mmol) were used. M.p. = 136 °C. Quantitative yield. $^1$H-NMR (CDCl$_3$) $\delta$ 7.72 (d, 1H, $J$ = 6.9 Hz, H-5), 7.38 (s, 1H, H-3), 7.07 (d, 1H, $J$ = 6.9 Hz, H-6), 2.48 (s, 3H, CH$_3$). $^{13}$C-NMR (CDCl$_3$) $\delta$ 144.6, 131.9, 127.5, 123.6, 121.1, 111.6, 88.6.

7-Chloro-8-iodo-2-phenylimidazo[1,2-a]pyridine (1d). Method A. 2-Amino-4-chloro-3-iodopyridine (1 g, 3.94 mmol) and bromoacetophenone (1.56 g, 7.87 mmol) were used. M.p. = 197 °C. 72% yield. $^1$H-NMR (CDCl$_3$) $\delta$ 8.03–7.94 (m, 4H, Ph-2,6, H-3, H-5), 7.44 (m, 2H, Ph-3,5), 7.36 (m, 1H, Ph-4), 6.84 (d, 1H, $J$ = 7.0 Hz, H-6). $^{13}$C-NMR (DMSO-d$_6$) $\delta$ 145.5, 145.2, 135.1, 133.1, 128.8, 128.1, 127.2, 125.7, 113.1, 111.5. 88.6.

Ethyl 7-chloro-8-iodoimidazo[1,2-a]pyridine-2-carboxylate (1e). Method B. 2-Amino-4-chloro-3-iodopyridine (1 g, 3.94 mmol) was used as starting material. M.p. = 208 °C. 71% yield. $^1$H-NMR (DMSO-d$_6$) $\delta$ 8.71 (s, 1H, H-3), 8.55 (d, 1H, $J$ = 7.3 Hz, H-5), 7.16 (d, 1H, $J$ = 7.3 Hz, H-6), 4.33 (q, 2H, $J$ = 7.0 Hz, CH$_2$), 1.32 (t, 3H, $J$ = 7.0 Hz, CH$_3$). $^{13}$C-NMR (DMSO-d$_6$) $\delta$ 162.2, 145.4, 137.0, 136.2, 127.9, 120.4, 114.5, 89.9, 60.5, 14.3.

3.2.3. Suzuki Cross-Coupling on Compounds 1a–c

8-Chloro-7-(4-fluorophenyl)-2-phenylimidazo[1,2-a]pyridine (2). Method C. To a solution of 1a (500 mg, 1.41 mmol) in a mixture of THF (2.7 mL) and water (0.3 mL) in a sealed tube, were added 4-fluorophenylboronic acid (296 mg, 2.11 mmol), Na$_2$CO$_3$ (449 mg, 4.24 mmol) and PdCl$_2$(dppf) (58 mg, 0.07 mmol, 5 mol%). The mixture was stirred at 75 °C for 1 h 30 min, 4-fluorophenylboronic acid (99 mg, 0.5 equiv.) and a few amount of PdCl$_2$(dppf) were added. After overnight stirring at 75 °C and cooling to room temperature, CH$_2$Cl$_2$ (50 mL) and water (50 mL) were added and the solution was extracted with CH$_2$Cl$_2$ (3 × 50 mL). The combined organic layer was dried with anhydrous MgSO$_4$ and evaporated under reduced pressure. The crude residues were purified by column chromatography (alumina, CH$_2$Cl$_2$). M.p. = 211 °C. 90% yield. $^1$H-NMR (CDCl$_3$) $\delta$ 8.09 (d, 1H, $J$ = 6.9 Hz, H-5), 8.02 (m, 2H, Ph-2,6), 7.92 (s, 1H, H-3), 7.52 (dd, 2H, $J$ = 8.8–5.2 Hz, F-Ph-2,6), 7.45 (m, 2H, Ph-3,5), 7.37 (m, 1H, Ph-4), 7.18 (t, 2H, $J$ = 8.8 Hz, F-Ph-3,5), 6.80 (d, 1H, $J$ = 6.9 Hz, H-6). $^{13}$C-NMR (CDCl$_3$) $\delta$ 162.6, 147.1, 134.6, 133.2, 133.1, 131.1, 128.7, 128.3, 126.4, 123.4, 115.5, 114.8, 109.4. (2C not found) Anal. Calcd for C$_{19}$H$_{12}$ClFN$_2$: C, 70.70; H, 3.75; N, 8.68. Found: C, 70.94; H, 3.67; N, 8.73.

Ethyl 8-chloro-7-(4-fluorophenyl)imidazo[1,2-a]pyridine-2-carboxylate (3). Method C: 1b (500 mg, 1.43 mmol), 4-fluorophenylboronic acid (300 mg, 2.14 mmol then 100 mg, 0.71 mmol), Na$_2$CO$_3$ (454 mg, 4.38 mmol) and PdCl$_2$(dppf) (58 mg, 0.07 mmol, 5 mol%) were used. M.p. = 199 °C. 87% yield. $^1$H-NMR (CDCl$_3$) $\delta$ 8.27 (s, 1H, H-3), 8.15 (d, 1H, $J$ = 7.2 Hz, H-5), 7.50 (dd, 2H, $J$ = 8.7–5.4 Hz, F-Ph-2,6), 7.17 (t, 2H, $J$ = 8.7 Hz, F-Ph-3,5), 6.90 (d, 1H, $J$ = 7.2 Hz, H-6), 4.46 (q, 2H, $J$ = 7.2 Hz, CH$_2$), 1.42 (t, 3H, $J$ = 7.2 Hz, CH$_3$). $^{13}$C-NMR (CDCl$_3$) $\delta$ 162.7, 162.7, 143.1, 137.7, 136.0, 132.6,
131.1, 124.1, 121.5, 118.3, 116.4, 115.5, 61.3, 14.3. Anal. Calcd for C_{16}H_{12}ClFN_2O_2: C, 60.29; H, 3.79; N, 8.79. Found: C, 60.51; H, 3.57; N, 8.81.

8-Chloro-7-(4-fluorophenyl)-2-methylimidazo[1,2-a]pyridine (4). Method C. 1c (500 mg, 1.71 mmol), 4-fluorophenylboronic acid (359 mg, 2.56 mmol then 120 mg, 0.85 mmol), Na_2CO_3 (545 mg, 5.14 mmol) and PdCl_2(dppf) (70 mg, 0.09 mmol, 5 mol%) were used. M.p. = 164 °C. 89% Yield. 1H-NMR (CDCl_3) \( \delta \) 8.06 (d, 1H, \( J = 6.9 \) Hz, H-5), 7.52 (dd, 2H, \( J = 8.7–5.5 \) Hz, F-Ph-2,6), 7.46 (s, 1H, H-3), 7.19 (t, 2H, \( J = 8.7 \) Hz, F-Ph-3,5), 6.81 (d, 1H, \( J = 6.9 \) Hz, H-6), 2.56 (s, 3H, CH_3). 13C-NMR (CDCl_3) \( \delta \) 162.7, 144.0, 133.0, 131.1, 123.3, 115.5, 114.7, 111.1, 14.13. (3C not found) Anal. Calcd for C_{14}H_{10}ClFN_2: C, 64.50; H, 3.87; N, 10.75. Found: C, 64.36; H, 3.91; N, 10.83.

3.2.4. General Procedure for Sonogashira Cross-Coupling Reaction

8-Chloro-7-(p-tolylethynyl)-2-phenylimidazo[1,2-a]pyridine (5). Method D. To a solution of 1a (500 mg, 1.41 mmol) in DMF (6 mL), were added Et_3N (1 mL, 7.06 mmol), PCy_3HBF_4 (156 mg, 0.42 mmol), p-tolylacetylene (213 mg, 1.84 mmol), Pd(PPh_3)_4 (163 mg, 0.14 mmol) and CuI (50 mg, 0.26 mmol). The mixture was heated at 90 °C by microwave irradiation for 30 min. After cooling to room temperature, water (50 mL) was added and the solution was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried with anhydrous MgSO_4 and evaporated under reduced pressure. The crude residues were purified by flash chromatography (silica, cyclohexane/EtOAc (7:3)). M.p. = 176 °C. 71% yield. 1H-NMR (CDCl_3) \( \delta \) 8.04–7.95 (m, 3H, Ph-2,6, H-5), 7.88 (s, 1H, H-3), 7.55–7.40 (m, 4H, Ph-3,5, CH_3-Ph-2,6), 7.35 (m, 1H, Ph-4), 7.20 (d, 2H, \( J = 7.9 \) Hz, CH_3-Ph-3,5), 6.99 (d, 1H, \( J = 6.8 \) Hz, H-6), 2.39 (s, 3H, CH_3). 13C-NMR (CDCl_3) \( \delta \) 147.4, 139.4, 132.9, 131.7, 129.2, 128.7, 128.6, 128.4, 126.4, 123.2, 119.3, 118.6, 115.0, 110.2, 98.1, 84.6, 21.6 (1C not found). Anal. Calcd for C_{22}H_{15}ClN_2: C, 77.08; H, 4.41; N, 8.17. Found: C, 77.24; H, 4.46; N, 8.07.

Ethyl 8-chloro-7-(p-tolylethynylimidazo[1,2-a]pyridine-2-carboxylate (6). Method D. 1b (500 mg, 1.43 mmol), Et_3N (1 mL, 7.14 mmol), PCy_3HBF_4 (158 mg, 0.43 mmol), p-tolylacetylene (215 mg, 1.86 mmol), Pd(PPh_3)_4 (165 mg, 0.14 mmol) and CuI (50 mg, 0.26 mmol) were used. M.p. = 211 °C. 77% yield. 1H-NMR (CDCl_3) \( \delta \) 8.21 (s, 1H, H-3), 8.04 (d, 1H, \( J = 7.2 \) Hz, H-5), 7.49 (d, 2H, \( J = 8.1 \) Hz, CH_3-Ph-2,6), 7.19 (d, 2H, \( J = 8.1 \) Hz, CH_3-Ph-3,5), 6.97 (d, 2H, \( J = 7.2 \) Hz, H-6), 4.46 (q, 2H, \( J = 7.5 \) Hz, CH_2), 2.39 (s, 3H, CH_3), 1.43 (t, 3H, \( J = 7.5 \) Hz, CH_3). 13C-NMR (CDCl_3) \( \delta \) 162.5, 142.7, 139.8, 137.7, 131.8, 129.3, 126.0, 124.0, 120.6, 119.0, 116.5, 99.5, 84.0, 61.4, 21.6, 14.32 (1C not found). Anal. Calcd for C_{19}H_{15}ClN_2O_2: C, 67.36; H, 4.46; N, 8.27. Found: C, 67.49; H, 4.41; N, 8.38.

7-Chloro-8-(p-tolylethynyl)-2-phenylimidazo[1,2-a]pyridine (7). Method D. 1d (250 mg, 0.71 mmol), Et_3N (0.5 mL, 3.53 mmol), PCy_3HBF_4 (78 mg, 0.21 mmol), p-tolylacetylene (107 mg, 0.92 mmol), Pd(PPh_3)_4 (81 mg, 0.07 mmol) and CuI (25 mg, 0.13 mmol) were used. M.p. = 118 °C. 60% yield. 1H-NMR (CDCl_3) \( \delta \) 8.00 (m, 3H, H-5, Ph-2,6), 7.84 (s, 1H, H-3), 7.62 (d, 2H, \( J = 8.0 \) Hz, CH_3-Ph-2,6), 7.44 (m, 2H, Ph-3,5), 7.34 (m, 1H, Ph-4), 7.20 (d, 2H, \( J = 8.0 \) Hz, CH_3-Ph-3,5), 6.85 (d, 1H, \( J = 7.4 \) Hz, H-6), 2.39 (s, 3H, CH_3). 13C-NMR (CDCl_3) \( \delta \) 146.9, 139.3, 133.1, 132.1, 129.1, 128.9, 128.6, 128.3, 126.3, 126.2, 124.5, 119.6, 115.8, 114.2, 108.9, 81.4, 21.6 (1C not found). Anal. Calcd for C_{22}H_{15}ClN_2O_2: C, 77.08; H, 4.41; N, 8.17. Found: C, 77.25; H, 4.43; N, 8.19.
Ethyl 7-chloro-8-(p-tolylethynyl)imidazo[1,2-a]pyridine-2-carboxylate (8). Method D. 1e (250 mg, 0.71 mmol), Et3N (0.5 mL, 3.53 mmol), PCy3HBF4 (78 mg, 0.21 mmol), p-tolylacetylene (107 mg, 0.92 mmol), Pd(PPh3)4 (81 mg, 0.21 mmol), and CuI (25 mg, 0.13 mmol) were added. M.p. = 175 °C. 50% yield. 1H-NMR (CDCl3) δ 8.20 (s, 1H, H-3), 8.10 (d, 1H, J = 7.2 Hz, H-5), 7.55 (d, 2H, J = 8.0 Hz, CH3-Ph-2,6), 7.17 (d, 2H, J = 8.0 Hz, CH3-Ph-3,5), 6.95 (d, 1H, J = 7.2 Hz, H-6), 4.44 (q, 2H, J = 7.1 Hz, CH2), 2.37 (s, 3H, CH3), 1.42 (t, 3H, J = 7.1 Hz, CH3). 13C-NMR (CDCl3) δ 162.7, 144.8, 139.5, 137.6, 135.0, 132.0, 129.0, 125.2, 119.2, 118.0, 115.9, 113.8, 102.8, 80.9, 61.3, 21.6, 14.3. Anal. Calcd for C19H15ClN2O2: C, 67.36; H, 4.46; N, 8.27. Found: C, 67.21; H, 4.47; N, 8.46.

3.2.5. General Procedure for Cyanation Reaction

8-Chloro-2-phenylimidazo[1,2-a]pyridine-7-carbonitrile (9). Method E. To a solution of 1a (400 mg, 1.13 mmol) in DMF (793 µL), CuCN (132 mg, 1.47 mmol) was added. The tube was evacuated and back filled with nitrogen. Then the reaction mixture was heated at 150 °C or 200 °C by microwave irradiation for 15 min. After cooling to room temperature, an aqueous solution of NH4OH 10% (50 mL) and CH2Cl2 (50 mL) were added and the organic layer was washed with an aqueous solution of NH4OH (3 × 50 mL), dried with anhydrous MgSO4 and evaporated under reduced pressure. The crude residues were purified on column chromatography (silica gel, CH2Cl2). The reaction mixture was heated at 200 °C by microwave irradiation. M.p. = 200 °C. 72% yield. 1H-NMR (CDCl3) δ 8.71 (s, 1H, H-3), 8.67 (d, 1H, J = 7.0 Hz, H-5), 8.01 (m, 2H, Ph-2,6), 7.48 (m, 2H, Ph-3,5), 7.39 (m, 1H, Ph-4), 7.30 (d, 1H, J = 7.0 Hz, H-6). 13C-NMR (CDCl3) δ 147.4, 140.7, 132.4, 128.9, 128.8, 127.0, 125.9, 115.6, 113.6, 112.6, 106.2. Anal. Calcd for C14H8ClN3: C, 66.28; H, 3.18; N, 16.56. Found: C, 65.94; H, 3.33; N, 16.72.

Ethyl 8-chloro-7-cyanoimidazo[1,2-a]pyridine-2-carboxylate (10). Method E. 1b (400 mg, 1.14 mmol) was used as starting material. The reaction mixture was heated at 200 °C by microwave irradiation. M.p. = 229 °C. 63% yield. 1H-NMR (CDCl3) δ 8.35 (s, 1H, H-3), 8.20 (d, 1H, J = 7.2 Hz, H-6), 7.05 (d, 1H, J = 7.0 Hz, H-5), 7.01 (m, 2H, Ph-2,6), 7.48 (m, 2H, Ph-3,5), 7.39 (m, 1H, Ph-4), 7.30 (d, 1H, J = 7.0 Hz, H-6). 13C-NMR (CDCl3) δ 161.9, 141.3, 139.8, 131.4, 125.3, 120.0, 114.4, 114.0, 109.3, 61.8, 14.3. Anal. Calcd for C11H8ClN3O2: C, 52.92; H, 3.23; N, 16.83. Found: C, 53.16; H, 3.48; N, 16.97.

7-Chloro-2-phenylimidazo[1,2-a]pyridine-8-carbonitrile (11). Method E. 1d (400 mg, 1.13 mmol) was used as starting material. The reaction mixture was heated at 150 °C by microwave irradiation. M.p. = 197 °C. 69% yield. 1H-NMR (CDCl3) δ 8.22 (d, 1H, J = 7.2 Hz, H-5), 7.96 (m, 2H, PH-2,6), 7.91 (s, 1H, H-3), 7.45 (m, 2H, Ph-3,5), 7.37 (m, 1H, Ph-4), 6.90 (d, 1H, J = 7.2 Hz, H-6). 13C-NMR (CDCl3) δ 148.4, 143.3, 137.3, 132.2, 129.0, 128.8, 126.4, 113.5, 112.6, 109.3, 102.0 (1 C not found). Anal. Calcd for C14H8ClN3: C, 66.28; H, 3.18; N, 16.56. Found: C, 66.34; H, 3.35; N, 16.51.

Ethyl 7-chloro-8-cyanoimidazo[1,2-a]pyridine-2-carboxylate (12). Method E. 1e (400 mg, 1.14 mmol) was used as starting material. The reaction mixture was heated at 150 °C by microwave irradiation. M.p. = 227 °C. 46% yield. 1H-NMR (CDCl3) δ 8.31 (d, 1H, J = 7.2 Hz, H-5), 8.28 (s, 1H, H-3), 7.06 (d, 1H, J = 7.4 Hz, H-6), 4.48 (q, 2H, J = 7.1 Hz, CH2), 1.45 (t, 3H, J = 7.1 Hz, CH3). 13C-NMR
N-(8-Chloro-2-phenylimidazo[1,2-a]pyridin-7-yl)aniline (13). Method F. To a solution of 1a (100 mg, 0.28 mmol) in DME (3 mL) under argon, were added successively rac-BINAP (53 mg, 0.085 mmol), t-BuONa (81 mg, 0.85 mmol), Pd(PPh3)4 (33 mg, 0.03 mmol), Cul (10 mg, 0.053 mmol) and aniline (77 µL, 0.85 mmol). The mixture was heated at 85 °C by microwave irradiation for 45 min. After cooling to room temperature, water (50 mL) was added and the solution was extracted with EtOAc (3 × 50 mL), dried with anhydrous MgSO4 and evaporated under reduced pressure. The crude residues were purified by flash chromatography (silica, cyclohexane/EtOAc (7:3)). M.p. = 170 °C. 48% yield. 

1H-NMR (CDCl3) δ 7.93 (m, 2H, Ph-2,6), 7.82 (d, 1H, J = 7.4 Hz, H-5), 7.67 (s, 1H, H-3), 7.47–7.28 (m, 5H, Ph-3,4,5, Ph-NH-3,5), 7.15 (m, 3H, Ph-NH-2,4,6), 6.75 (d, 1H, J = 7.4 Hz, H-6), 6.42 (s, 1H, NH). 13C-NMR (CDCl3) δ 139.7, 138.2, 133.4, 129.7, 128.6, 128.1, 126.2, 124.5, 124.3, 121.9, 120.1, 108.3, 104.3 (2C not found). Anal. Calcd for C19H14ClN3: C, 71.36; H, 4.41; N, 13.14. Found: C, 71.55; H, 4.39; N, 13.26.

Ethyl 8-chloro-7-(cyclohexylamino)imidazo[1,2-a]pyridine-2-carboxylate (14). Method G. To a solution of 1b (100 mg, 0.29 mmol) in dioxane (3 mL), were added Pd2dba3 (11 mg, 0.01 mmol), Xantphos (20 mg, 0.03 mmol), K2CO3 (591 mg, 4.29 mmol) and cyclohexylamine (0.42 mL, 3.71 mmol). The mixture was irradiated under microwaves at 150 °C during 1 h 15 min. After cooling to room temperature, EtOAc (50 mL) and water (50 mL) were added. The solution was extracted with EtOAc (3 × 50 mL), dried with anhydrous MgSO4 and evaporated under reduced pressure. The crude residues were purified by flash chromatography [silica, cyclohexane/EtOAc (7:3)]. M.p. = 176 °C. 40% yield. 1H-NMR (CDCl3) δ 7.98 (s, 1H, H-3), 7.90 (d, 1H, J = 7.0 Hz, CH2), 3.37 (m, 1H, CyHex), 2.02 (m, 2H, CyHex), 1.80 (m, 2H, CyHex), 1.66 (m, 1H, CyHex), 1.32 (m, 9H, CH3, CyHex). 13C-NMR (CDCl3) δ 163.3, 144.7, 141.3, 136.6, 124.8, 116.5, 104.2, 99.6, 60.9, 51.8, 33.6, 25.4, 24.6, 14.4. Anal. Calcd for C16H20ClN3O2: C, 59.72; H, 6.26; N, 13.06. Found: C, 59.88; H, 6.23; N, 12.97.

N-(7-Chloro-2-phenylimidazo[1,2-a]pyridin-8-yl)aniline (15). Method F. 1d (100 mg, 0.28 mmol) was used as starting material. M.p. = 167 °C. 51% yield. 1H-NMR (CDCl3) δ 7.92 (s, 1H, H-3), 7.76 (d, 1H, J = 7.2 Hz, H-5), 7.43 (m, 2H, Ph-3,5), 7.32 (m, 3H, Ph-4, Ph-NH-3,5), 7.00 (m, 4H, Ph-NH-2,6,4, NH), 6.79 (d, 1H, J = 7.2 Hz, H-6). 13C-NMR (CDCl3) δ 145.3, 142.2, 141.6, 133.2, 128.7, 128.6, 128.1, 127.3, 126.0, 121.9, 119.4, 119.2, 119.0, 115.7, 109.3. Anal. Calcd for C16H20ClN3O2: C, 59.72; H, 6.26; N, 13.06. Found: C, 59.88; H, 6.23; N, 12.97.

Ethyl 7-chloro-8-(cyclohexylamino)imidazo[1,2-a]pyridine-2-carboxylate (16). Method G. 1e (100 mg, 0.29 mmol) was used as starting material. M.p. = 90 °C. 66% yield. 1H-NMR (CDCl3) δ 8.03 (s, 1H, H-3), 7.49 (d, 1H, J = 7.2 Hz, H-5), 6.77 (d, 1H, J = 7.2 Hz, H-6), 4.43 (q, 2H, J = 7.0 Hz, CH2), 2.05 (m, 2H, CyHex), 1.77 (m, 2H, CyHex), 1.63 (m, 2H, NH, CyHex), 1.28 (m, 9H, CH3, CyHex).
$^{13}$C-NMR (CDCl$_3$) δ 162.0, 157.0, 144.9, 133.7, 126.7, 118.5, 117.8, 114.7, 61.3, 53.2, 34.5, 25.6, 24.9, 14.3. Anal. Calcd for C$_{16}$H$_{20}$ClN$_3$O$_2$: C, 59.72; H, 6.26; N, 13.06. Found: C, 59.95; H, 6.32; N, 13.01.

3.2.7. Substitution of the Chlorine Atom in Position 8 of Compounds 2–6, 9–10, 14

**Ethyl 7-(4-fluorophenyl)-8-(p-tolyl)imidazo[1,2-a]pyridine-2-carboxylate** (17). Method H. To a solution of 3 (100 mg, 0.31 mmol) in a mixture of dioxane (0.5 mL) and ethanol (0.3 mL), were added p-tolylboronic acid (60 mg, 0.44 mmol), K$_2$CO$_3$ (88 mg, 0.63 mmol) and Pd(PPh$_3$)$_4$ (36 mg, 0.031 mmol). The mixture was heated at 150 °C by microwave irradiation for 15 min. After cooling to room temperature, water (50 mL) was added and the solution was extracted with CH$_2$Cl$_2$ (3 × 50 mL). The organic layer was dried with anhydrous MgSO$_4$ and evaporated under reduced pressure. The crude residue was purified by column chromatography (silica gel, CH$_2$Cl$_2$). M.p. = 241 °C. 95% yield. $^1$H-NMR (CDCl$_3$) δ 8.25 (s, 1H, H-3), 8.19 (d, 1H, $J = 7.2$ Hz, H-5), 7.22 (d, 2H, $J = 7.9$ Hz, CH$_3$-Ph-2,6), 7.12 (dd, $J = 8.7$–5.4 Hz, 2H, F-Ph-2,6), 7.03 (d, 2H, $J = 7.9$ Hz, CH$_3$-Ph-3,5), 6.92 (m, 3H, F-Ph-3,5, H-6), 4.39 (q, 2H, $J = 7.2$ Hz, CH$_2$), 2.30 (s, 3H, CH$_3$), 1.38 (t, 3H, $J = 7.2$ Hz, CH$_3$). $^{13}$C-NMR (CDCl$_3$) δ 163.1, 161.9, 145.3, 137.6, 137.2, 135.9, 135.2, 131.3, 131.0, 129.3, 128.7, 124.5, 117.3, 117.2, 115.2, 61.0, 21.2, 14.3. (1C not found) Anal. Calcd for C$_{23}$H$_{19}$FN$_2$O$_2$: C, 73.78; H, 5.11; N, 7.48. Found: C, 74.03; H, 5.08; N, 7.56.

**Ethyl 7-(4-fluorophenyl)-8-(4-methoxyphenyl)imidazo[1,2-a]pyridine-2-carboxylate** (18). Method H. 4-Methoxyphenylboronic acid (96 mg, 0.63 mmol) was used. The crude residue was purified by column chromatography (silica gel, CH$_2$Cl$_2$). M.p. = 199 °C. 76% yield. $^1$H-NMR (CDCl$_3$) δ 8.26 (s, 1H, H-3), 8.20 (d, 1H, $J = 7.2$ Hz, H-5), 7.28 (d, 2H, $J = 8.7$ Hz, CH$_3$O-Ph-2,6), 7.12 (dd, 2H, $J = 8.7$–5.4 Hz, F-Ph-2,6), 6.96–6.91 (m, 3H, H-6, F-Ph-3,5), 6.78 (d, 2H, $J = 8.7$ Hz, CH$_3$O-Ph-3,5), 4.40 (q, 2H, $J = 7.2$ Hz, CH$_2$), 3.78 (s, 3H, CH$_3$O), 1.39 (t, 3H, $J = 7.2$ Hz, CH$_3$). $^{13}$C-NMR (CDCl$_3$) δ 162.6, 161.9, 159.1, 144.9, 136.6, 136.3, 134.7, 132.3, 131.2, 128.3, 125.9, 124.9, 117.5, 117.4, 115.2, 113.3, 61.1, 55.2, 14.3. Anal. Calcd for C$_{23}$H$_{19}$FN$_2$O$_3$: C, 70.76; H, 4.91; N, 7.18. Found: C, 70.84; H, 5.11; N, 7.01.

**7-(4-Fluorophenyl)-8-(p-tolyl)-2-phenylimidazo[1,2-a]pyridine** (19). Method I. To a solution of 2 (100 mg, 0.31 mmol) in a mixture of DME (2 mL) and water (1 mL), were added p-tolylboronic acid (84 mg, 0.62 mmol), Na$_2$CO$_3$ (66 mg, 0.62 mmol) and Pd(PPh$_3$)$_4$ (18 mg, 0.016 mmol, 5 mol%). The mixture was heated at 120 °C for 30 min by microwave irradiation. After cooling to room temperature, water (50 mL) was added and the solution was extracted with CH$_2$Cl$_2$ (3 × 50 mL). The organic layer was dried with anhydrous MgSO$_4$ and evaporated under reduced pressure. The crude residue was purified by column chromatography (silica gel, CH$_2$Cl$_2$). M.p. = 222 °C. 90% yield. $^1$H-NMR (CDCl$_3$) δ 8.11 (d, 1H, $J = 6.9$ Hz, H-5), 7.95 (m, 2H, Ph-2,6), 7.91 (s, 1H, H-3), 7.42–7.28 (m, 5H, CH$_3$-Ph-2,6, Ph-3,4,5), 7.17–7.11 (m, 4H, F-Ph-2,6, CH$_3$-Ph-3,5), 6.94 (t, 2H, $J = 8.7$ Hz, F-Ph-3,5), 6.85 (d, 1H, $J = 6.9$ Hz, H-6), 2.36 (s, 3H, CH$_3$). $^{13}$C-NMR (CDCl$_3$) δ 161.8, 146.3, 145.4, 137.3, 135.9, 134.6, 133.7, 131.7, 131.4, 131.3, 128.6, 128.5, 127.8, 126.3, 123.9, 115.7, 115.1, 108.3, 21.3 (1C not found). Anal. Calcd for C$_{26}$H$_{19}$FN$_2$: C, 82.52; H, 5.06; N, 7.40. Found: C, 82.77; H, 5.39; N, 7.28.
7-(4-Fluorophenyl)-2-methyl-8-(p-tolyl)imidazo[1,2-a]pyridine (20). Method I. 4 (100 mg, 0.38 mmol), p-tolylboronic acid (104 mg, 0.77 mmol), Na₂CO₃ (82 mg, 0.77 mmol, 2 eq) and Pd(PPh₃)₄ (22 mg, 0.02 mmol, 5 mol%) were used. The mixture was heated for 60 min. The crude residue was purified by flash chromatography (silica, CH₂Cl₂/MeOH (99:1)). M.p. = 195 °C. 84% yield. ¹H-NMR (CDCl₃) δ 8.11 (d, 1H, J = 7.2 Hz, H-5), 7.45 (s, 1H, H-3), 7.18 (d, 2H, J = 8.1 Hz, CH₃-Ph-2,6), 7.11–7.08 (m, 4H, F-Ph-2,6, CH₃-Ph-3,5), 6.90 (t, 2H, J = 8.7 Hz, F-Ph-3,5), 6.82 (d, 1H, J = 7.2 Hz, H-6), 2.44 (s, 3H, CH₃), 2.29 (s, 3H, CH₃). ¹³C-NMR (CDCl₃) δ 161.7, 144.6, 143.7, 137.1, 135.7, 134.3, 131.8, 131.3, 130.7, 128.7, 127.3, 123.7, 114.9, 114.9, 109.9, 21.2, 14.4. Anal. Calcd for C₂₁H₁₇FN₂: C, 79.72; H, 5.42; N, 8.85. Found: C, 79.95; H, 5.48; N, 8.75.

7-(4-Fluorophenyl)-8-(4-methoxyphenyl)-2-phenylimidazo[1,2-a]pyridine (21). Method I. 2 (100 mg, 0.31 mmol), 4-methoxyphenylboronic acid (94 mg, 0.62 mmol) were used. The mixture was heated for 30 min. The crude residue was purified by column chromatography (silica gel, CH₂Cl₂). M.p. = 201 °C. 82% yield. ¹H-NMR (CDCl₃) δ 8.15 (d, 1H, J = 7.0 Hz, H-5), 7.99–7.89 (m, 3H, Ph-2,6, H-3), 7.43–7.27 (m, 5H, Ph-3,4,5, CH₃O-Ph-2,6), 7.12 (dd, 2H, J = 9–5.4 Hz, F-Ph-2,6), 6.94 (t, 2H, J = 8.7 Hz, F-Ph-3,5), 6.89–6.78 (m, 3H, CH₃O-Ph-3,5, H-6), 3.81 (s, 3H, CH₃O). ¹³C-NMR (CDCl₃) δ 161.9, 159.0, 146.0, 145.3, 135.9, 134.8, 133.5, 132.7, 131.4, 128.6, 127.9, 126.9, 126.3, 124.0, 115.8, 115.2, 113.4, 108.5, 55.2 (1C not found). Anal. Calcd for C₂₆H₁₉FN₂O: C, 79.17; H, 4.86; N, 7.10. Found: C, 79.35; H, 5.91; N, 7.24.

7-(4-Fluorophenyl)-2-methyl-8-(pyridin-4-yl)imidazo[1,2-a]pyridine (22). Method I. 4 (100 mg, 0.38 mmol), pyridin-4-ylboronic acid (76 mg, 0.54 mmol), Na₂CO₃ (82 mg, 0.77 mmol) and Pd(PPh₃)₄ (22 mg, 0.02 mmol, 5 mol%) were used. The mixture was heated for 60 min. The crude residue was purified by flash chromatography (silica, CH₂Cl₂/MeOH (99:1)). M.p. = 188 °C. 80% yield. ¹H-NMR (CDCl₃) δ 8.54 (d, 2H, J = 6.0 Hz, Pyr-2,6), 8.15 (d, 1H, J = 6.9 Hz, H-5), 7.46 (s, 1H, H-3), 7.31 (dd, 2H, J = 6.0 Hz, Pyr-3,5), 7.08 (dd, 2H, J = 8.7–5.4 Hz, F-Ph-2,6), 6.94 (t, 2H, J = 8.7 Hz, F-Ph-3,5), 6.87 (d, 1H, J = 6.9 Hz, H-6), 2.47 (s, 3H, CH₃). ¹³C-NMR (CDCl₃) δ 162.2, 148.9, 144.1, 143.2, 135.7, 134.4, 131.3, 126.2, 125.0, 124.0, 115.7, 115.5, 110.3, 14.2 (1C not found). Anal. Calcd for C₁₉H₁₄FN₃: C, 75.23; H, 4.65; N, 13.85. Found: C, 75.52; H, 4.56; N, 13.98.

8-(Fur-2-yl)-7-(p-tolylethynyl)-2-phenylimidazo[1,2-a]pyridine (23). Method I. 5 (100 mg, 0.29 mmol), fur-2-ylboronic acid (65 mg, 0.58 mmol), Na₂CO₃ (62 mg, 0.58 mmol) and Pd(PPh₃)₄ (17 mg, 0.02 mmol, 5 mol%) were used. The mixture was heated for 75 min. The crude residue was purified by flash chromatography (silica, cyclohexane/EtOAc (7:3)). M.p. > 300 °C. 80% yield. ¹H-NMR (CDCl₃) δ 8.08–7.96 (m, 4H, H-5, Ph-2,6, Fur-3), 7.91 (s, 1H, H-3), 7.74 (d, 1H, J = 1.7–0.9 Hz, Fur-5), 7.53–7.40 (m, 4H, Ph-3,5, CH₃-Ph-2,6), 7.34 (m, 1H, Ph-4), 7.21 (d, 2H, J = 7.9 Hz, CH₃-Ph-3,5), 6.98 (d, 1H, J = 6.8 Hz, H-6), 6.70 (dd, 1H, J = 3.4–1.7 Hz, Fur-4), 2.41 (s, 3H, CH₃). ¹³C-NMR (CDCl₃) δ 148.6, 145.8, 143.0, 139.0, 133.0, 131.5, 129.2, 128.7, 128.2, 126.2, 123.0, 120.5, 120.2, 117.2, 115.2, 114.5, 111.9, 109.4, 96.0, 88.5, 21.6 (1C not found). Anal. Calcd for C₂₆H₁₈N₂O: C, 83.40; H, 4.85; N, 7.48. Found: C, 83.56; H, 4.91; N, 7.34.

2-Phenyl-8-(thien-3-yl)imidazo[1,2-a]pyridine-7-carbonitrile (24). Method I. 9 (100 mg, 0.40 mmol), thien-3-ylboronic acid (71 mg, 0.55 mmol), Na₂CO₃ (84 mg, 0.79 mmol) and Pd(PPh₃)₄ (23 mg,
0.02 mmol, 5 mol%) were used. The mixture was heated for 15 min. The crude residue was purified by flash chromatography (silica, petroleum ether/EtOAc (100:0) to (20:80)). M.p. = 193 °C. 71% yield. 1H-NMR (CDCl3) δ 8.48 (dd, 1H, J = 3.0–1.3 Hz, Th-2), 8.11 (d, 1H, J = 7.0 Hz, H-5), 8.05 (dd, 1H, J = 5.1–1.3 Hz, Th-4), 7.99 (m, 3H, H-3, Ph-2,6), 7.52 (dd, 1H, J = 5.1–3.0 Hz, Th-5), 7.45 (m, 2H, Ph-3,5), 7.37 (m, 1H, Ph-4), 7.01 (d, 1H, J = 7.0 Hz, H-6). M.p. = 193 °C. 71% yield.

2-Phenyl-8-(pyridin-4-yl)imidazo[1,2-a]pyridine-7-carbonitrile (25). Method I. 9 (100 mg, 0.40 mmol), pyridin-4-ylboronic acid (78 mg, 0.55 mmol), Na2CO3 (84 mg, 0.79 mmol), Pd(PPh3)4 (23 mg, 0.02 mmol, 5 mol%) were used. The mixture was heated for 15 min. The crude residue was purified by flash chromatography [silica, cyclohexane/EtOAc (7:3)]. M.p. = 278 °C. 42% yield. 1H-NMR (CDCl3) δ 8.84 (d, 2H, J = 5.8 Hz, Pyr-2,6), 8.78 (d, 1H, J = 7.0 Hz, H-5), 8.74 (s, 1H, H-3), 7.96 (m, 2H, Ph-2,6), 7.84 (m, 2H, Pyr-3,5), 7.47 (m, 2H, Ph-3,5), 7.36 (m, 2H, H-6, Ph-4). 13C-NMR (CDCl3) δ 149.8, 147.5, 141.8, 140.7, 132.6, 132.4, 128.9, 128.6, 127.8, 126.0, 124.7, 117.4, 113.3, 112.5, 104.9. Anal. Calcd for C19H12N4: C, 77.01; H, 4.08; N, 18.91. Found: C, 77.12; H, 3.97; N, 18.89.

Ethyl 7-(cyclohexylamino)-8-(p-tolyl)imidazo[1,2-a]pyridine-2-carboxylate (26). Method H. 14 (100 mg, 0.31 mmol), p-tolylboronic acid (84.3 mg, 0.62 mmol) were used. The crude residue was purified by flash chromatography [silica, cyclohexane/EtOAc (7:3)]. M.p. = 169 °C. 27% yield. 1H-NMR (CDCl3) δ 8.04 (d, 1H, J = 7.5 Hz, H-5), 8.00 (s, 1H, H-3), 7.35 (d, 2H, J = 8.0 Hz, CH3-Ph-2,6), 6.65 (d, 1H, J = 7.5 Hz, H-6), 4.34 (q, 2H, J = 7.0 Hz, CH2), 4.15 (s, 1H, NH), 3.32 (m, 1H, CyHex), 2.39 (s, 3H, CH3), 1.94 (m, 2H, CyHex), 1.64 (m, 3H, CyHex), 1.20 (m, 8H, CH3, CyHex). 13C-NMR (CDCl3) δ 163.4, 146.9, 142.5, 137.7, 135.8, 130.4, 129.9, 129.6, 125.6, 115.7, 108.4, 105.3, 60.7, 52.1, 33.6, 25.5, 24.7, 21.3, 14.3. Anal. Calcd for C23H27FN3O2: C, 73.18; H, 7.21; N, 11.13. Found: C, 73.39; H, 7.18; N, 11.09.

Ethyl 8-(1H-indol-6-yl)-7-(p-tolyleny1)imidazo[1,2-a]pyridine-2-carboxylate (27). Method H. 6 (100 mg, 0.33 mmol), indol-6-ylboronic acid (96.6 mg, 0.66 mmol), K2CO3 (83 mg, 0.59 mmol) and Pd(PPh3)4 (34 mg, 0.03 mmol) were used. The crude residue was purified by flash chromatography [silica, cyclohexane/EtOAc (7:3)]. M.p. = 242 °C. 35% yield. 1H-NMR (CDCl3) δ 10.17 (bs, 1H, NH), 8.17–8.09 (m, 2H, H-5, H-3), 7.78 (s, 1H, Indol-7), 7.39 (d, 1H, J = 8.1 Hz, Indol-4*), 2.27 (s, 3H, CH3), 1.14 (t, 3H, CH3), 1.02 (m, 3H, CyHex). δ C-NMR (CDCl3) δ 161.6, 143.7, 139.2, 135.4, 134.6, 133.5, 131.6, 129.1, 129.8, 126.2, 125.6, 124.5, 121.2, 119.2, 121.3, 119.0, 118.6, 118.0, 114.0, 101.1, 97.0, 87.0, 61.5, 21.5, 14.0. (1 C not found) Anal. Calcd for C27H21N3O2: C, 77.18; H, 5.05; N, 10.02. Found: C, 77.47; H, 4.98; N, 10.13.

Ethyl 7-cyano-8-(pyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxylate (28). Method H. 10 (100 mg, 0.4 mmol), pyridin-4-ylboronic acid (80 mg, 0.56 mmol), K2CO3 (112 mg, 0.8 mmol), Pd(PPh3)4 (46 mg, 0.04 mmol) were used. The crude residue was purified by flash chromatography [silica, cyclohexane/EtOAc (100:0) to (10:90)]. M.p. = 185 °C. 31% yield. 1H-NMR (CDCl3) δ 8.86 (d, 2H, J = 6.0 Hz, Pyr-2,6), 8.40 (s, 1H, H-3), 8.35 (d, 1H, J = 7.0 Hz, H-5), 7.91 (d, 2H, J = 6.0 Hz, Pyr-3,5),
Molecules 2012, 17

7.19 (d, 1H,  = 7.0 Hz, H-6), 4.45 (q, 2H,  = 7.1 Hz, CH2), 1.41 (t, 3H,  = 7.1 Hz, CH3). 13C-NMR (CDCl3) δ 162.2, 149.9, 142.2, 139.9, 126.8, 124.6, 119.3, 116.4, 115.0, 107.5, 61.7, 14.3. (2C not found) Anal. Calcd for C16H12N4O2: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.92; H, 4.28; N, 19.04.

Ethyl 7-cyano-8-(fur-2-yl)imidazo[1,2-a]pyridine-2-carboxylate (29). Method H. 10 (100 mg, 0.4 mmol), fur-2-ylboronic acid (63 mg, 0.56 mmol), K2CO3 (112 mg, 0.8 mmol), Pd(PPh3)4 (46 mg, 0.04 mmol) were used. The crude residue was purified by flash chromatography [silica, cyclohexane/EtOAc (7:3)]. M.p. = 185 °C. 34% yield. 1H-NMR (CDCl3) δ 8.29–8.22 (m, 2H, H-3, Fur-3), 8.07 (d, 1H,  = 7.2 Hz, H-5), 7.78 (dd, 1H,  = 1.7–0.8 Hz, Fur-5), 7.08 (d, 1H,  = 7.2 Hz, H-6), 6.71 (dd, 1H,  = 3.6–1.7 Hz, Fur-4), 4.48 (q, 2H,  = 7.2 Hz, CH2), 1.46 (t, 3H,  = 7.2 Hz, CH3). 13C-NMR (CDCl3) δ 162.4, 148.8, 145.3, 140.1, 138.5, 123.7, 122.2, 119.3, 118.9, 117.9, 116.2, 113.0, 61.5, 14.3. (1 C not found) Anal. Calcd for C15H11N3O3: C, 64.05; H, 3.94; N, 14.94. Found: C, 63.92; H, 4.08; N, 15.02.

Ethyl 7-(cyclohexylamino)-8-(pyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxylate (30). Method H. 14 (100 mg, 0.31 mmol), pyridin-4-ylboronic acid (76.2 mg, 0.62 mmol) were used. The crude residue was purified by flash chromatography [silica, cyclohexane/EtOAc (6:4)]. M.p. = 182 °C. 28% yield. 1H-NMR (CDCl3) δ 8.72 (d, 2H,  = 5.1 Hz, Pyr-2,6), 7.98 (m, 2H, H-5, H-3), 7.57 (d, 2H,  = 5.1 Hz, Pyr-3,5), 6.65 (d, 1H,  = 7.7 Hz, H-6), 4.35 (q, 2H,  = 7.0 Hz, CH2), 4.26 (m, 1H, NH), 3.35 (m, 1H, CyHex), 1.91 (m, 2H, CyHex), 1.66 (m, 3H, CyHex), 1.40–1.05 (m, 8H, CH3, CyHex). 13C-NMR (CDCl3) δ 163.4, 150.6, 149.9, 146.0, 142.3, 136.4, 126.6, 125.8, 121.4, 115.9, 105.0, 60.9, 52.0, 33.5, 25.4, 24.7, 14.3. Anal. Calcd for C21H24N4O2: C, 69.21; H, 6.64; N, 15.37. Found: C, 69.38; H, 6.71; N, 15.24.

7-(4-Methoxyphenyl)-2-phenyl-8-(p-tolylethynyl)imidazo[1,2-a]pyridine (31). Method I. 7 (100 mg, 0.29 mmol), 4-methoxyphenylboronic acid (88 mg, 0.58 mmol), Na2CO3 (62 mg, 0.58 mmol), Pd(PPh3)4 (17 mg, 0.014 mmol, 5 mol%) were used. The mixture was heated for 30 min. The crude residue was purified by flash chromatography [silica, cyclohexane/EtOAc (7:3)]. M.p. = 84 °C. 56% yield. 1H-NMR (CDCl3) δ 8.12–8.01 (m, 3H, H-5, Ph-2,6), 7.87 (s, 1H, H-3), 7.75 (m, 2H, CH3O-Ph-2,6), 7.46 (m, 4H, Ph-3,5, CH3-Ph-2,6), 7.34 (m, 1H, Ph-4), 7.16 (d, 2H,  = 7.7 Hz, CH3-Ph-3,5), 7.03 (m, 2H, CH3O-Ph-3,5), 6.89 (d, 1H,  = 7.0 Hz, H-6), 3.89 (s, 3H, CH3O), 2.38 (s, 3H, CH3). 13C-NMR (CDCl3) δ 159.7, 146.3, 145.8, 140.2, 138.7, 133.5, 131.7, 131.0, 130.5, 129.0, 128.6, 128.0, 126.3, 124.4, 120.2, 114.5, 113.6, 109.6, 108.4, 98.6, 84.3, 55.4, 21.6. Anal. Calcd for C29H22N2O: C, 84.03; H, 5.35; N, 6.76. Found: C, 84.13; H, 5.34; N, 6.81.

Ethyl 7-(4-methoxyphenyl)-8-(p-tolylethynyl)imidazo[1,2-a]pyridine-2-carboxylate (32). Method H. 8 (100 mg, 0.30 mmol), 4-methoxyphenylboronic acid (65 mg, 0.42 mmol) were used. The crude residue was purified by flash chromatography [silica, cyclohexane/EtOAc (7:3)]. M.p. = 240 °C. 69% yield. 1H-NMR (CDCl3) δ 8.22 (s, 1H, H-3), 8.13 (d, 1H,  = 7.2 Hz, H-5), 7.75 (d, 2H,  = 9 Hz, CH3O-Ph-2,6), 7.41 (d, 2H,  = 8.1 Hz, CH3-Ph-2,6), 7.12 (d, 2H,  = 8.1 Hz, CH3O-Ph-3,5), 7.08–6.98 (m, 3H, H-6, CH3-Ph-3,5), 4.47 (q, 2H,  = 7.2 Hz, CH3), 3.89 (s, 3H, CH3O), 2.35 (s, 3H, CH3), 1.46 (t, 3H,  = 7.2 Hz, CH3). 13C-NMR (CDCl3) δ 163.0, 160.0, 145.5, 141.8, 138.9, 137.1, 131.8, 130.6, 130.4, 129.0, 124.8, 119.9, 117.6, 116.3, 113.7, 110.9, 99.6, 83.6, 61.3, 55.4, 21.6, 14.4. Anal. Calcd for C26H22N2O3: C, 76.08; H, 5.40; N, 6.82. Found: C, 76.24; H, 5.29; N, 6.64.
7-(4-Methoxyphenyl)-2-phenylimidazo[1,2-a]pyridine-8-carbonitrile (33). Method I. 11 (100 mg, 0.40 mmol), 4-methoxynaphthalenylboronic acid (84 mg, 0.55 mmol), Na2CO3 (84 mg, 0.79 mmol) and Pd(PPh3)4 (23 mg, 0.02 mmol, 5 mol%) were used. The mixture was heated for 15 min. The crude residue was purified by flash chromatography [silica, cyclohexane/EtOAc (7:3)]. M.p. = 185 °C. 61% yield. 1H-NMR (CDCl3) δ 8.26 (d, 1H, J = 7.0 Hz, H-5), 8.00 (m, 2H, Ph-2,6), 7.88 (s, 1H, H-3), 7.62 (d, 2H, J = 9.0 Hz, CH3O-Ph-2,6), 7.44 (m, 2H, Ph-3,5), 7.35 (m, 1H, Ph-4), 7.02 (d, 2H, J = 9.0 Hz, CH3O-Ph-3,5), 6.90 (d, 1H, J = 7.0 Hz, H-6), 3.86 (s, 3H, CH3O). 13C-NMR (CDCl3) δ 160.8, 147.5, 144.6, 144.1, 132.7, 130.0, 128.7, 128.5, 128.4, 128.3, 126.3, 115.5, 114.4, 113.5, 108.8, 98.1, 55.4. Anal. Calcd for C21H15N3O: C, 77.52; H, 4.65; N, 12.91. Found: C, 77.68; H, 4.53; N, 12.94.

7-(4-Methylphenyl)-N,2-diphenylimidazo[1,2-a]pyridin-8-amine (34). Method I. 15 (100 mg, 0.53 mmol), p-tolylboronic acid (362 mg, 2.66 mmol), Na2CO3 (112.4 mg, 1.06 mmol) and Pd(PPh3)4 (30.6 mg, 0.03 mmol, 5 mol%) were used. The mixture was heated for 30 min. The crude residue was purified by flash chromatography [silica, cyclohexane/EtOAc (70:30)] to give a white solid. M.p. = 237 °C. 44% yield. 1H-NMR (CDCl3) δ 7.98 (m, 2H, Ph-3,5), 7.87 (m, 2H, H-3, H-5), 7.45 (m, 2H, Ph-2,6), 7.34 (m, 3H, Ph-4, CH3-Ph-2,6), 7.00 (m, 4H, CH3-Ph-3,5, Ph-NH-3,5), 6.88 (d, 1H, J = 7.0 Hz, H-6), 6.72 (m, 3H, Ph-NH-2,4,6), 2.27 (s, 3H, CH3). 13C-NMR (CDCl3) δ 141.8, 136.9, 135.4, 131.3, 130.0, 129.6, 128.9, 128.7, 128.5, 128.1, 127.9, 126.1, 120.7, 118.6, 118.2, 116.8, 108.8, 21.1 (2C not found). Anal. Calcd for C26H21N3: C, 83.17; H, 5.64; N, 11.19. Found: C, 83.34; H, 5.77; N, 11.18.

3.2.8. General Procedures for Double-Coupling Approach

3-[8-(4-Methoxyphenyl)-2-phenylimidazo[1,2-a]pyridin-7-yl]aniline (35). Method J. To a solution of 1a (100 mg, 0.28 mmol) in DME (2 mL) and water (1 mL), were added 3-aminophenylboronic acid (39 mg, 0.28 mmol), Na2CO3 (90 mg, 0.85 mmol) and Pd(PPh3)4 (16 mg, 0.014 mmol). After irradiation under microwaves for 30 min at 95 °C, 4-methoxynaphthalenylboronic acid (60 mg, 0.40 mmol) and Pd(PPh3)4 (16 mg, 0.014 mmol) were added. The mixture was irradiated under microwaves during 30 min at 120 °C. After cooling to room temperature, CH2Cl2 (50 mL) and water (50 mL) were added and the solution was extracted with CH2Cl2 (3 × 50 mL). The combined organic layer was dried with anhydrous MgSO4 and evaporated under reduced pressure. The crude residue was purified by flash chromatography (alumina, CH2Cl2) to give a yellow solid. M.p. = 230 °C. 44% yield. 1H-NMR (CDCl3) δ 8.10 (d, 1H, J = 7.0 Hz, H-5), 7.94 (m, 3H, H-3, Ph-3,5), 7.42 (m, 4H, Ph-2,6, CH3O-Ph-2,6), 7.31 (m, 1H, Ph-4), 7.02 (t, 1H, J = 7.7 Hz, H2N-Ph-5), 6.86 (m, 3H, H-6, CH3O-Ph-3,5), 6.55 (m, 3H, H2N-Ph-4,6,2), 3.81 (s, 3H, CH3O), 3.23 (bs, 2H, NH2). 13C-NMR (CDCl3) δ 158.8, 146.1, 146.0, 145.5, 141.0, 135.8, 133.7, 132.6, 130.6, 128.9, 128.5, 127.8, 127.3, 126.2, 123.6, 120.3, 116.4, 115.9, 113.8, 113.2, 108.2, 55.1. Anal. Calcd for C26H21N3O: C, 79.77; H, 5.41; N, 10.73. Found: C, 79.92; H, 5.38; N, 10.63.

2-Phenyl-8-(pyridin-4-yl)-7-(thien-3-yl)imidazo[1,2-a]pyridine (36). Method J. Thien-3-ylboronic acid (39 mg, 0.28 mmol, 1 eq) and pyridin-4-ylboronic acid (56 mg, 0.40 mmol, 1.4 eq) were used. The crude residue was purified by flash chromatography [silica, cyclohexane/EtOAc (99:1)] to give a white solid. M.p. = 273 °C. 43% yield. 1H-NMR (CDCl3) δ 8.62 (dd, 2H, J = 4.5–1.5 Hz, Pyr-2,6), 8.16 (d, 1H, J = 7.0 Hz, H-5), 7.92 (m, 3H, H-3, Ph-3,5), 7.49 (dd, 2H, J = 4.5–1.5 Hz, Pyr-3,5), 7.40 (m, 2H,
8-(4-Fluorophenyl)-2-phenyl-7-(p-tolyl)imidazo[1,2-a]pyridine (37). Method K. To a solution of 1d (100 mg, 0.28 mmol) in DME (2 mL) and water (1 mL), were added 4-fluorophenylboronic acid (79 mg, 0.56 mmol), Na$_2$CO$_3$ (90 mg, 0.85 mmol) and Pd(PPh$_3$)$_4$ (16 mg, 0.014 mmol). After irradiation under microwaves for 1 h 30 min at 95 °C, p-tolylboronic acid (77 mg, 0.56 mmol) and Pd(PPh$_3$)$_4$ (16 mg, 0.014 mmol) were added. The mixture was irradiated under microwaves for 30 min at 120 °C. After cooling to room temperature, CH$_2$Cl$_2$ (50 mL) and water (50 mL) were added and the solution was extracted with CH$_2$Cl$_2$ (3 × 50 mL). The organic layer was dried with anhydrous MgSO$_4$ and evaporated under reduced pressure. The crude residue was purified by flash chromatography [silica, cyclohexane/EtOAc (99:1)] to give a white solid. M.p. = 215 °C. 47% yield. 1H-NMR (CDCl$_3$) δ 8.14 (d, 1H, $J = 7.0$ Hz, H-5), 7.98–7.90 (m, 3H, H-3, Ph-3,5), 7.50–7.37 (m, 4H, Ph-2,6, F-Ph-3,5), 7.32 (m, 1H, Ph-4), 7.11–6.95 (m, 6H, F-Ph-2,6, CH$_3$-Ph-2,3,5,6), 6.92 (d, 1H, $J = 7.0$ Hz, H-6), 2.35 (s, 3H, CH$_3$). 13C-NMR (CDCl$_3$) δ 162.1, 146.3, 145.4, 136.9, 136.5, 133.7, 133.2, 131.0, 129.8, 129.6, 128.9, 128.5, 127.9, 126.2, 124.1, 115.9, 115.1, 114.8, 108.3, 21.1.

2-Phenyl-7-(p-tolylethynyl)imidazo[1,2-a]pyridine-8-carbonitrile (38). Method L. To a solution of 1d (100 mg, 0.28 mmol) in DMF (3 mL), was added CuCN (31 mg, 0.34 mmol). The mixture was irradiated under microwaves at 90 °C during 4 h. Then, 4-ethynyltoluene (47 µL, 0.37 mmol), Et$_3$N (198 µL, 1.41 mmol), Pd(PPh$_3$)$_4$ (33 mg, 0.03 mmol), PCy$_3$HBF$_4$ (31 mg, 0.08 mmol) and CuI (11 mg, 0.056 mmol) were added. The mixture was irradiated under microwaves at 130 °C during 1 h. After cooling to room temperature, a solution of NH$_4$OH 10% (50 mL) and EtOAc (50 mL) were added. The solution was extracted with EtOAc (3 × 50 mL), dried with anhydrous MgSO$_4$ and evaporated under reduced pressure. The crude residue was purified by flash chromatography [silica, cyclohexane/EtOAc (7:3)]. M.p. = 214 °C. 32% yield. 1H-NMR (CDCl$_3$) δ 8.22 (d, 1H, $J = 7.0$ Hz, 1H, H-5), 8.02 (m, 2H, Ph-2,6), 7.94 (s, 1H, H-3), 7.55 (m, 2H, CH$_3$-Ph-2,6), 7.46 (m, 2H, Ph-3,5), 7.38 (m, 1H, Ph-4), 7.21 (d, 2H, $J = 7.9$ Hz, CH$_3$-Ph-3,5), 6.95 (d, 1H, $J = 7.0$ Hz, H-6), 2.41 (s, 3H, CH$_3$). 13C-NMR (CDCl$_3$) δ 148.5, 140.4, 132.4, 132.2, 129.3, 128.8, 128.7, 128.0, 127.7, 126.5, 125.2, 118.3, 114.4, 114.2, 109.7, 100.5, 84.8, 21.7. Anal. Calcd for C$_{23}$H$_{15}$N$_3$: C, 82.86; H, 4.54; N, 12.60. Found: C, 82.97; H, 4.56; N, 12.68.

7-[4-(4-Fluorophenyl)piperazin-1-yl]-2-phenylimidazo[1,2-a]pyridine-8-carbonitrile (39). Method M. To a solution of 1d (100 mg, 0.28 mmol) in DMF (3 mL), CuCN (31 mg, 0.34 mmol) was added. The mixture was stirred at 90 °C during 4 h under microwave irradiation. Then DIPEA (0.1 mL, 0.57 mmol) and 4-fluorophenylpiperidine (98 mg, 0.57 mmol) were added. The mixture was heated at 130 °C during 1 h under microwaves irradiation. After cooling to room temperature, EtOAc (50 mL) and a solution of NH$_4$OH 10% (50 mL) were added. The solution was extracted with EtOAc (3 × 50 mL), dried with anhydrous MgSO$_4$ and evaporated under reduced pressure. The crude residue was purified
by flash chromatography [silica, cyclohexane/EtOAc (7:3)]. M.p. = 224 °C. 67% yield. $^1$H-NMR (CDCl$_3$) $\delta$ 8.06 (d, 1H, $J$ = 7.5 Hz, H-5), 7.97 (m, 2H, Ph-2,6), 7.71 (s, 1H, H-3), 7.42 (m, 2H, Ph-3,5), 7.33 (m, 1H, Ph-4), 7.06–6.89 (m, 4H, F-Ph), 6.55 (d, 1H, $J$ = 7.5 Hz, H-6), 3.79–3.69 (m, 4H, pip), 3.36–3.27 (m, 4H, pip). $^{13}$C-NMR (CDCl$_3$) $\delta$ 157.7, 154.0, 147.2, 146.6, 145.4, 133.0, 129.1, 128.7, 128.2, 126.2, 118.5, 116.0, 115.8, 107.6, 105.3, 85.3, 50.5, 50.2. Anal. Calcd for C$_{24}$H$_{20}$FN$_5$: C, 72.53; H, 5.07; N, 17.62. Found: C, 72.49; H, 5.01; N, 18.73.

Ethyl 8-cyano-7-(p-tolylethynyl)imidazo[1,2-a]pyridine-2-carboxylate (40). Method L. 1e (100 mg, 0.29 mmol) was used as starting material. M.p. = 93 °C. 43% yield. $^1$H-NMR (CDCl$_3$) $\delta$ 8.22 (s, 1H, H-3), 8.12 (d, 1H, $J$ = 7.2 Hz, H-5), 7.54 (d, 2H, $J$ = 8.0 Hz, CH$_3$-Ph-2,6), 7.17 (d, 2H, $J$ = 8.0 Hz, CH$_3$-Ph-3,5), 6.96 (d, 1H, $J$ = 7.2 Hz, H-6), 4.44 (q, 2H, $J$ = 7.2 Hz, CH$_2$), 2.38 (s, 3H, CH$_3$), 1.42 (t, 3H, $J$ = 7.2 Hz, CH$_3$). $^{13}$C-NMR (CDCl$_3$) $\delta$ 162.6, 144.6, 139.6, 137.3, 135.3, 132.0, 129.0, 125.3, 119.1, 118.1, 116.0, 113.7, 102.9, 80.8, 61.4, 21.6, 14.3 (1 C not found). Anal. Calcd for C$_{20}$H$_{15}$N$_3$O$_2$: C, 72.94; H, 4.59; N, 12.76. Found: C, 73.27; H, 4.68; N, 12.81.

Ethyl 8-cyano-7-[4-(4-fluorophenyl)piperazin-1-yl]imidazo[1,2-a]pyridine-2-carboxylate (41). Method M. 1e (100 mg, 0.29 mmol) was used as starting material. M.p. = 193 °C. 54% yield. $^1$H-NMR (CDCl$_3$) $\delta$ 8.20–7.91 (m, 2H, H-3, H-5), 7.07–6.88 (m, 4H, F-Ph), 6.67 (d, 1H, $J$ = 7.0 Hz, H-6), 4.43 (q, 2H, $J$ = 7.0 Hz, CH$_2$), 3.83 (bs, 4H, pip), 3.33 (bs, 4H, H-pip), 1.42 (t, 3H, $J$ = 7.0 Hz, CH$_3$). $^{13}$C-NMR (CDCl$_3$) $\delta$ 162.8, 157.9, 154.4, 145.3, 137.5, 132.5, 129.5, 123.6, 118.7, 117.2, 115.9, 107.4, 84.5, 61.3, 50.7, 49.9, 14.3. Anal. Calcd for C$_{21}$H$_{20}$FN$_5$O$_2$: C, 64.11; H, 5.12; N, 17.80. Found: C, 64.49; H, 5.08; N, 17.94.

4. Conclusions

The reactivity of the 7-chloro-8-iodo- and 8-chloro-7-iodoimidazo[1,2-a]pyridines 1a–e variously substituted on the 2 position, towards Suzuki-Miyaura, Sonogashira, and Buchwald-Hartwig cross-coupling reactions as well as cyanation was evaluated. Various methodologies are proposed to introduce aryl, heteroaryl, alkyne, amine or cyano groups in the two positions depending on the nature of the substituent present in position 2. The sensitivity of the 2-ester group obliged us to adapt the reaction conditions, notably when a base was required. Moreover, the presence of the 2-ester seemed to lower the reactivity of the 8 position towards the Sonogashira and the cyanation reactions.

In both series, the substitution was totally regioselective due to the differences in reactivity between the iodine and chlorine atoms. Nevertheless, the difficulty in our cases was to substitute the chlorine atom in the second step. Until now, only hetero(aryl) groups could be introduced though Suzuki-Miyaura cross-coupling. We overcame this problem evaluating the both regioisomers in parallel.

The double coupling approach was also studied allowing the one pot Suzuki/Suzuki, cyanation/ Sonogashira and cyanation/Buchwald reactions leading to polyfunctionalized imidazo[1,2-a]pyridines. New heterogeneous double coupling approaches are under investigations.

Acknowledgments

The authors thank Frédéric Montigny from the SAVIT, Tours (France) for NMR spectrometry.
References

1. Nordqvist, A.; Nilsson, M.T.; Lagerlund, O.; Muthas, D.; Gising, J.; Yahiaoui, S.; Odell, L.R.; Srinivasa, B.R.; Larhed, M.; Mowbray, S.L.; et al. Synthesis, biological evaluation and X-ray crystallographic studies of imidazo[1,2-a]pyridine-based Mycobacterium tuberculosis glutamine synthetase inhibitors. *Med. Chem. Commun.* 2012, 3, 620–626.

2. Bode, M.L.; Gravestock, D.; Moleele, S.S.; van der Westhuizen, C.W.; Pelly, S.C.; Steenkamp, P.A.; Hoppe, H.C.; Khan, T.; Nkabinde, L.A. Imidazo[1,2-a]pyridin-3-amines as potential HIV-1 non-nucleoside reverse transcriptase inhibitors. *Bioorg. Med. Chem.* 2011, 19, 4227–4237.

3. Hieke, M.; Rödl, C.B.; Wisniewska, J.M.; la Buscato, E.; Stark, H.; Schubert-Zsilavecz, M.; Steinhilber, D.; Hofmann, B.; Proschak, E. SAR-study on a new class of imidazo[1,2-a]pyridine-based inhibitors of 5-lipoxygenase. *Bioorg. Med. Chem. Lett.* 2012, 22, 1969–1975.

4. Dahan-Farkas, N.; Langley, C.; Rousseau, A.L.; Yadav, D.B.; Davids, H.; de Koning, C.B. 6-Substituted imidazo[1,2-a]pyridines: Synthesis and biological activity against colon cancer cell lines HT-29 and Caco-2. *Eur. J. Med. Chem.* 2011, 46, 4573–4583.

5. El Akkaoui, A.; Bassoude, I.; Koubachi, J.; Bertina-Raboin, S.; Mouaddib, A.; Guillaumet, G. Pd-catalyzed regiocontrolled Sonogashira and Suzuki cross-coupling reaction of 3,6-dihalogenoimidazo[1,2-a]pyridines: One-pot double-coupling approach. *Tetrahedron* 2011, 67, 7128–7138.

6. Szabo, R.; Crozet, M.D.; Vanelle, P. Microwave assisted double Suzuki-Miyaura cross-coupling in the 6,8-dibromoimidazo[1,2-a]pyridine series. *Synthesis* 2008, 1, 127–135.

7. Kettle, J.G.; Brown, S.; Crafter, C.; Davies, B.R.; Dudley, P.; Fairley, G.; Faulder, P.; Fillery, S.; Greenwood, H.; Hawkins, J.; et al. Diverse Heterocyclic Scaffolds as Allosteric Inhibitors of AKT. *J. Med. Chem.* 2012, 55, 1261–1273.

8. Trabanco, A.A.; Tresadern, G.; Macdonald, G.J.; Vega, J.A.; de Lucas, A.I.; Matesanz, E.; Garcia, A.; Linares, M.L.; Alonso de Diego, S.A.; Alonso, J.M.; et al. Imidazo[1,2-a]pyridines: Orally Active Positive Allosteric Modulators of the Metabotropic Glutamate 2 Receptor. *J. Med. Chem.* 2012, 55, 2688–2701.

9. Tresadern, G.; Cid, J.M.; Macdonald, G.J.; Vega, J.A.; de Lucas, A.I.; Garcia, A.; Matesanz, E.; Linares, M.L.; Oehrlich, D.; Lavreysen, H.; et al. Scaffold hopping from pyridones to imidazo[1,2-a]pyridines. New positive allosteric modulators of metabotropic glutamate 2 receptor. *Bioorg. Med. Chem. Lett.* 2010, 20, 175–179.

10. Cid-Nunez, J.M.; Trabanco-Suarez, A.A.; Macdonald, G.J. Indole and Benzoxazine Derivatives As Modulators of Metabotropic Glutamate Receptors. PCT Int. Appl. WO 2010060589, 2010.

11. Barrio, J.R.; Petric, A.J.; Satyamurthy, N. Methods for Binding Agents to β-Amyloid Plaques. PCT Int. Appl. WO 2005040337, 2005.

12. Enguehard, C.; Renou, J.-L.; Collot, V.; Hervet, M.; Rault, S.; Gueiffier, A. Reactivity of 3-iodoimidazo[1,2-a]pyridines using a Suzuki-Type cross-coupling reaction. *J. Org. Chem.* 2000, 65, 6572–6575.

13. Enguehard, C.; Hervet, M.; Théry, I.; Renou, J.-L.; Fauvelle, F.; Gueiffier, A. (Hetero)arylation of 6-halogenoimidazo[1,2-a]pyridines differently substituted at C(2): Influence of the 2-substituent on the Suzuki cross-coupling reaction. *Helv. Chim. Acta* 2001, 84, 3610–3615.
14. Ince, S.; Haegebarth, A.; Politz, O.; Neuhaus, R.; Bömer, U.; Scott, W. Imidazopyrimidine and Imidazopyridine Derivatives As Inhibitors of the PI3K/Akt Pathway and Their Preparation and Use for the Treatment of Diseases. PCT Int. Appl. WO 2012007345, 2012.

15. Snégaroff, K.; Nguyen, T.T.; Marquise, N.; Halauko, Y.S.; Harford, P.J.; Roisnel, T.; Matulis, V.E.; Ivashkevich, O.A.; Chevallier, F.; Wheatley, A.E.H.; et al. Deprotonative metalation of chloro- and bromopyridines using amido-based bimetallic species and regioselectivity-computed CH acidity relationships. Chem. Eur. J. 2011, 17, 13284–13297.

16. Blum, C.A.; Caldwell, T.; Zheng, X.; Bakthavatchalam, R.; Capistoti, S.; Brielmann, H.; de Lombaert, S.; Kershaw, M.T.; Matson, D.; Krause, J.E.; et al. Discovery of novel 6,6-heterocycles as transient receptor potential vanilloid (TRPV1) antagonists. J. Med. Chem. 2010, 53, 3330–3348.

17. Schroeder, G.M.; An, Y.; Cai, Z.-W.; Chen, X.-T.; Clark, C.; Cornelius, L.A.M.; Dai, J.; Gullo-Brown, J.; Gupta, A.; Henley, B.; et al. Discovery of N-(4-(2-amino-3-chloropyridin-4-yloxy)-3-fluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (BMS-777607), a selective and orally efficacious inhibitor of the Met Kinase Superfamily. J. Med. Chem. 2009, 52, 1251–1254.

Sample Availability: Samples of all compounds are available from the authors.

© 2012 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0__).