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Regiocontrolled functionalization of 2,3-dihalogenoimidazo[1,2-*a*]pyridines by Suzuki-Miyaura and Sonogashira cross-coupling reactions

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An efficient method for regiocontrolled functionalization of 2,3-dihalogenoimidazo[1,2-*a*]pyridine was developed. This sequence allowed the selective introduction of aryl, heteroaryl, alkyl and alkynyl substituents at both 2- and 3-positions, by using Suzuki-Miyaura and Sonogashira cross-coupling reactions. Library of compounds diversely substituted on 2 and 3-positions can be easily prepared from a common, stable and easily accessible starting material.

Introduction

The significant and potential biological activities of compounds sharing the imidazo[1,2-*a*]pyridine moiety have been widely exploited in various pharmacological areas.[1] Indeed, this heterocycle is the key scaffold in many commercially available drugs, including Zolpidem and Zolimidine or drug candidates like GSK812397 (figure 1). Consequently, there is a continued effort to provide new methods for efficient functionalization of imidazo[1,2-*a*]pyridines, including regiocontrolled Pd-catalyzed cross-coupling reactions.[2]

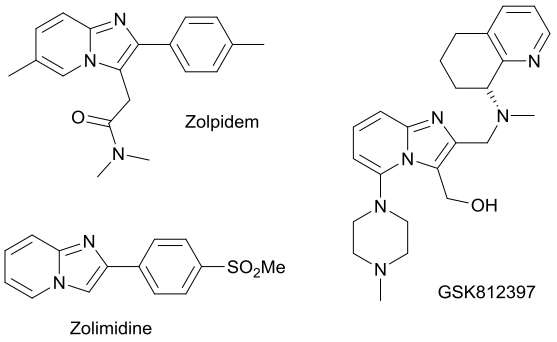
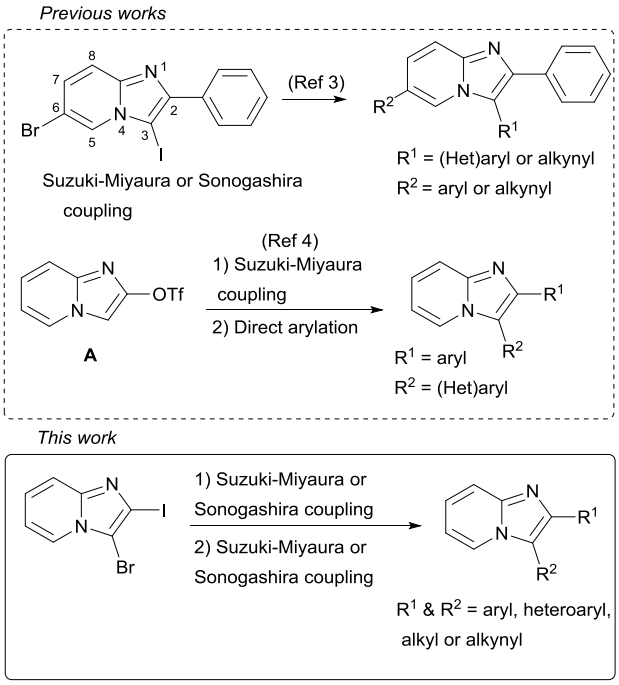


Figure 1 : imidazo[1,2-*a*]pyridine-based drugs

To date, most of the methods developed for achieving regiocontrolled functionalization are limited to reaction at 3-position and 6-position (scheme 1).[3] To the best of our knowledge, only one method, developed by Marchand *et al.*, allowed the selective functionalization at the 2- and 3-position.[4]

Thus, 2,3-diarylimidazo[1,2-*a*]pyridines can be prepared from triflate **A**, *via* Suzuki-Miyaura cross-coupling at the 2-position followed by direct arylation at the 3-position.



Scheme 1 : regiocontrolled Pd-catalyzed functionalization of imidazo[1,2-*a*]pyridines

Despite the elegance of this method, it suffers from several drawbacks, for instance difficult synthesis and storage of triflate derivatives, and most importantly the limitation of arylation at the 2-position and arylation or heteroarylation at the 3-position. Besides this method the 2-position is usually set by the heterocyclization step (*e.g.* reaction between 2-aminopyridines and α-halogenoketones or Groebke-Blackburn-Bienaymé reaction).[5] Thus the pharmacomodulation of this position is

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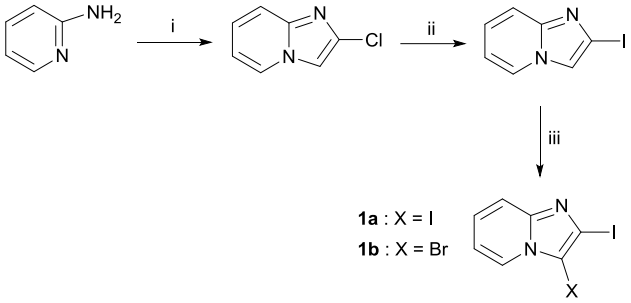
tedious, due to the fact that the synthesis is divergent from the first step.

We report herein a general method for regiocontrolled Pd-catalyzed functionalisation of 2,3-dihalogenoimidazo[1,2-*a*]pyridine that are air- and moisture-stable. Our method allowed regioselective arylation, heteroarylation, alkylation and alkynylation at both 2 and 3-positions. Thus, preparation of a library of compounds with every possible combination of substituents is possible, from a common starting material.

Results and discussion

Starting material preparation

The 2,3-dihalogenoimidazo[1,2-*a*]pyridines **1a** and **1b** were prepared in a three-step sequence, from cheap starting material. 2-chloro and 2-iodoimidazopyridines were prepared according to the literature procedures[4,6] and **1a-b** were synthetized by reaction with NIS or NBS, respectively.

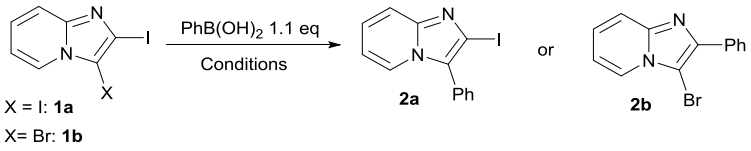


Scheme 2 : Synthesis of **1a-b**. Reagents and conditions: (i) a) $ClCH_2CO_2H$, Et_3N, H_2O, 90°C, 5h, then EtOH, 5°C, 2h. b) $POCl_3$, toluene, reflux, overnight, 76%. (ii) NaI, HI, CH_3CN, reflux, 9h, 87%. (iii) X = Br: NBS, CH_3CN, r.t., 1h, 90%. X = I: NIS, CH_3CN, r.t., 3h, 92%.

Optimisation of selective Suzuki-Miyaura coupling on **1a** and **1b**

In our fist attempts we tried to optimize the first Suzuki-Miyaura cross-coupling between **1a** and phenylboronic acid (Table 1). The first try with 5% $Pd(PPh_3)_4$, Na_2CO_3 (2 equiv) in DME/H_2O (2:1) at 100°C for 4h (entry 1) gave only incomplete conversion (50%). The product **2a** has been identified as 2-iodo-3-phenylimidazo[1,2-*a*]pyridine according to literature data[7], proving the higher reactivity of the 3-position over the 2-position. Increasing the reaction time to 24h insured complete starting material consumption, but gave **2a** in only 53% isolated yield, due to the formation of a large amount of deiodinated adduct (entry 2). Changing DME to 1,4-dioxane gave similar result (entry 3). In order to overcome the formation of this side-product, microwave heating was applied for 2h at 120°C (entry 4) or 30min at 100°C with 10% $Pd(PPh_3)_4$ (entry 5). Unfortunately both attempts were unsuccessful, furnishing **2a** in 35% yield and a 50/50 ratio of **1a**/**2a**, respectively. Thus other solvent system (toluene/H_2O, entry 6), base (NaOH, entry 7) or palladium catalyst ($Pd(OAc)_2$ 5%/XPhos 10%, entry 8) were unsuccessfully tested, yielding only low conversion, of 20-50%. Moreover, some different reaction conditions were tested (entries 9 and 10) but only modest results were obtained, 35% conversion and 54% yield, respectively. We therefore turned our attention to the Suzuki-Miyaura cross-coupling between **1b** and phenylboronic acid. To our delight the first attempt with 5% $Pd(PPh_3)_4$, Na_2CO_3 (2 equiv) in dioxane/H_2O (2:1) at 100°C for 24h (Table 1, entry 11) provided **2b**, with a complete selective reaction on the iodine and a good yield (73%). The structure of **2b** was confirmed by comparison to the literature data.[8] Despite the higher reactivity of the 3-position observed with **1a**, the reaction is directed toward the iodo-substituted 2-position over the bromo-substituted 3-position in the case of **1b**.

Table 1 : optimization of Suzuki-Miyaura coupling between **1a** or **1b** and phenylboronic acid



Entry	X	[Pd]	Base (eq)	Solvent	Time/ T	Results
1	I (**1a**)	$Pd(PPh_3)_4$ 5%	Na_2CO_3 (2)	DME/H_2O (2:1)	4h/100°C	**1a**/**2a** : 50/50[a]
2	I (**1a**)	$Pd(PPh_3)_4$ 5%	Na_2CO_3 (2)	DME/H_2O (2:1)	24h/100°C	**2a** : 53%[b]
3	I (**1a**)	$Pd(PPh_3)_4$ 5%	Na_2CO_3 (2)	dioxane/H_2O (2:1)	24h/100°C	**2a** : 54%[b]
4	I (**1a**)	$Pd(PPh_3)_4$ 5%	Na_2CO_3 (2)	dioxane/H_2O (2:1)	2h/120°C (MW)	**2a** : 35%[b]
5	I (**1a**)	$Pd(PPh_3)_4$ 10%	Na_2CO_3 (2)	dioxane/H_2O (2:1)	30min/100°C (MW)	**1a**/**2a** : 50/50[a]
6	I (**1a**)	$Pd(PPh_3)_4$ 5%	Na_2CO_3 (2)	toluene/H_2O (2:1)	24h/100°C	**1a**/**2a** : 80/20[a]
7	I (**1a**)	$Pd(PPh_3)_4$ 5%	NaOH (2)	toluene/H_2O (2:1)	24h/100°C	**1a**/**2a** : 80/20[a]
8	I (**1a**)	$Pd(OAc)_2$ 5% XPhos 10%	Na_2CO_3 (2)	dioxane/H_2O (2:1)	24h/100°C	**1a**/**2a** : 50/50[a]
9	I (**1a**)	$Pd(OAc)_2$ 5% PPh_3 10%	K_2CO_3 (2)	DMF	24h/100°C	**1a**/**2a** : 65/35[a]
10	I (**1a**)	$Pd(PPh_3)_4$ 5%	K_3PO_4 2M (2)	toluene/EtOH (2:0.1)	24h/100°C	**2a** : 54%[b]
11	Br (**1b**)	$Pd(PPh_3)_4$ 5%	Na_2CO_3 (2)	dioxane/H_2O (2:1)	24h/100°C	**2b** : 73%[b]
12	Br (**1b**)	$Pd(PPh_3)_4$ 5%	Na_2CO_3 (2)	dioxane/H_2O (2:1)	1h/120°C (MW)	**2b** : 79%[b]

a) Determined from crude ^1H NMR analysis. b) Isolated yield.

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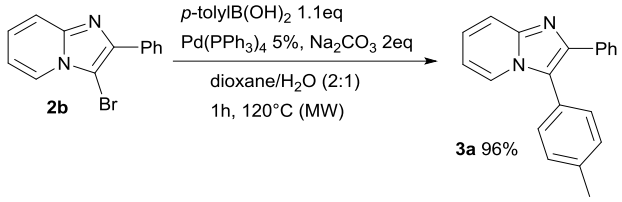
Optimization of the reaction time led us to apply microwave heating for 1h at 120°C, leading to complete conversion in 79% isolated yield (Table 1, entry 12).

With this first reaction in hands, we then investigated the reactivity of the brominated 3-position (Scheme 3). The same conditions applied to the coupling between **2b** and *p*-tolylboronic acid furnished product **3a** with excellent yield (96%).



Scheme 3 : synthesis of **3a**

The NMR data for **3a** are in perfect agreement with literature[9], and the structure was further confirmed by X-ray crystal structure analysis (Figure 2).[10] With optimized conditions for both 2 and 3-positions, we then focused on exploration of the scope of this sequence.

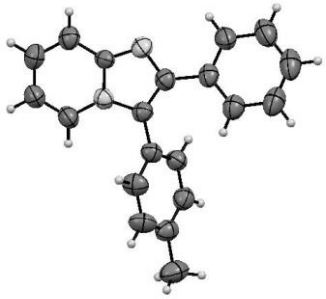
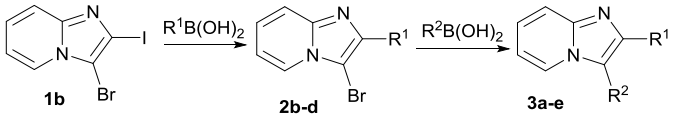


Figure 2: ORTEP diagram for **3a**

Scope of selective Suzuki-Miyaura coupling on **1b**

The selective Suzuki-Miyaura coupling of **1b** with diverse boronic acids was undertaken (Table 2). Starting from **2b**, the coupling at the 3-position can be realized with various aryl groups (entries 1 and 2) as well as heteroaryls (entry 3) to furnish product **3a-c** in good to excellent yields (67-97%). Noteworthy, alkylboronic acid such as $MeB(OH)_2$ can also be utilized in the reaction (entry 4, 76%). Concerning the 2-position, heteroaryles can be used, such as $thienylB(OH)_2$ (entry 5, **2c**, 80%), with further functionalization of 3-position yielding to **3e** (88%). $MeB(OH)_2$ gave the corresponding product only in a moderate yield (entry 6, 42%) when applied to the first Suzuki-Miyaura coupling, and required longer reaction time. Unfortunately **2d** can't be used for further reaction with $PhB(OH)_2$, ending in complex, inseparable mixture. The regioselective formation of **2c** and **2d** from **1b** was confirmed by mass spectrometry, with *m/z* and isotopic pattern indicating brominated compounds.

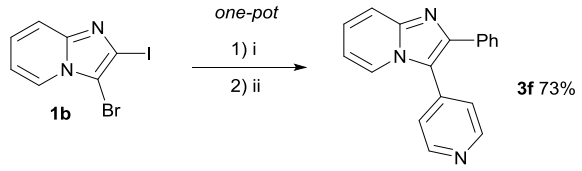
Table 2 : scope of Suzuki-Miyaura coupling between **1b** and various boronic acids



Entry	R^1	yield[a]	R^2	yield[a]
1	Ph : **2b**	79%[b]	*p*-tolyl : **3a**	96%[b]
2	**2b**	-	*p*-MeO-Ph : **3b**	97%[b]
3	**2b**	-	2-furyl : **3c**	67%[b]
4	**2b**	-	Me : **3d**	76%[b]
5	3-Thienyl : **2c**	80%[b]	Ph : **3e**	88%[b]
6	Me : **2d**	42%[c]	Ph	0%[b]

a) Isolated yield. b) Reagents and conditions: 5% $Pd(PPh_3)_4$, boronic acid (1.1eq), Na_2CO_3 (2eq), dioxane/H_2O (2:1), 120°C (MW), 1h. c) Reagents and conditions: 5% $Pd(PPh_3)_4$, boronic acid (1.1eq), Na_2CO_3 (2eq), dioxane/H_2O (2:1), 120°C (MW), 2h30.

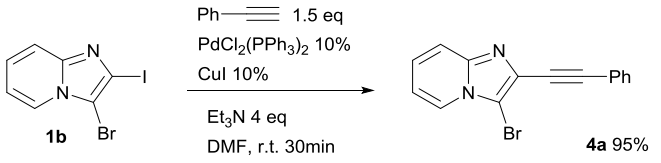
This selective functionalisation of **1b** with Suzuki-Miyaura cross-coupling have also been realized in a one-pot process. The reaction proceeded smoothly, even if the product purification can be highly challenging, depending on the substituent's nature. Product **3f** can be obtained with good yield (73%) from coupling between **1b** and $PhB(OH)_2$, followed by 4-$PyrB(OH)_2$ (Scheme 4).



Scheme 4: One-pot selective coupling of **1b**. Reagents and conditions: (i) 5% $Pd(PPh_3)_4$, Na_2CO_3 (2eq), $PhB(OH)_2$ (1.1eq), dioxane/H_2O (2:1), 120°C (MW), 1h. (ii) 5% $Pd(PPh_3)_4$, Na_2CO_3 (2eq), 4-pyridylB(OH)$_2$ (1.1eq), dioxane/H_2O (2:1), 120°C (MW), 1h.

Optimisation of selective Sonogashira coupling on **1b**

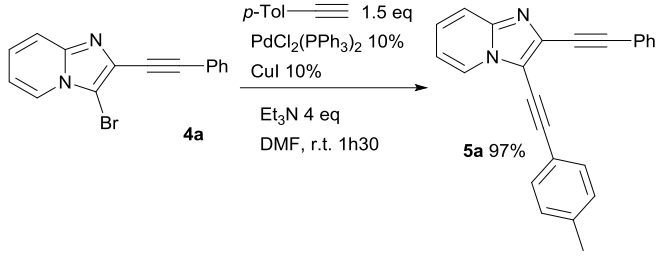
A first attempt of Sonogashira coupling between **1b** and phenylacetylene provided compound **4a** in excellent yield 95% and complete selectivity toward the more reactive C-I position (Scheme 5).



Scheme 5: selective Sonogashira coupling between **1b** and phenylacetylene

Introducing alkyne moiety at 2-position on imidazo[1,2-*a*]pyridine skeleton is a challenging task, and only few reports in the literature describing such a transformation, including: 1) Bestmann-Ohira reaction with aldehydes[11], yielding only terminal alkynes, 2) heterocyclizations furnishing 2-bromoimidazo[1,2-*a*]pyridines[7] (from bromoalkynes) or 2-iodoimidazo[1,2-*a*]pyridines[12] (from alkynes) and further used for Sonogashira coupling, both setting the 3-position from the beginning, and limiting it to available alkynes side chains and 3) Groebke-Blackburn-Bienaymé[13] reaction with propargylic aldehydes, limiting the 3-position to amine function. Some other groups published[14] or patented[6,15] Sonogashira coupling using 2-iodoimidazo[1,2-*a*]pyridines but without any substituents at 3-position.

We then tried to perform Sonogashira coupling on the remaining C-Br position. Indeed, product **5a** could be obtained from **4a** in a very high yield (97%) with the same catalytic system, by heating at 80°C for 1.5h (Scheme 6).

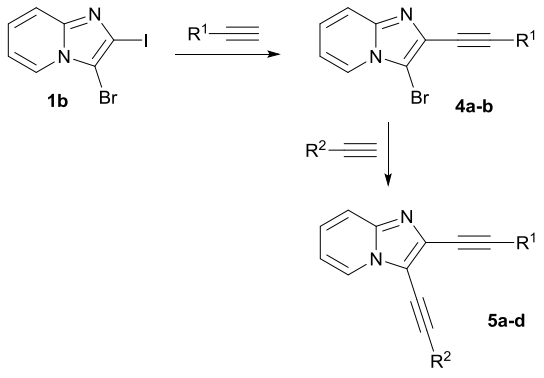


Scheme 6: Sonogashira coupling between **4a** and p-tolylacetylene

Scope of selective Sonogashira coupling on **1b**

In order to investigate the scope of selective Sonogashira coupling on **1b**, several alkynes were introduced in 2 and 3-position (Table 3). After the first coupling on 2-position using phenylacetylene, the further functionalization of **4a** can be performed with aryl (entry 1) or alkyl (entry 2) substituted alkynes with good to excellent yields (82-97%). The use of alkyne with a heteroatom at the side chain gave the desired product in moderate yield (entry 3, 42%) and required longer reaction time (7h). The first Sonogashira coupling proceeds with cyclopropylacetylene as well (entry 4), furnishing **4b** in 98% yield. Further reaction on **4b** with phenylacetylene (entry 4) gave **5d** in moderate yield (54%).

Table 3: Scope of Sonogashira coupling between **1b** and alkynes

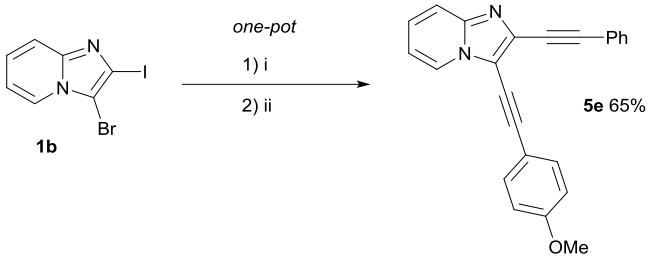


Entry	R^1	yield[a]	R^2	yield[a]
1	Ph: **4a**	95%[b]	*p*-tolyl: **5a**	97%[c]
2	**4a**	-	c-Pr: **5b**	82%[c]
3	**4a**	-	CH_2OMe: **5c**	42%[d]
4	c-Pr: **4b**	98%[b]	Ph: **5d**	54%[c]

a) Isolated yield. b) Reagents and conditions: $PdCl_2(PPh_3)_2$ 10%, CuI 10%, alkynes (1.5eq), Et_3N (4eq), DMF, r.t. 30min. c) Reagents and conditions: $PdCl_2(PPh_3)_2$ 10%, CuI 10%, alkynes (1.5eq), Et_3N (4eq), DMF, 80°C, 1h30. d) Reagents and conditions: $PdCl_2(PPh_3)_2$ 10%, CuI 10%, alkynes (1.5eq), Et_3N (4eq), DMF, r.t. 7h.

The regioselective formation of **4a** and **4b** from **1b** was confirmed by mass spectrometry, with *m/z* and isotopic pattern indicating brominated compounds.

The selective synthesis of 2,3-diynes can be also performed in a one-pot manner. Compound **5e** was obtained by a reaction of **1b** and phenylacetylene for 30min at room temperature, followed by addition of *p*-methoxyphenylacetylene and heating at 80°C for 1.5h, in a good 65% yield (Scheme 7).

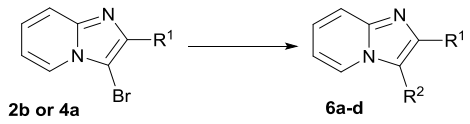


Scheme 7: One-pot selective Sonogashira coupling on **1b.** Reagents and conditions: (i) $PdCl_2(PPh_3)_2$ 10%, CuI 10%, phenylacetylene (1.5eq), Et_3N (4eq), DMF, r.t. 30min. (ii) $PdCl_2(PPh_3)_2$ 10%, CuI 10%, p-methoxyphenylacetylene (1.5eq), Et_3N (4eq), DMF, 80°C, 1h30.

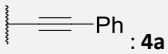
Selective Suzuki-Miyaura and Sonogashira coupling on **1b**

Combination of Suzuki-Miyaura and Sonogashira coupling have been ultimately investigated, in order to prepare compounds **6a-d** with aryles and alkynes as substituents (Table 4). Sonogashira coupling of either **2b** (entry 1) or **2d** (entry 2) with phenylacetylene proceeded smoothly, and products **6a** and **6b** were obtained in good 76% and 67% yields, respectively. Suzuki-Miyaura coupling on 3-position of **4a** (entries 3-4) succeeded as well, with both alkyl and aryl, yielding **6c** and **6d** in 70% and 89% yields, respectively. Noteworthy, both isomers **6b** and **6c** could be easily prepared in a minimum of steps from **1b**, which is impossible to achieve by using other methods.

Table 4: synthesis of compounds **6a-d**



Entry	R^1	R^2	yield[a]
1	Ph: **2b**	Ph : **6a**	76%[b]
2	Me: **2d**	Ph : **6b**	67%[b]

3	 : **4a**	Me: **6c**	70%[c]
4	 : **4a**	4-pyr: **6d**	89%[d]

a) Isolated yield. b) Reagents and conditions: $PdCl_2(PPh_3)_2$ 10%, CuI 10%, alkynes (1.5eq), Et_3N (4eq), DMF, r.t. 3h30. c) 5% $Pd(PPh_3)_4$, boronic acid (1.1eq), Na_2CO_3 (2eq), dioxane/H_2O (2:1), 120°C (MW), 2h. d) 5% $Pd(PPh_3)_4$, boronic acid (1.1eq), Na_2CO_3 (2eq), dioxane/H_2O (2:1), 120°C (MW), 1h.

Conclusions

This work presents an efficient method for selective functionalization of 2-iodo-3-bromoimidazo[1,2-*a*]pyridine by Sonogashira and Suzuki-Miyaura cross-coupling reactions. This strategy allows easy access to libraries of molecules, with every possible combination of substituents at 2- and 3-positions, from a simple, stable starting material and readily available boronic acids or alkynes, and in a minimal number of steps. Various aryl, heteroaryl, alkyl, and alkynyl groups can be introduced using this method. Some of the products reported here (*e.g.* 2,3-diynes) are otherwise difficult to access. Feasibility of additional cross-coupling reaction (*e.g.* Stille or Buchwald cross-coupling) are currently under investigation.

Experimental

General procedure for Suzuki coupling at C-2 position or C-3 position.

1b (646mg, 2mmol, 1eq or **2b-d** for C-3 functionalization), $Pd(PPh_3)_4$ (116mg, 0.1mmol, 5%), Na_2CO_3 (424mg, 4mmol, 2eq) and boronic acid (2.2mmol, 1.1eq) were introduced into a microwave tube. The tube was sealed with a rubber septum and then evacuated and refilled with argon thrice. 1,4-Dioxane (8mL) and water (4mL) were then added. The reaction mixture was heated using microwave iradiation at 120°C for 1h. After cooling, the reaction mixture was partitioned between EtOAc (10mL) and water (10mL). The aqueous phase was extracted twice with EtOAc (10mL). Organic phases were combined, dried over $MgSO_4$ and evaporated to dryness. The crude mixture was purified by column chromatography (silica, eluent: mixture of CH_2Cl_2 and EtOAc).

General procedure for Sonogashira coupling at C-2 position.

1b (161mg, 0.5mmol, 1eq), $PdCl_2(PPh_3)_2$ (35mg, 0.05mmol, 10%) and CuI (10mg, 0.05mmol, 10%) were introduced into a screw-cap test tube. The tube was sealed with a rubber septum and then evacuated and refilled with argon thrice. DMF (2mL), Et_3N (278µL, 2mmol, 4eq) and alkyne (0.55mmol, 1.1eq) were then added. The reaction mixture was stirred for 30 minutes at room temperature. The reaction mixture was partitioned between CH_2Cl_2 (10mL) and brine (10mL). The aqueous phase was extracted twice with CH_2Cl_2 (10mL). Organic phases were reunited, dried over $MgSO_4$ and evaporate to dryness. The crude mixture was purified by column chromatography (silica, eluent: mixture of petroleum ether and diethylether).

General procedure for Sonogashira coupling at C-3 position.

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4a-b (0.5mmol, 1eq), $PdCl_2(PPh_3)_2$ (35mg, 0.05mmol, 10%) and CuI (10mg, 0.05mmol, 10%) were introduced into a screw-cap test tube. The tube was sealed with a rubber septum and then evacuated and refilled with argon thrice. DMF (2mL), Et_3N (278µL, 2mmol, 4eq) and alkyne (0.55mmol, 1.1eq) were then added. The reaction mixture was stirred for 1h30 at 80°C. After cooling, the reaction mixture was partitioned between CH_2Cl_2 (10mL) and brine (10mL). The aqueous phase was extracted twice with CH_2Cl_2 (10mL). Organic phases were reunited, dried over $MgSO_4$ and evaporated to dryness. The crude mixture was purified by column chromatography (silica, eluent: mixture of petroleum ether and diethylether).

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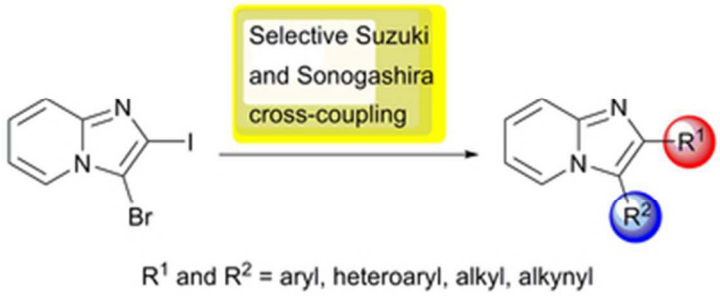

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