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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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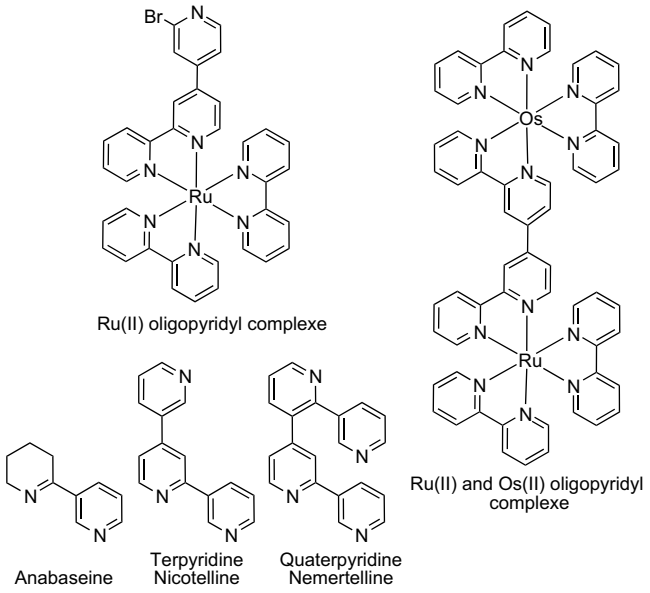


**Figure 1.** Oligopyridine derivatives.

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.

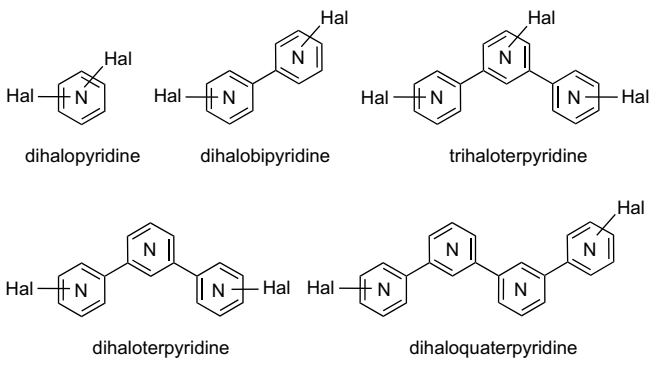


**Figure 2.** Nomenclature of haloligopyridines.

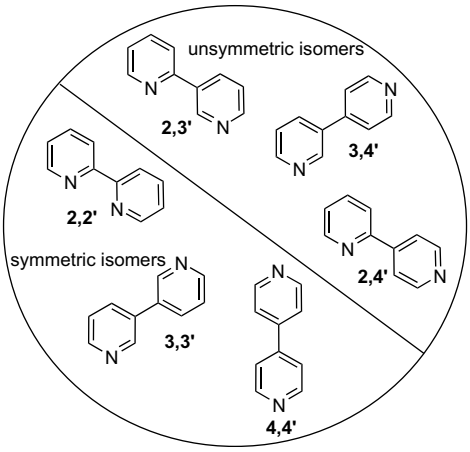


**Figure 3.** Unsubstituted bipyridines.

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

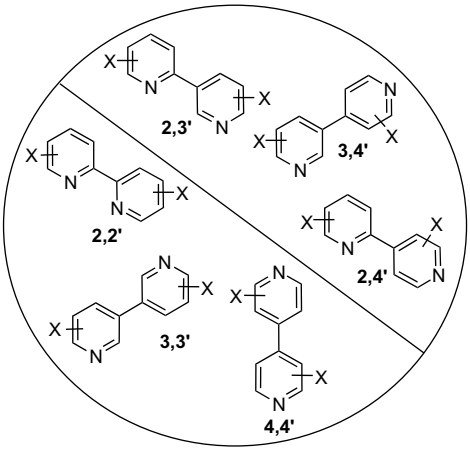


**Figure 4.** Symmetric and unsymmetric dihalobipyridines.