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A general synthesis of halo-oligopyridines. The Garlanding concept

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ABSTRACT

This paper sets forth a global synthetic strategy based on the Garlanding concept to design and to produce halo-oligopyridines. This strategy allows to prepare an infinite number of these new compounds and hence to create a library of halo-oligopyridines. This article is focused on the basic principle of the Garlanding concept and on the demonstration of its feasibility.

1. Introduction

Oligopyridines are widely described in the literature because of their great importance in metallosupramolecular chemistry where 2,2′-bipyridines, 2,2′:6′,2″-terpyridines, and 2,2′:6′,2″:6″,2‴-quaterpyridines were reported as bi-, tri-, and tetra-dentate chelates, respectively. Indeed, these oligopyridyl complexes commonly act as bridging ligands with many transition metals, twisting about the central bond to adopt a helical conformation, which binds two metals in a bis-bidentate fashion.[1] The most common oligopyridine chelates are the oligopyridyl complexes of ruthenium(II) (Fig. 1).[2] Oligopyridine complexes serve as luminescent probes in biochemical, medicinal diagnostics, or materials science.[3] They also contribute to formation of micelles as new drug delivery systems.[4–7] Apart from these uses as supramolecular systems, oligopyridine derivatives were evaluated for their antitumor cytotoxicity,[8] antiprion activity[9] and for their ability to block hydrophilic porin channels.[10]

Moreover, among these oligopyridines, there are pyridine-based neurotoxic substances, called nemertines, that have been isolated from marine worms.[11,12] Extracts from the hoplonemertine contain derivatives of pyridyl alkaloids, such as anabaseine, and the hoplonemertine *Amphiporus angulatus (Fabricius)* contains a particularly diverse groups of bipyridyl and tetrapyridyl compounds: 2,3′-bipyridine, a fully aromatic analog of anabaseine and nemertelline.[13]

The synthesis of some terpyridine natural products, particularly the one known as nicotelline,[14] which was extracted from tobacco, was reported.[15,16] Few papers have been published on the synthesis and structural determination of the quaterpyridine, nemertelline.[17] An efficient total synthesis of this quaterpyridine has been developed in our laboratory.[18]

However, despite the great importance of oligopyridines, very few general strategies of efficient access to all isomers of these compounds have been studied.[19] Generally, in oligopyridines complexes, pyridines are only linked together by a C–C bond on C2[20] using a direct homocoupling approach with catalytic loading of long reaction time, which limits its practical applications.

First of all, we have to clarify the nomenclature we have adopted in this paper. A dihalobipyridine was given to a bipyridine bearing a halogen atom on each pyridine ring; a trihaloterpyridine was given to a terpyridine bearing a halogen atom on each pyridine ring. A dihaloterpyridine was given to a terpyridine bearing a halogen atom on each pyridine ring at the extremities and a dihaloquaterpyridine was given to a quaterpyridine bearing a halogen atom on each pyridine pattern at the extremities (Fig. 2). Moreover, each pyridine ring was identified with a prime symbol (′), double prime symbol (″), triple prime symbol (‴) etc.

In this paper we envisaged a new methodology to prepare halo-oligopyridines starting from dihalopyridines, taking into account our experience in the halopyridylboronic acids synthesis and in the

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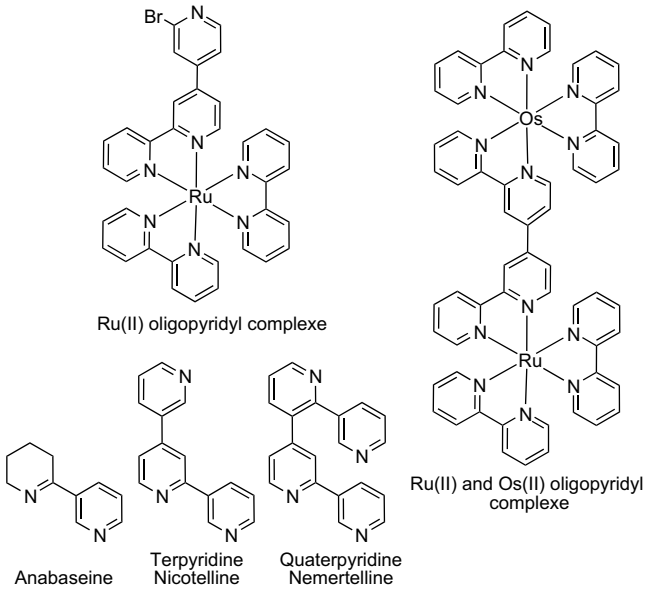


Figure 1. Oligopyridine derivatives.

knowledge of their ability as coupling partners in Suzuki–Miyaura cross-coupling reaction.[21]

Thus, these dihalopyridines can serve both as starting materials in the synthesis of the corresponding halopyridylboronic acids and as partners to couple with the latter acids to give dihalobipyridines. In turn, these dihalobipyridines could be used in a second Suzuki–Miyaura cross-coupling reaction to couple with halopyridylboronic acids leading to dihaloter- and quarter-pyridines. The obtained dihalo-oligopyridines may be engaged further in the same reaction as starting materials and so on.

There are six families of unsubstituted bipyridines, classified according to the positions at which the two pyridine rings are linked together (Fig. 3). Some are natural products, extracted from tobacco leaves and roots, and others were prepared using different chemical coupling procedures to achieve a direct pyridine–pyridine linkage where Stille and Suzuki–Miyaura cross-couplings are useful approaches. Besides, substitutions in symmetric and unsymmetric bipyridines by halogens have to be considered (Fig. 4). According to all the free substitution positions and taking into account all the halo isomers, iodo-, bromo-, chloro-, and fluoro-isomer, we have theoretically counted 888 different dihalobipyridines, more than 12,000 dihaloterpyridines and more than 140,000 trihaloterpyridines.

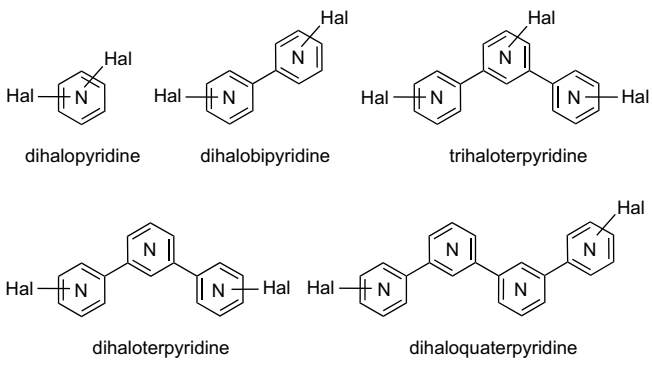


Figure 2. Nomenclature of haloligopyridines.

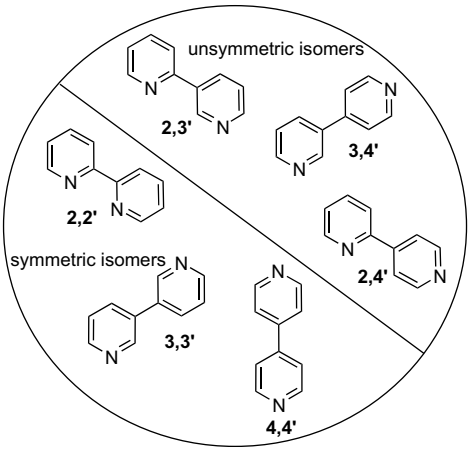


Figure 3. Unsubstituted bipyridines.

The regioselective control of the pyridine–pyridine linkage becomes more complex to manage and beyond a cross-coupling approach, it is necessary to set up a strategy for a regioselective synthesis of the desired halo-oligopyridines. This cross-coupling strategy should be efficient, short, convergent, and highly flexible leading to a selective coupling with the desired halogen. Recent reports showed that regioselective couplings are generally achievable for a wide range of polyhaloheteroaromatics and such regioselectivity is predictable.[22–24]

This paper deals with our preliminary results concerning the utility of Suzuki–Miyaura cross-coupling reactions in the regioselective synthesis and the first examples of synthesis of new oligopyridines, whether halogenated or not, as new analogs of nemertelline have been described.

2. Results and discussion

Firstly, from a synthetic point of view, Suzuki–Miyaura cross-coupling reaction was highly useful to obtain the desired halo-oligopyridines. Dihalopyridines were used as starting materials to couple with halopyridinylboronic acids and esters that we previously prepared from a regioselective halogen-metal exchange using *n*-BuLi or a directed *ortho*-metalation using LDA starting from appropriate mono- or di-halopyridines[25] (Scheme 1).

Secondly, it is necessary to verify the regioselectivity of the reaction and to specify, which reactivities are promoted, which conditions are more convenient, and which partners have to be chosen

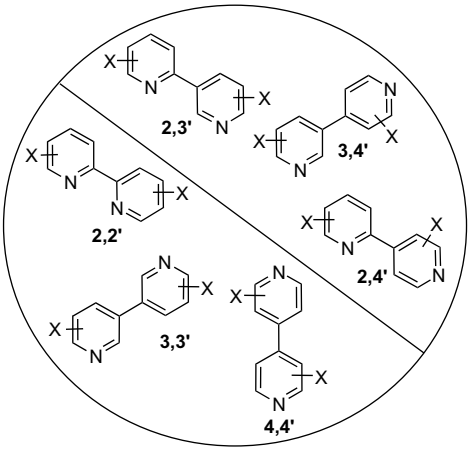
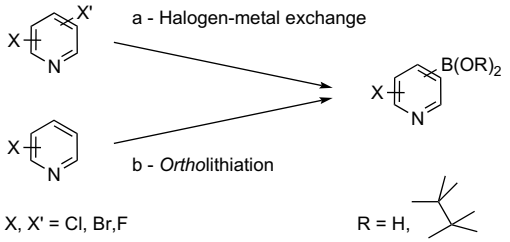


Figure 4. Symmetric and unsymmetric dihalobipyridines.



Scheme 1. Synthesis of halopyridinylboronic acids and esters. Reagents and conditions: (a): (1) *n*-BuLi, B(O*i*Pr)$_3$, −78 °C; (2) hydrolysis or pinacol, AcOH, hydrolysis; (b): (1) LDA, B(O*i*Pr)$_3$, −60 °C; (2) hydrolysis or pinacol, AcOH, hydrolysis.

in order to obtain only one specific halo-oligopyridine. To carry out this study, three steps have to be mentioned:

- set up the standard conditions allowing to define reaction possibilities according to the present halogen, substituents, the positions and the availability of the boronic species,
- optimization of general procedures to enhance the efficiency of the cross-coupling reaction,
- application of these procedures in the synthesis of halo-oligopyridine series.

Several trials of cross-coupling procedures using different reaction conditions (base, catalyst, solvent, temperature, and reaction time) were attempted. Accordingly, we have determined the most convenient conditions,[26] where Na_2CO_3 was used as base, $Pd(Ph_3)_4$ as catalyst, 1,4-dioxane as solvent. In our case, these conditions were adapted to control the coupling reaction and not to couple everywhere. The completion of the reaction was determined indicated by the total consumption of the halide (checked by thin layer chromatography).

More precisely, in this work, one has to focus on three key points:

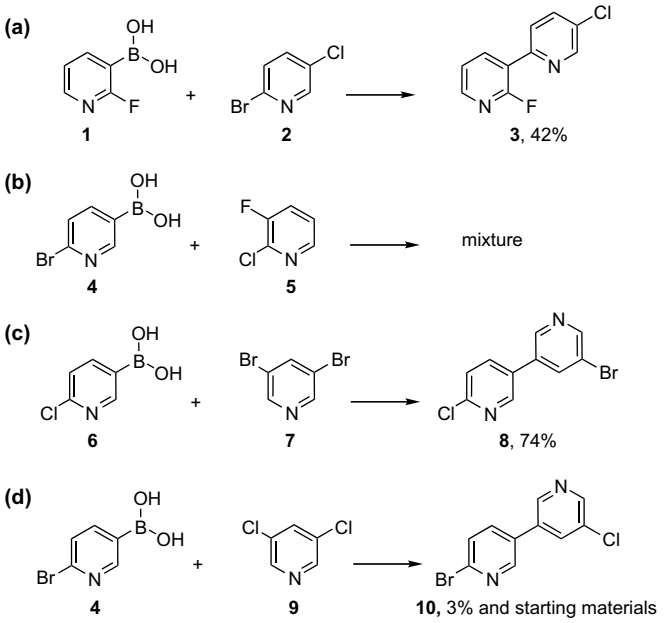
- the number of halogens on the pyridine nucleus and which one could be engaged in the cross-coupling reaction,
- the nature of halogens on the pyridine ring, taking in consideration that the order of reactivity is I>Br≫Cl>F for the same position on the pyridine ring,
- the position of halogens; indeed, the α- and γ-position are generally more reactive than the β-one.

However, when the halogen of the halopyridylboronic acids is engaged in the cross-coupling reaction, then the prediction of reaction product will be rather complicated. Four possibilities have to be considered:

- if the halogen of the dihalopyridine is in a sensitive position and its reactivity is better than the halogen set on the boronic acid (Scheme 2a),
- if the halogen set on the dihalopyridine is in a sensitive position but its reactivity is lower than the halogen set on the boronic acid (Scheme 2b),
- if the halogen set on the dihalopyridine is in a lowest sensitive position but its reactivity is better than the halogen set on the boronic acid (Scheme 2c),
- if the halogen set on the dihalopyridine is in a lowest sensitive position and its reactivity is lower than the halogen set on the boronic acid (Scheme 2d).

The reactions illustrating these four possibilities were carried out and are shown in Scheme 2, equations a to d:

When the exchanged halogen (the more reactive one) was that of the dihalopyridine (entries a and c), only one product was obtained in each case namely 5-chloro-2′-fluoro-2,3′-bipyridine **3** (42%) and

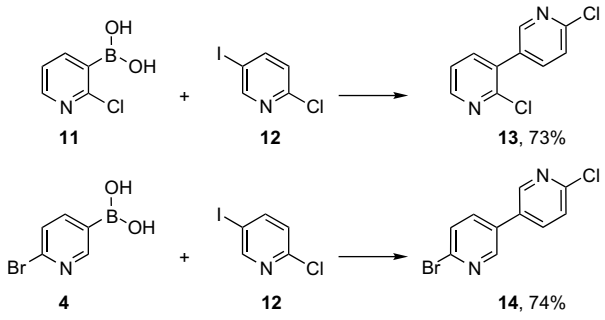


Scheme 2. Synthesis of 5-chloro-2′-fluoro-2,3′-bipyridine **3**, 5-bromo-6′-chloro-3,3′-bipyridine **8**, and 6-bromo-5′-chloro-3,3′-bipyridine **10**. Reagents and conditions: halopyridylboronic acid **1**, **4**, or **6** 1.1 equiv, dihalopyridine **2**, **5**, **7**, or **9** 1 equiv, Na_2CO_3 aq 2.5 equiv, $Pd(PPh_3)_4$ 5%, 1,4-dioxane, reflux, 8 h.

5-bromo-6′-chloro-3,3′-bipyridine **8** (74%), respectively. On the other hand, when the more reactive halogen (the exchanged one) was that of the boronic acid, a mixture of products difficult to separate was obtained (entry b). In entry d, a small amount of 6-bromo-5′-chloro-3,3′-bipyridine **10** (3%) was obtained with starting materials as a majority. Thus the choice of the position and the nature of the halogen and also its position are important factors in such a reaction.

In fact, it was difficult to predict a priori the regioselectivity of the reaction when the dihalopyridine carries two different halogen atoms as in case of using 2-chloro-5-iodopyridine **12** as starting material. In this case, would the coupling occur with the chlorine atom situated in the α-position (more reactive position but less reactive halogen)? Or with the iodine atom found in the β-position (less reactive position but more reactive halogen)? Briefly, what about the reactivities of the two halogens in this case? Are they similar or different?

Practically, as shown in Scheme 3, the coupling reaction took place with the more reactive iodine atom at the β-position without the formation of any trace of a product formed via α-coupling. This result was the same when two differently hindered halopyridylboronic acids **11** and **4** were used, where the reaction products were identified as 2,6′-dichloro-3,3′-bipyridine **13** and 6-bromo-6′-chloro-3,3′-bipyridine **14** in 73% and 74% yield, respectively.

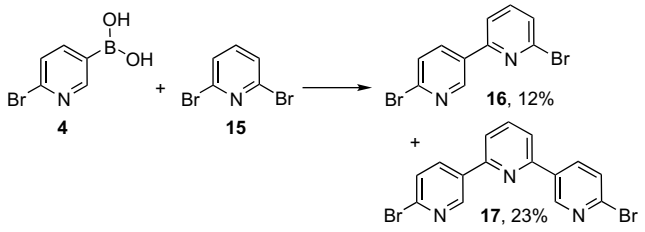


Scheme 3. Synthesis of 2,6′-dichloro-3,3′-bipyridine **13** and 6-bromo-6′-chloro-3,3′-bipyridine **14**. Reagents and conditions: halopyridylboronic acids **11** and **4** 1.1 equiv, dihalopyridine **12** 1 equiv, Na_2CO_3 aq 2.5 equiv, $Pd(PPh_3)_4$ 5%, 1,4-dioxane, reflux, 8 h.

Thus, it is important to consider the nature of the halogen and its position with respect to the pyridine nitrogen: in fact, the greater reactivity of the iodo group is able to overcome the intrinsic electronic bias of the pyridine ring system.[27] This behavior is expected to be of a general potential use in these cross-coupling reactions: a halogen atom of higher reactivity attached to a less reactive position for nucleophilic substitutions (β) will be a better partner than a halogen atom of lower reactivity attached to more reactive position (α or γ).

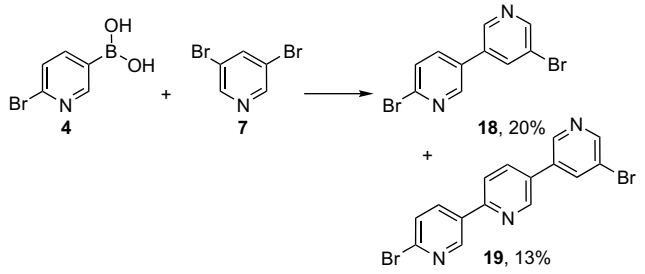
In fact, we have studied such regioselective reactions through several examples using both symmetric and unsymmetric dihalopyridines.

First, when a symmetric compound such as 2,6-dibromopyridine **15** was allowed to react with 1.1 equiv of the boronic acid **4**, 6,6′-dibromo-2,3′-bipyridine **16** was obtained with only 33% yield. This low yield indicates a lack of selectivity between the two halogens attached to these two reactive positions. When this reaction was carried using 2 equiv of boronic acid, a mixture of 6,6′-dibromo-2,3′-bipyridine **16** (12%) and 6,6″-dibromo-3,2′:6′,3″-terpyridine **17** (23%) was obtained (Scheme 4).[28] So, we can foresee that the residual bromide in 6-position of 6,6′-dibromo-2,3′-bipyridine **16** is more reactive than one of the bromide in α-position of 2,6-dibromopyridine **15**, then the dihaloterpyridine **17** was generated to the detriment of the dihalobipyridine **16**.



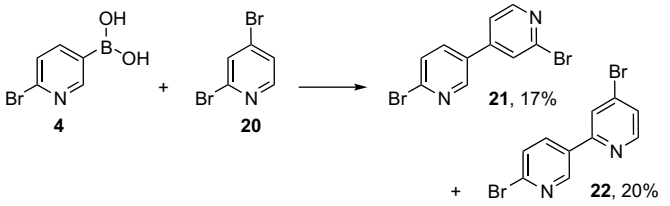
Scheme 4. Synthesis of 6,6′-dibromo-2,3′-bipyridine **16** and 6,6′-dibromo-3,2′:6′,3″-terpyridine **17**. Reagents and conditions: halopyridylboronic acid **4** 2 equiv, dihalopyridine **15** 1 equiv, Na_2CO_3 aq 2.5 equiv, $Pd(PPh_3)_4$ 5%, 1,4-dioxane, reflux, 8 h.

Unlike compound **15**, the two bromine atoms of 3,5-dibromopyridine **7** are located in β-position. The reaction of **7** with 1.1 equiv of the boronic acid **4** led to a mixture of 5,6′-dibromo-3,3′-bipyridine **18** (20%) and 5″,6-dibromo-3,2′:5′,3″-terpyridine **19** (13%) as shown in Scheme 5. Thus, the formation of **19** showed that the boronic acid has reacted selectively with the bromine atom at the α-position of **18** rather than with that at the β-position of **7**. However, when 2 equiv of boronic acid was used, the yield was inverted in favor of the terpyridine giving a mixture of **18** (11%) and **19** (27%). Here again, the reactivity of the α-bromine atom at 6′-position of 5,6′-dibromo-3,3′-bipyridine **18** is better than the β-one at the 3- or 5-position of 3,5-dibromopyridine **7**.[28]



Scheme 5. Synthesis of 5,6′-dibromo-3,3′-bipyridine **18** and 5″,6-dibromo-3,2′:5′,3″-terpyridine **19**. Reagents and conditions: halopyridylboronic acid **4** 1.1 equiv, dihalopyridine **7** 1 equiv, Na_2CO_3 aq 2.5 equiv, $Pd(PPh_3)_4$ 5%, 1,4-dioxane, reflux, 8 h.

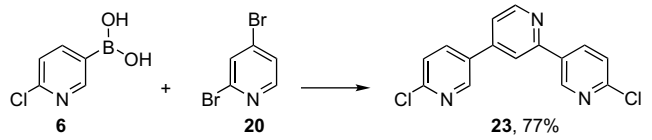
Secondly, using asymmetric compounds, such as 2,4-dibromopyridine **20**, allowed us to find out that both halo substituents, attached to the reactive positions α and γ have the equivalent reactivity. In this case, using 1.1 equiv of boronic acid **4**, the reaction gave a mixture of 6,2′-dibromo-3,4′-bipyridine **21** and 4,6′-dibromo-2,3′-bipyridine **22** in similar yields 17% and 20%, respectively (Scheme 6).[28] We did not observe the formation of terpyridines (mass spectrometry).



Scheme 6. Synthesis of 6,2′-dibromo-3,4′-bipyridine **21** and 4,6′-dibromo-2,3′-bipyridine **22**. Reagents and conditions: halopyridylboronic acid **4** 1.1 equiv, dihalopyridine **20** 1 equiv, Na_2CO_3 aq 2.5 equiv, $Pd(PPh_3)_4$ 5%, 1,4-dioxane, reflux, 8 h.

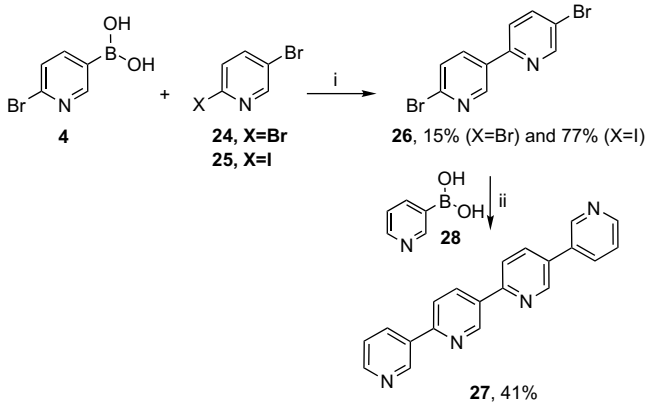
In order to explore the utility of our methodology in the synthesis of new terpyridines and quaterpyridines, analogs of nicotelline and nemertelline, the synthesis of one example of each family was described in this first part.[29]

Thus, as shown in Scheme 7, 6,6″-dichloro-3,2′;4′,3″-terpyridine **23** could be easily prepared in a good yield (77%) via Suzuki–Miyaura cross-coupling reaction of 6-chloropyridin-3-yl boronic acid **6** (2.5 equiv) and with 2,4-dibromopyridine **20**. We obtained one product only confirming the regioselectivity of the cross-coupling reaction toward the more reactive bromine atom at the reactive α-position of the 6-chloro-2′-bromo-3,4′-bipyridine intermediate.



Scheme 7. Synthesis of 6,6″-dichloro-3,2′;4′,3″-terpyridine **23**. Reagents and conditions: boronic acid **6** 2.5 equiv, dihalopyridine **20** 1 equiv, Na_2CO_3 aq 5 equiv, $Pd(PPh_3)_4$ 10%, 1,4-dioxane, reflux, 8 h.

On the other hand, the synthesis of 3,2′:5′,2″:5″,3‴-quaterpyridine **27** is shown in Scheme 8. Thus, the Suzuki–Miyaura cross-coupling reaction between the boronic acid **4** and 2,5-dibromopyridine **24** gave the corresponding 5,6′-dibromo-2,3′-bipyridine **26**, but in a rather poor yield (15%), along with by-products. The yield of **26** could be ameliorated when the



Scheme 8. Synthesis of 5,6′-dibromo-2,3′-bipyridine **26** and 3,2′:5′,2″:5″,3‴-quaterpyridine **27**. Reagents and conditions: (i) halopyridylboronic acid **4** 1.1 equiv, dihalopyridine **24** or **25** 1 equiv, Na_2CO_3 aq 2.5 equiv, $Pd(PPh_3)_4$ 5%, 1,4-dioxane, reflux, 24 h; (ii) pyridylboronic **28** 2.5 equiv, **26** 1 equiv, Na_2CO_3 aq 5 equiv, $Pd(PPh_3)_4$ 10%, 1,4-dioxane, reflux, 24 h.

reaction was repeated using 5-bromo-2-iodopyridine **25** to give **26** in 77% yield. The quaterpyridine **27** could be successfully obtained in 41% yield through the reaction of 5,6′-dibromo-2,3′-bipyridine **26** with 2.5 equiv of 3-pyridyl boronic acid **28**.

3. Conclusion

These examples were selected as model reactions to explore under what conditions regiochemically exhaustive functionalization reactions can be carried out. We have developed conditions for efficient, short, convergent, and highly flexible cross-coupling reactions. These reactions proceed with a high degree of regioselectivity and reasonable-to-good overall yield. The implementation of this strategy will allow to create a library of diverse of novel halooligopyridines. Exploration of this methodology is currently under investigation, i.e., several building possibilities, and the results will be reported in due course elsewhere.

4. Experimental section

4.1. General procedure

Commercial reagents were used as received without additional purification. Melting points were determined on a Kofler heating bench. IR spectra were recorded on a Perkin Elmer BX FTIR spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a JEOL Lambda 400 spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard and coupling constants in hertz. The NMR spectrum of quaterpyridine **27** was recorded on a Brücker Avance DRX 400 spectrometer. Mass spectra were recorded on a JEOL JMS GCMate spectrometer at ionizing potential of 70 eV (EI) and with pfk as internal standard for high-resolution procedure, or were performed using a spectrometer LC-MS Waters alliance 2695 (ESI$^+$). Chromatography was carried out on a column using flash silica gel 60 Merck (0.063–0.200 mm) as the stationary phase. Thin layer chromatography (TLC) was performed on 0.2 mm precoated plates of silica gel 60F$_{264}$ (Merck) and spots were visualized using an ultraviolet-light lamp. Elemental analyses for new compounds were performed at the 'Institut de Recherche en Chimie Organique Fine' (Rouen).

Starting materials were purchased from Aldrich, Acros Organics, and Alfa Aesar and used without purification.

4.2. General procedure for the coupling reactions[30]

A mixture of halopyridylboronic acid (1.1 equiv), halopyridine (1 equiv), tetrakis(triphenylphosphine) palladium(0) (5 mol %), and aqueous Na_2CO_3 (2.5 equiv) in 1,4-dioxane was heated at 80 °C for 1 h then under reflux until the complete consumption of aryl halide (TLC). The reaction mixture was extracted with ethyl acetate. The organic layer was separated, dried over $MgSO_4$, and concentrated till dryness. The residue was chromatographied on silica gel (cyclohexane/ethylacetate, 80:20) to afford halooligopyridines.

4.2.1. 5-Chloro-2′-fluoro-2,3′-bipyridine ***3***

Beige solid (42%). Mp 102 °C. IR (KBr): 2962, 1576, 1108, 761 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.69 (d, $^4J_{HH}$=2.5, 1H), 8.55 (ddd, $^3J_{HH}$=7.4, $^4J_{HH}$=2.0, $^4J_{HF}$=9.7, 1H), 8.27 (ddd, $^3J_{HH}$=4.9, $^4J_{HH}$=2.0, $^4J_{HF}$=3.5, 1H), 7.88 (d, $^3J_{HH}$=8.5, 1H), 7.78 (dd, $^3J_{HH}$=8.5, $^4J_{HH}$=2.5, 1H), 7.35 (dd, $^3J_{HH}$=7.4, $^3J_{HH}$=4.9, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=160.0 (d, $^1J_{CF}$=239.4), 149.0 (d, $^3J_{CF}$=6.5), 148.8, 147.9 (d, $^3J_{CF}$=14.8), 141.0 (d, $^5J_{CF}$=3.3), 131.7, 124.7 (d, $^4J_{CF}$=11.5), 122.1 (d, $^4J_{CF}$=4.2), 121.2 (d, $^2J_{CF}$=26.4); *m*/*z*: 208; HRMS (EI) calcd for $C_{10}H_6ClFN_2$ (M$^{+\bullet}$) 208.0203, found 208.0200.

4.2.2. 5-Bromo-6′-chloro-3,3′-bipyridine ***8***

Beige solid (74%). Mp 115 °C. IR (KBr): 3035, 1449, 830 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.50 (dd, $^3J_{HH}$=4.8, $^4J_{HH}$=1.8, 2H), 7.68 (dd, $^3J_{HH}$=7.5, $^4J_{HH}$=1.8, 2H), 7.38 (dd, $^3J_{HH}$=7.5, $^3J_{HH}$=4.8, 2H). Anal. Calcd for $C_{10}H_6BrClN_2$: C, 44.56; H, 2.24; N, 10.39. Found: C, 44.54; H, 2.29; N, 10.34.

4.2.3. 6-Bromo-5′-chloro-3,3′-bipyridine ***10***

Beige solid (3%). Mp 100 °C. IR (KBr): 2916, 1701, 1461, 721 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.94 (d, $^4J_{HH}$=2.9, 1H), 8.73 (d, $^4J_{HH}$=4.8, 1H), 8.21 (dd, $^4J_{HH}$=2.9, $^3J_{HH}$=8.8, 1H), 7.84–7.80 (m, 1H), 7.74 (d, $^3J_{HH}$=8.8, 1H), 7.61 (d, $^3J_{HH}$=8.8, 1H). Anal. Calcd for $C_{10}H_6BrClN_2$: C, 44.56; H, 2.24; N, 10.39. Found: C, 44.53; H, 2.22; N, 10.33.

4.2.4. 2,6′-Dichloro-3,3′-bipyridine ***13***

Beige solid (73%). Mp 124 °C. IR (KBr): 3391, 3042, 2360, 1548, 1405, 1347, 1112, 994, 803, 738, 642 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.48–8.47 (m, 2H), 7.81 (dd, $^3J_{HH}$=7.8, $^4J_{HH}$=1.9, 1H), 7.69 (dd, $^3J_{HH}$=6.8, $^4J_{HH}$=1.9, 1H), 7.45 (d, $^3J_{HH}$=8.8, 1H), 7.38 (dd, $^3J_{HH}$=4.4, $^3J_{HH}$=7.8, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.3, 151.5, 149.6, 149.5, 139.5, 132.3, 132.1, 130.2, 123.9, 122.8; HRMS (EI): *m*/*z* calcd for $C_{10}H_6Cl_2N_2$ (M$^{+\bullet}$) 223.9908, found 223.9910.

4.2.5. 6-Bromo-6′-chloro-3,3′-bipyridine ***14***

Beige solid (74%). Mp >250 °C. IR (KBr): 3035, 1576, 1449, 1338, 1111, 1094, 995 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.59 (d, $^4J_{HH}$=1.9, 1H), 8.57 (d, $^4J_{HH}$=2.9, 1H), 7.83 (dd, $^3J_{HH}$=8.8, $^4J_{HH}$=2.9, 1H), 7.73 (dd, $^3J_{HH}$=7.8, $^4J_{HH}$=1.9, 1H), 7.62 (d, $^3J_{HH}$=7.8, 1H), 7.46 (d, $^3J_{HH}$=8.8, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=151.8, 148.2, 147.7, 142.3, 136.9, 136.7, 131.6, 131.3, 128.5, 124.7; HRMS (EI) calcd for $C_{10}H_6BrClN_2$ (M$^{+\bullet}$) 267.9402, found 267.9401.

4.2.6. 6,6′-Dibromo-2,3′-bipyridine ***16***

White solid (20%). Mp 177 °C. IR (KBr): 3029, 1463, 1430, 1261, 1090, 1003, 804, 703 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.90 (d, $^4J_{HH}$=2.9, 1H), 8.23 (dd, $^3J_{HH}$=8.8, $^4J_{HH}$=2.9, 1H), 7.69 (d, $^3J_{HH}$=8.6, 1H), 7.64–7.57 (m, 2H), 7.60 (d, $^3J_{HH}$=7.8, 1H), 7.50 (d, $^3J_{HH}$=7.8, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=153.3, 154.8, 149.0, 148.4, 143.4, 139.3, 137.0, 128.4, 127.7, 119.0; *m*/*z*: 314; HRMS (EI) calcd for $C_{10}H_6Br_2N_2$ (M$^{+\bullet}$) 311.8897, found 311.8905.

4.2.7. 6,6′-Dibromo-3,2′:6′,3″-terpyridine ***17***

Beige solid (23%). Mp 200 °C. IR (KBr): 2961, 1568, 1452, 1281, 1091, 1017, 818, 791 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ=10.24 (s, 2H), 7.90 (d, $^3J_{HH}$=4.6, 2H), 7.80 (d, $^3J_{HH}$=4,6, 1H), 7.40 (d, $^3J_{HH}$=8.7, 2H), 7.14 (d, $^3J_{HH}$=8.7, 2H); MS (EI) *m*/*z*: 389–391–393 [M$^+$]$^\bullet$, 310–312 [M$^+$−Br]$^\bullet$, 230 [M$^+$−2Br]$^\bullet$.

4.2.8. 5,6′-Dibromo-3,3′-bipyridine ***18***

White solid (20%). Mp 177 °C. IR (KBr): 3029, 1463, 1430, 1261, 1090, 1003, 804, 703 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.67 (s, 1H), 8.51 (s, 1H), 7.69 (d, $^3J_{HH}$=8.6, 1H), 7.58 (s, 1H), 7.26 (s, 1H), 7.09 (d, $^3J_{HH}$=8.6, 1H); MS (EI) *m*/*z*: 312–314–316 [M$^+$]$^\bullet$, 233–235 [M$^+$−Br]$^\bullet$, 154 [M$^+$−2Br]$^\bullet$.

4.2.9. 5″,6-Dibromo-3,2′:5′,3″-terpyridine ***19***

White solid (13%). Mp 182 °C. IR (KBr): 3028, 2359, 1463, 1430, 1089, 805, 703, 640 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ=8.74 (d, $^4J_{HH}$=1.7, 1H), 8.73 (d, $^4J_{HH}$=1.7, 1H), 8.57 (s, 1H), 8.58 (s, 1H), 8.04 (s, 1H), 7.75 (d, $^3J_{HH}$=8.2, 1H), 7.64 (d, $^3J_{HH}$=8.2, 1H), 7.35 (d, $^3J_{HH}$=8.6, 1H), 7.12 (d, $^3J_{HH}$=8.6, 1H); MS (EI) *m*/*z*: 389–391–393 [M$^+$]$^\bullet$, 310–312 [M$^+$−Br]$^\bullet$, 230 [M$^+$−2Br]$^\bullet$.

4.2.10. 6,2′-Dibromo-3,4′-bipyridine ***21***

Beige solid (17%). Mp <50 °C. IR (KBr): 2926, 1554, 1448, 1355, 1130, 1079, 825, 772, 744 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6):

δ=8.29 (d, $^3J_{HH}$=5.2, 1H), 8.27 (d, $^3J_{HH}$=5.4, 1H), 7.89 (s, 1H), 7.77 (s, 1H), 7.67 (d, $^3J_{HH}$=5.2, 1H), 7.64 (d, $^3J_{HH}$=5.4, 1H); *m*/*z*: 314; HRMS (EI) calcd for $C_{10}H_6Br_2N_2$ ($M^{+\bullet}$) 311.8897, found 311.8903.

4.2.11. 4,6′-Dibromo-2,3′-bipyridine **22**

Beige solid (20%). Mp 142 °C. IR (KBr): 3044, 1562, 1444, 1383, 1089, 1011, 823, 797 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ=9.09 (s, 1H), 8.58 (d, $^3J_{HH}$=5.1, 1H), 8.43 (d, 1H, $^3J_{HH}$=8.4), 8.40 (s, 1H), 7.79 (d, $^3J_{HH}$=8.4, 1H), 7.73 (d, $^3J_{HH}$=5.1, 1H); *m*/*z*: 314; HRMS (EI) calcd for $C_{10}H_6Br_2N_2$ ($M^{+\bullet}$) 311.8897, found 311.8891.

4.2.12. 6″,6-Dichloro-3,2′:4′,3″-terpyridine **23**

Halopyridylboronic acid (2.5 equiv), 1 equiv of halopyridine, 10 mol % tetrakis(triphenylphosphine) palladium(0), and 5 equiv aqueous Na_2CO_3 are used. White solid (77%). Mp 226 °C. IR (KBr): 3057, 1601, 1569, 1452, 1345, 1110, 1020, 1010, 831 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.96 (d, $^4J_{HH}$=2.5, 1H), 8.75 (d, $^3J_{HH}$=5.1, 1H), 8.65 (d, $^4J_{HH}$=2.6, 1H), 8.30 (dd, $^3J_{HH}$=8.4, $^4J_{HH}$=2.5, 1H), 7.88 (dd, $^3J_{HH}$=8.2, $^4J_{HH}$=2.6, 1H), 58 (s, 1H), 7.80 (s, 1H), 7.45–7.34 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.7, 150.9, 150.5, 148.1, 147.9, 145.3, 137.2, 137.1; HRMS (EI): *m*/*z*: 301 calcd for $C_{15}H_9Cl_2N_3$ ($M^{+\bullet}$) 301.0173, found 301.0162.

4.2.13. 5,6′-Dibromo-2,3′-bipyridine **26**

Yellow solid (77%). Mp 194 °C. IR (KBr): 3010, 1575, 1461, 1376, 1090, 1005, 823 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.92 (d, $^4J_{HH}$=2.0, 1H), 8.76 (d, $^4J_{HH}$=2.0, 1H), 8.18 (dd, $^3J_{HH}$=8.8, $^4J_{HH}$=2.0, 1H), 7.93 (dd, $^3J_{HH}$=8.8, $^4J_{HH}$=2.0, 1H), 7.64 (d, $^3J_{HH}$=8.8, 1H), 7.60 (d, $^3J_{HH}$=8.8, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=152.1, 151.3, 148.3, 143.0, 139.7, 136.6, 133.1, 128.2, 121.3, 120.6; HRMS (EI): *m*/*z* calcd for $C_{10}H_6Br_2N_2$ ($M^{+\bullet}$) 311.8897, found 311.8892.

4.2.14. 3,2′:5′,2″:5″,3‴-Quaterpyridine **27**

Pyridylboronic acid (2.5 equiv), 1 equiv of halopyridine, 10 mol % tetrakis(triphenylphosphine) palladium(0), and 5 equiv aqueous Na_2CO_3 are used. Beige solid (41%). Mp 198 °C. IR (KBr): 3420, 3036, 1584, 1465, 1360, 1013, 804, 710 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=9.40 (dd, $^4J_{HH}$=2.3, $^5J_{HH}$=0.8, 1H), 9.31 (dd, $^4J_{HH}$=2.3, $^5J_{HH}$=0.8, 1H), 9.01 (dd, $^4J_{HH}$=2.3, $^5J_{HH}$=0.8, 1H), 8.95 (dd, $^4J_{HH}$=2.3, $^5J_{HH}$=0.8, 1H), 8.72 (dd, $^4J_{HH}$=1.8, $^3J_{HH}$=4.8, 1H), 8.71 (dd, $^4J_{HH}$=1.8, $^3J_{HH}$=4.8, 1H), 8.54 (dd, $^3J_{HH}$=8.3, $^4J_{HH}$=2.3, 1H), 8.44 (ddd, $^3J_{HH}$=7.9, $^4J_{HH}$=2.3, $^4J_{HH}$=1.8, 1H), 8.06 (dd, $^3J_{HH}$=8.3, $^4J_{HH}$=2.3, 1H), 7.98 (ddd, $^3J_{HH}$=7.9, $^4J_{HH}$=2.3, $^4J_{HH}$=1.6, 1H), 7.97 (dd, $^3J_{HH}$=8.2, $^5J_{HH}$=0.8, 1H), 7.94 (dd, $^3J_{HH}$=8.3, $^5J_{HH}$=0.8, 1H), 7.48 (ddd, $^3J_{HH}$=7.9, $^3J_{HH}$=4.8, $^5J_{HH}$=0.8, 1H), 7.47 (ddd, $^3J_{HH}$=7.9, $^3J_{HH}$=4.8, $^5J_{HH}$=0.8, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=155.5, 154.3, 150.6, 149.9, 148.9, 148.8, 148.7, 148.6, 135.8, 135.7, 134.8, 134.7, 134.6, 133.7, 133.4, 133.1, 124.3, 124.1, 120.9 (2C); HRMS (EI): *m*/*z* calcd for $C_{20}H_{14}N_4$ ($M^{+\bullet}$) 310.1218, found 310.1208.

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28. These yields are particularly low. We did not observe debromination of the boronic acid but we noticed a protodeboronation reaction in such a way that we recovered small amounts of starting materials. Moreover, in cross-coupling reactions, we often observed a polymerization reaction leading to by-products, which are not isolated.
29. Preparation of other ter- and quater-pyridines will be described in a following paper.
30. Unless otherwise specified.