Versatile tools in the construction of substituted 2,2′-bipyridines—cross-coupling reactions with tin, zinc and boron compounds

Marko Hapke,*[a] Lars Brandt[b] and Arne Lützen*[c]

Received 19th August 2008
First published as an Advance Article on the web 24th October 2008
DOI: 10.1039/b810973g

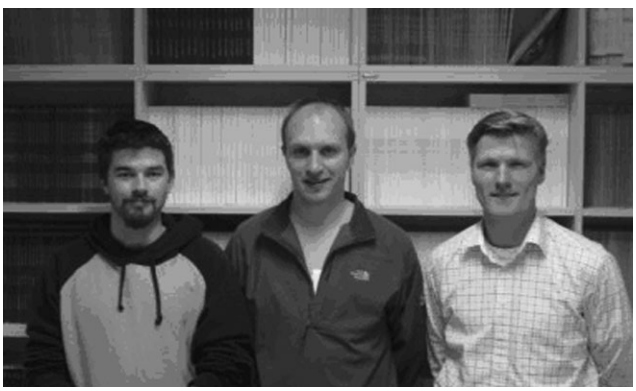
2,2′-Bipyridines are among the most widely used classes of chelating ligands that have found applications in the fields of coordination chemistry, supra-, nano- and macromolecular chemistry, analytical and photochemistry, but also in asymmetric synthesis and natural product chemistry. Hence, there is a huge demand for efficient synthetic approaches to functionalized derivatives. Modern cross-coupling procedures have been proven to be particularly effective in this context. This *critical review* will give an overview about the advances made so far focussing mainly on cross-coupling reactions with tin, zinc and boron compounds for the achievement of interesting, versatile and unusual substitution patterns (156 references).

1. Introduction

2,2′-Bipyridines establish a class of chelating heterocyclic ligands that can account for one of the most impressive records when it comes to the versatility of application.[1] The areas of occurrence and application are extremely widespread. This can be explained by the ability of 2,2′-bipyridines to form stable complexes with a large number of metal ions of different size and charge. Furthermore the bipyridine core offers a myriad of possibilities in terms of modification by different substitution patterns which led to its manifold use as attractive building blocks in supra-, nano- and macromolecular chemistry,[2–4] as well as, in the areas of analytical and photochemistry.[5] The latter actually gains momentum in the light of the search for alternative sources of energy such as the conversion of sunlight.[6] Furthermore, bipyridines are still in the focus as a class of chiral ligands for asymmetric transformations,[7,8] while they can also act as achiral ligands in some fascinating, unusual reactions.[9–13] Finally, even some natural products are descending from the bipyridine core, such as caerulomycins,[14,15] collismycins,[16] and camptothecin and its derivatives that are an important class of topoisomerase inhibitors.[17] Also, streptonigrin and lavendamycin contain the bipyridine biaryl system as the backbone of their structurally interesting molecular scaffold.[18]

Given the large number of applications it does not come as a surprise that an immense demand of differently substituted derivatives and selective transformations to synthesise or modify them came along. Gratifyingly, Newkome, Schubert *et al.* have recently very nicely compiled the synthetic progress made towards the synthesis of 2,2′-bipyridine derivatives since the last review of the matter in the early 1980s.[19] The general possibilities for synthesising symmetrically or non-symmetrically functionalised 2,2′-bipyridines are visualised in Scheme 1.

[a] *Leibniz-Institut für Katalyse e. V. an der Universität Rostock (LIKAT), Albert-Einstein-Str. 29a, D-18059 Rostock, Germany. E-mail: marko.hapke@catalysis.de; URL: http://www.catalysis.de*
[b] *Carl von Ossietzky-University of Oldenburg, Institute for Pure and Applied Chemistry, Technical Chemistry, P.O. Box 2503, D-26111 Oldenburg, Germany*
[c] *Kekulé-Institute of Organic Chemistry and Biochemistry, University of Bonn, Gerhard-Domagk-Str. 1, D-53121 Bonn, Germany. E-mail: arne.luetzen@uni-bonn.de; Fax: +49 228 739608; Tel: 49 228 737533*

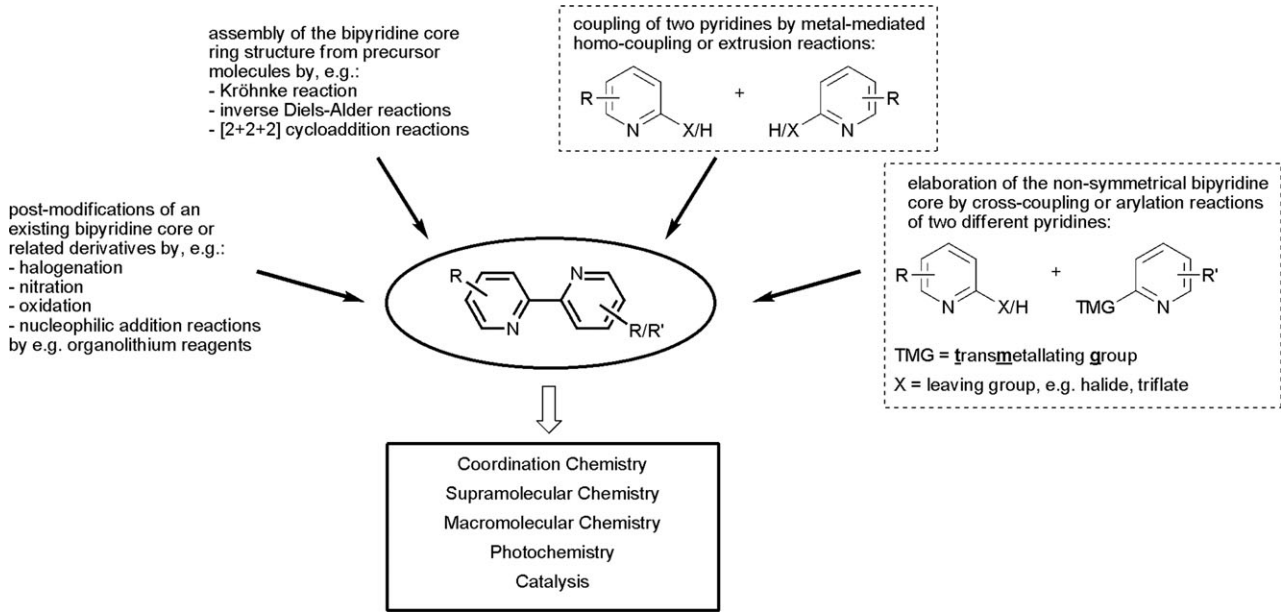


Lars Brandt, Marko Hapke and Arne Lützen

Marko Hapke received his PhD from the University of Oldenburg. He joined LIKAT in 2006, after postdoctoral studies with J. F. Hartwig at Yale University. He is now junior research group leader with his research interests being selective and exceptional transformations catalysed by transition metal complexes.

Lars Brandt studied chemistry at the University Oldenburg from where he graduated in 2005 with a diploma thesis dealing with the application of new synthetic methods for the synthesis of 2,2′-bipyridines. He is now working towards his PhD in the field of technical chemistry.

Arne Lützen is Professor at the Kekulé-Institute of Organic Chemistry and Biochemistry at the University of Bonn since 2006. His work is focussing on organic synthesis and supramolecular chemistry.



Scheme 1 Overview on the general possibilities for synthesising functionalised 2,2′-bipyridines.

For symmetrical 2,2′-bipyridines, the synthetic approaches are in the predominant number of cases modifications of the existing bipyridine core structures or homo-coupling reactions of suitable pyridine precursor molecules.

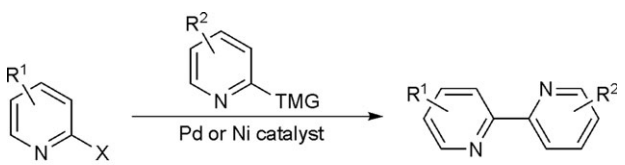
For non-symmetrically substituted 2,2′-bipyridines the synthetic approach is comparatively more complicated. Kröhnke was the first to report a systematical synthetic procedure that circumvents the stepwise and more or less unselective approach, to monofunctionalise only one of the two pyridine moieties of the bipyridine.[20]

Despite all advances in synthetic procedures accomplished in recent decades, these protocols could not keep up with the ever-growing demand for non-symmetrically functionalised 2,2′-bipyridines as building blocks for the many purposes mentioned at the beginning. Thus, the problem prevailed to selectively address a specific substitution pattern without the need of multistep total synthesis and based on rational design. A general approach to address these problems was finally found in the area of cross-coupling reactions that were initially focused on the general difficulty to prepare biaryls under moderate conditions and that could be considered to be a rather alchemical field in its very beginning.[21–23] However, in the last three decades the transition metal-catalysed cross-coupling reactions have evolved into a truly mature methodology. Hence, these reactions are broadly used and became a prominent member of the bipyridine chemists' toolbox. Nevertheless, some adventures are yet to be discovered. In our critical review we will focus on the recent progress in cross-coupling chemistry with organotin, organozinc and organoborane reagents for the flexible access to a number of very interesting 2,2′-bipyridine building blocks.

2. Synthesis of 2,2′-bipyridines by cross-coupling reactions

2.1 General considerations

The hour of birth for the modern cross-coupling chemistry was the discovery of the Ullmann reaction more than a century ago.[24] It is not so long ago since the synthesis of biaryls was at some stage routinely done by an Ullmann homo-coupling reaction, which included also the postmodification of the homo-coupled product to finally assemble the non-symmetrical biaryl. This limitation of the ancestor reaction was overcome by the evolution of cross-coupling protocols.[25,26] The most prominent cross-coupling reactions include the Stille, Negishi, Suzuki–Miyaura, Kumada and Hiyama coupling reaction. They have all found application in the synthesis and functionalisation of heteroaromatic compounds as well as in the preparation of 2,2′-bipyridines, however to a very different extent.[27–29] More precisely, only the first three of them have seen more or less successful or broad use. The general reaction diagram is presented in Scheme 2.



X = leaving group, in most cases halides or triflate
TMG = transmetallating group

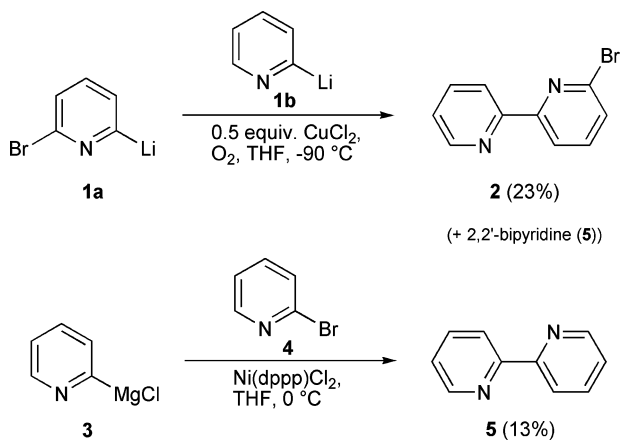
Stille coupling (TMG = e.g. $SnMe_3$, $SnBu_3$)
Negishi coupling (TMG = ZnCl, ZnBr)
Suzuki-Miyaura coupling (TMG = e.g. Bpin, $B(OR)_2$, BR_2, BF_3K)
Kumada coupling (TMG = MgCl, MgBr)
Hiyama coupling (TMG = e.g. SiR_3, $Si(OR)_3$)

Scheme 2 Overview on the cross-coupling approaches for 2,2′-bipyridines.

There are two main problems associated with the synthesis of the 2,2′-bipyridine core by cross-coupling reactions: (a) the coordination ability of the product can have adverse effects on the catalytic cycle, and (b) the synthesis of the pyridyl derivative, especially with the appropriate transmetallating group (TMG) can be problematic. The first "problem" is connected to a normally desired property of 2,2′-bipyridines as a

coordinating unit, that forms stable transition metal complexes with a large number of transition metal ions.[30–32] In the catalytic cycle the formation of the bipyridine product introduces a chelating ligand into the reaction system that can compete with the substrate for the catalyst metal, thus blocking it from further catalytic activity. The second problem is connected to the exposed position of the TMG substituent being in the α-position to the electronegative pyridine ring nitrogen, which comes along with an inherently higher reactivity at this position. While this is in general a highly desired feature, it can cause problems in the preparation of the organometallic coupling reagent, as we will exemplify later when discussing the Suzuki–Miyaura coupling reaction.

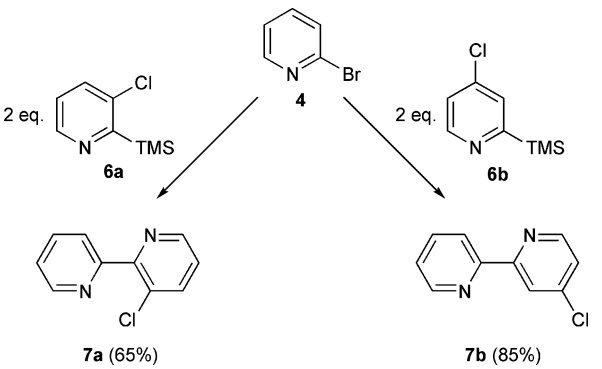
In the dawn of cross-coupling reactions being utilised in bipyridine chemistry the first examples used transmetallation reagents derived from 2-pyridyllithium or magnesium reagents. These reagents in general exhibit a high reactivity, which limits the number of possible functional groups attached to the substrates. However, the obtained yields of coupled product either for the copper-catalysed coupling of 2-lithiopyridines **1a** and **1b**[33] or the Ni(dppp)Cl_2-catalysed coupling of 2-pyridylmagnesium chloride **3**[34] were rather low (Scheme 3). To overcome the functionality tolerance problems, Knochel and co-workers have established protocols for the magnesation of functionalised aryl and heteroaryl halides at low temperatures with Grignard reagents and subsequent palladium-catalysed nucleophilic substitution with a second aryl halide.[35] While this approach is very useful especially for acceptor-substituted aryl compounds, it has only been exemplified with a limited number of pyridines so far, but might be an interesting possibility in the future.[36] However, only a few synthetic studies on the synthesis of non-symmetrical bipyridines other than connected in the 2- and 2′-position with aryl-Grignard reagents under palladium or nickel catalysis have been reported.[37–39] Therefore, no general procedure *via* Kumada-type couplings has been reported for the synthesis of 2,2′-bipyridines up to date.



Scheme 3 Early examples for the synthesis of 2,2′-bipyridines **2** and **5** by cross-coupling reactions.

The Hiyama coupling is very rare in bipyridine chemistry and only one single example related to the preparation of 2,2′-bipyridines has been reported just recently.[40] The application of siloxane-based aryl-aryl couplings with the focus on heteroaromatic systems including some non-2,2′-bipyridine compounds has been compiled recently in detail.[41] Organosilanes combine some advantages that other transmetallation reagents do not possess in this combination. They are in many cases easy to prepare, stable reagents and not as toxic as their homologous organotin compounds. However, because of the absence of polarisation of the C–Si bond, they either need activated silicon moieties or the use of additives such as fluoride to activate the silicon as a leaving group by hypercoordination.

Although some pyridyl silanes or siloxanes are already known,[42,43] Gros and co-workers evaluated the use of the simple trimethylsilyl (TMS) group for this purposes, using TBAF as the fluoride source, that provides the necessary hypercoordination for efficient transmetallation.[40] They reacted two different chloro-2-pyridyltrimethylsilanes **6** with 2-bromopyridine (**4**) under palladium catalysis at room temperature in DMF and obtained the chloro-substituted 2,2′-bipyridines **7a** and **7b** in good to very good yield (Scheme 4). The addition of copper(I) iodide was found to be crucial under these conditions as its absence led to considerable homo-coupling of the aryl halide in several other cases. It was assumed that the copper compound is responsible for the efficient transmetallation by forming a 2-pyridylcopper species.



Scheme 4 Synthesis of chloro-substituted 2,2′-bipyridines **7** by the Hiyama cross-coupling reaction.

The 2-position to the pyridyl nitrogen is also considered to be important for a successful transmetallation, because the adjacent nitrogen atom can coordinate the palladium metal, therefore leading to a complex where all the groups are located in an ideal position to achieve the transmetallation. This "complex-induced proximity effect" (CIPE) was already utilised in a number of cases with 2-pyridylsilyl groups.[44–46] Thus, although the Hiyama coupling has not found application in the convergent synthesis of more complex molecules containing the bipyridine fragment yet, it certainly has the potential for future application.

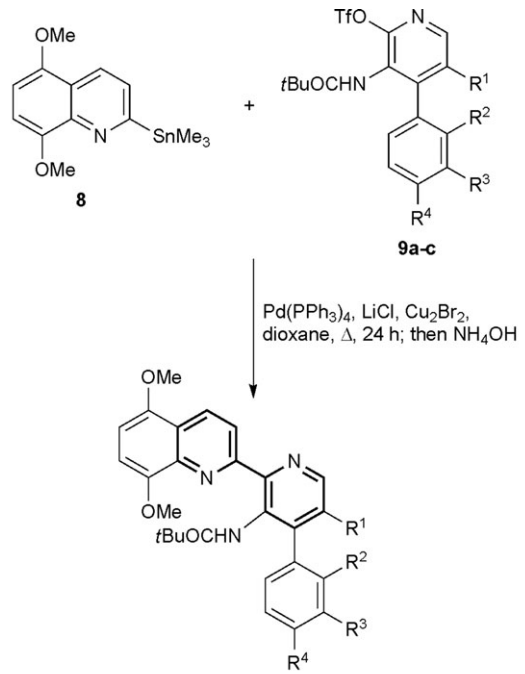
An intriguing reaction was recently reported by Suzuki and co-workers, in which hydrogen was acting as the leaving group. They found a dinuclear ruthenium complex which is active in the dehydrogenative coupling of 4-substituted pyridines, yielding symmetrical bipyridines. While the reaction runs at high temperature and the yields are more or less mediocre, this approach fascinates by its only byproduct being

hydrogen and the avoidance of any other reagents, pointing out the potential of future cross-coupling reactions with hydrogen as the leaving group.[47]

2.2 The Stille reaction in the synthesis of 2,2′-bipyridines

Aside from the rather exotic cross-coupling examples mentioned so far, the Stille cross-coupling reaction definitely belongs to the workhorses not only in general cross-coupling chemistry but also in the coupling of pyridines.[48] The review of Newkome, Schubert *et al*. accounted a large number of examples that were reported.[19]

The reaction offers the advantage, that the required stannyl pyridines can easily be prepared in relatively large amounts from bromo-, iodo- and even chloropyridines as well as from non-functionalised pyridines and are quite air- and moisture-stable and storable compounds. The coupling process itself accepts a large number of functional groups and is also compatible with other cross-coupling reactions. In recent years a number of efficient catalyst systems for the Stille reaction have emerged, including the coupling with normally unreactive chloroarenes.[49,50] The major drawbacks are the high toxicity of the utilised stannyl reagents and the problematic removal of the tin byproducts from the desired coupling products.

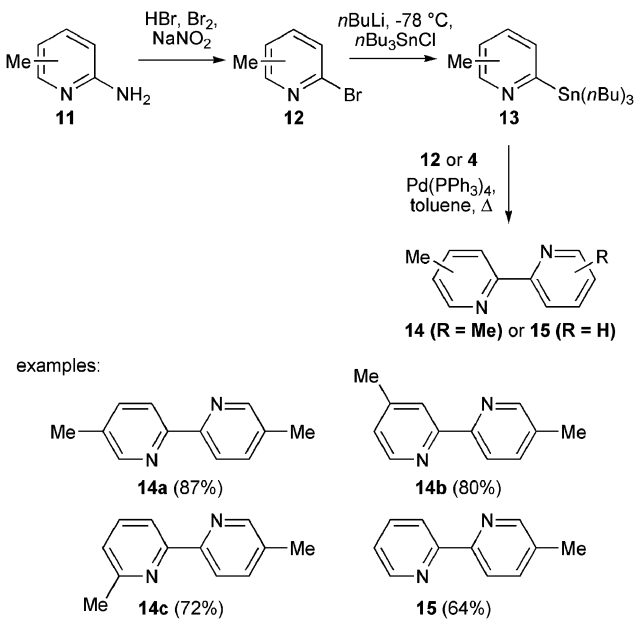


9a/10a: R^1 = H, R^2 = $OCONEt_2$, R^3 = R^4 = OMe; yield **10a**: 68%
9b/10b: R^1 = H, R^2 = OCH_2Ph, R^3 = R^4 = OMe; yield **10b**: 64%
9c/10c: R^1 = Me, R^2 = R^3 = R^4 = H; yield **10c**: 82%

Scheme 5 Synthesis of the 2,2′-bipyridine backbones **10a–c** by the Stille reaction in synthetic investigations towards Streptonigrin analogues.

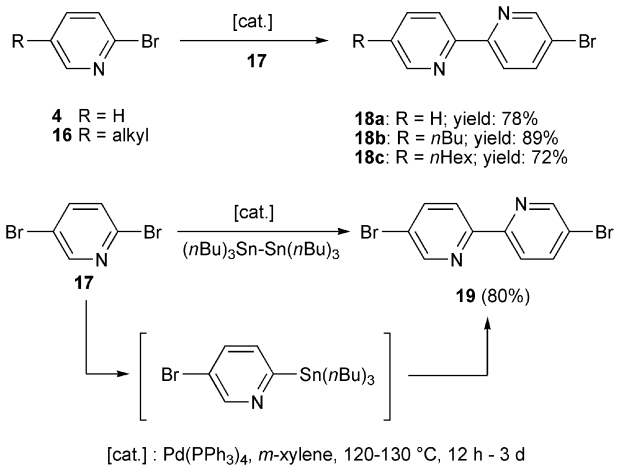
An early example which employed classic Stille cross-coupling methodology in preparing bipyridine-related adducts was described by Godard *et al*. for the preparation of Streptonigrin and Lavendamycin analogues **10a–c**.[51] They convergently prepared two different pyridine and quinoline derivatives to be coupled in a late step of the overall sequence (Scheme 5). In their investigation the authors were able to show that both, 2-pyridyl triflates **9a–c** as well as 2-pyridyl chlorides can be coupled with stannane **8**, although the triflates gave better yields (64–82% compared to 50% obtained with the respective chlorides). They used standard conditions for the Stille coupling with $Pd(PPh_3)_4$ as the catalyst and LiCl and Cu_2Br_2 as frequently used additives.[52] In the case of the 2-pyridyl chloride rather harsh conditions (refluxing toluene for 48 h) had to be applied. Another example stemming from the synthesis of non-symmetrical quaterpyridines was reported by Zoltewicz and Cruskie, where they synthesised the bipyridine cores from 2-stannylpyridine and a 2-pyridyl chloride with yields reaching up to 58% with the $Pd(PPh_3)_4$ catalyst.[53,54]

A first systematic investigation into the synthesis of substituted 2,2′-bipyridines and terpyridines including large scale preparations by the Stille approach was undertaken by Schubert *et al*. nearly a decade ago (Scheme 6).[55,56] They used 2-aminopicolines (**11**) as starting materials to synthesise the 2-bromopicolines (**12**) using the Sandmeyer reaction. Subsequent lithiation and quenching with nBu_3SnCl furnished the 2-stannylpyridines **13**. From the combination of **12** or **4** and **13** using the standard catalyst $Pd(PPh_3)_4$ in toluene and temperatures around 100 °C a number of differently mono- and dimethyl-substituted bipyridines **14** and **15** can be obtained in mostly good to very good yields, as is exemplified for the compounds **14a–c** and **15**. Further functionalisations such as silylations and brominations of the methyl substituent have also been reported.



Scheme 6 Synthesis of methyl-substituted 2,2′-bipyridines by the Stille cross-coupling reaction after Schubert *et al*.

The full potential of the Stille reaction in the synthesis of functionalised 2,2′-bipyridines has been demonstrated in recent years.[19] Some formerly unmentioned and new examples should be shortly discussed, that show advances and the broadness of the method. An exceptional example is the



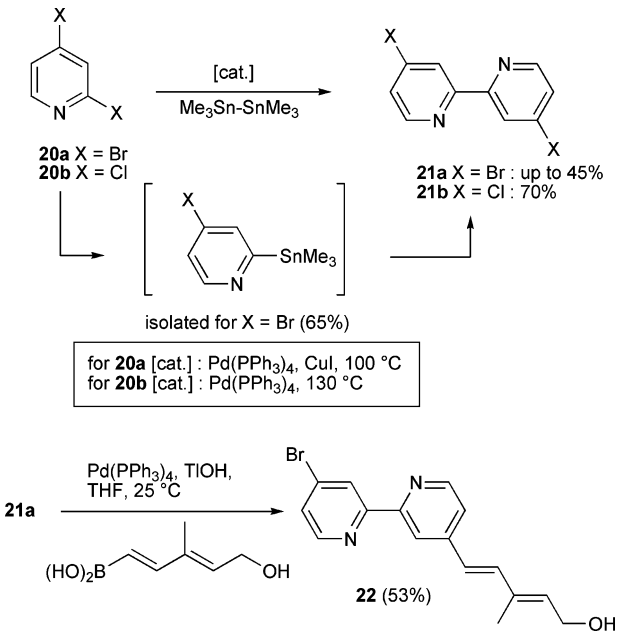
Scheme 7 Synthesis of 2,2′-bipyridines **18a–c** and **19** brominated in 5-positions *via* Stille cross-coupling reaction.

synthesis of halogenated 2,2′-bipyridines, that are excellent precursor molecules for further transformations. Their synthesis was for a long time left to chemistry under rather harsh conditions or multistep reactions.[57]

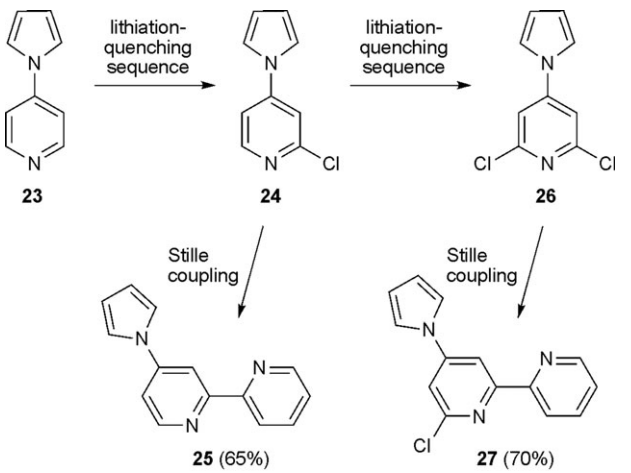
Michl and co-workers presented a cross-coupling approach for 2,2′-bipyridines brominated in the 5- and 5,5′-position, which also included the synthesis of several other derivatives (Scheme 7).[58] Using the standard palladium catalyst, the reaction proceeded smoothly, in good yields and nearly without formation of homo-coupling products in the case of the non-symmetrical bipyridines **18**. As a general feature for palladium-catalysed cross-coupling reactions with pyridines the halides in 2- or 6-position to the ring nitrogen are always more reactive towards oxidative addition to the transition metal center compared to the same halide at other ring positions due to the electron-withdrawing effect of the nitrogen, thus inducing a high regioselectivity. The homo-coupling procedure for the synthesis of **19** was developed from initial observations in the preparation of the non-symmetrical 2,2′-bipyridines **18**, where small amounts of **19** were identified as side-product. The optimised conditions (without formation of major side products) were found to be 50 mol% of hexa-*n*-butyldistannane together with the Pd(0) catalyst. The cross-coupling reaction is certainly preceded by an intermediate catalytic stannylation reaction.

The Stille coupling approach has very recently also been utilised for the synthesis of the 4,4′-dibrominated congener of **19**. In the work published by Cid and co-workers they modified the traditional multi-step synthesis, and in comparison developed a new approach including the use of hexamethyldistannane for the preparation of the 4,4′-dibromo- (**21a**) and 4,4′-dichloro-2,2′-bipyridine (**21b**) (Scheme 8).[59] The *in situ* coupling reaction using the distannane was very smooth for the 2,4-dichloropyridine (**20b**), showing high halogen-selectivity for the 2-position and giving only traces of side products. This is more difficult for the corresponding dibromopyridine **20a**, where problems with the regioselectivity of the coupling were observed. These problems were suspected to be caused by the high reaction temperature, that blurred the reactivity differences between the 2- and 4-position.

However, the isolation of the 2-stannylpyridine intermediate and subsequent reaction with the dibromopyridine gave the 4,4′-dibromo-2,2′-bipyridine (**21a**) in satisfying yield. In addition the reactivity of **21a** was investigated and the possibility of a selective Suzuki–Miyaura coupling to **22** was demonstrated as only one of the two equal bromo substituents was found to react (Scheme 8, lower part).



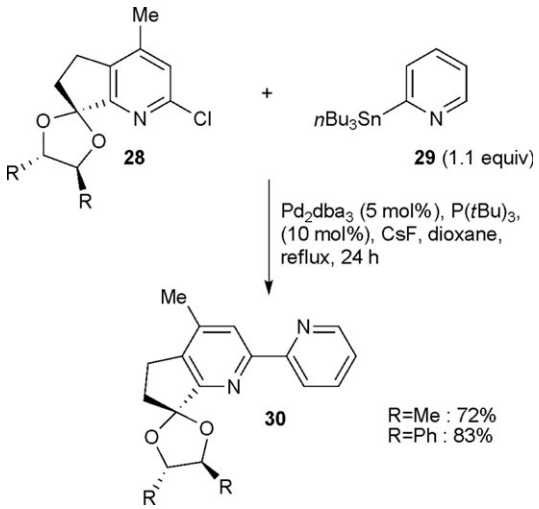
Scheme 8 Synthesis of 4,4′-dihalogenated 2,2′-bipyridines **21a**,**21b** by the Stille coupling approach and further functionalisation.



Scheme 9 Combination of a selective chlorination/Stille coupling approach.

The preparation of some monofunctionalised examples have been accounted for the Stille coupling recently. These reactions combine either the advances of modern other functionalisation reactions or the application of advanced catalyst

systems with the Stille reaction. The selective lithiation of a pyridine containing an electron-donating pyrrole nucleus in the 4-position (**23**) was investigated by Gros and Fort *et al.* and they were able to selectively functionalise the pyridine ring in the 2-position using the *n*BuLi–$Me_2N(CH_2)_2OLi$ reagent (BuLi–LiDMAE) to afford chloropyridine **24**, which was then coupled to yield the bipyridine compound **25** (Scheme 9).[60] This lithiation-electrophilic quenching approach can provide rapid access into pyridine precursor molecules with different functionalities, avoiding multi-step procedures and can even be employed to prepare 2,6-dichloropyridine **26** which could also be demonstrated to be a versatile building block for the assembly of substituted bipyridines such as **27**. The yields for the Stille coupling under standard conditions were between 65–70% and in case of the dichloropyridine only monofunctionalisation was observed without significant formation of the possible terpyridine. Here, the competitive inhibition of further reactions by complexation with the formed bipyridine is presumed to be responsible for this selectivity.



Scheme 10 Stille cross-coupling reaction in the synthesis of chiral 2,2′-bipyridine ligand **30**.

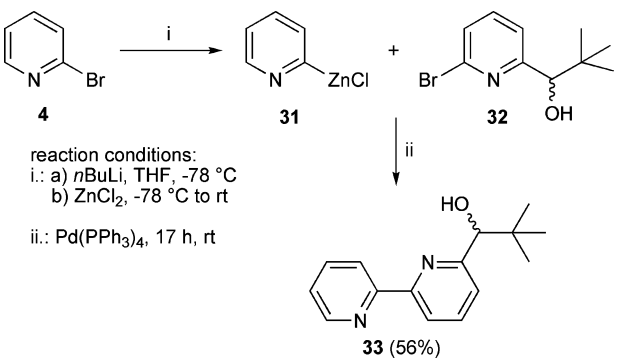
The Stille cross-coupling reaction was used as a synthetic tool in several other reports published during the last years for providing required 2,2′-bipyridine building blocks. Nearly all of the investigations utilised the standard coupling conditions with $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$ as the catalyst and chloro- or bromopyridines as the electrophilic coupling agent.[61–69]

In a recent work, however, the more electron-rich trialkylphosphane $PtBu_3$ was used in combination with a Pd(0) source and CsF as an additive.[70] The use of this highly active catalyst system was necessary since the reaction between the chloropyridine **28** and 2-(tri-*n*-butylstannyl)pyridine (**29**) with $Pd(PPh_3)_4$ was exceedingly slow even upon heating in benzene or toluene under reflux (Scheme 10). Under these modified conditions the yields for the product **30** of the cross-coupling reaction were as high as 83%. The reactivity problems with **28** were also observed in the nickel-catalysed homo-coupling reaction to make the symmetrical ligand. However, the problem could be solved by switching to the more reactive bromo derivative.

Other studies revealed that the Stille approach is not limited to homogenous conditions but can also be applied to solid-phase synthesis conditions.[71] Furthermore, some reports have also been published demonstrating the compatibility of stannylpyridines in Negishi cross-coupling reactions and subsequent Stille reaction to yield the projected 2,2′-bipyridines.[72]

2.3 The Negishi cross-coupling reaction as a versatile tool in the synthesis of functionalised 2,2′-bipyridines

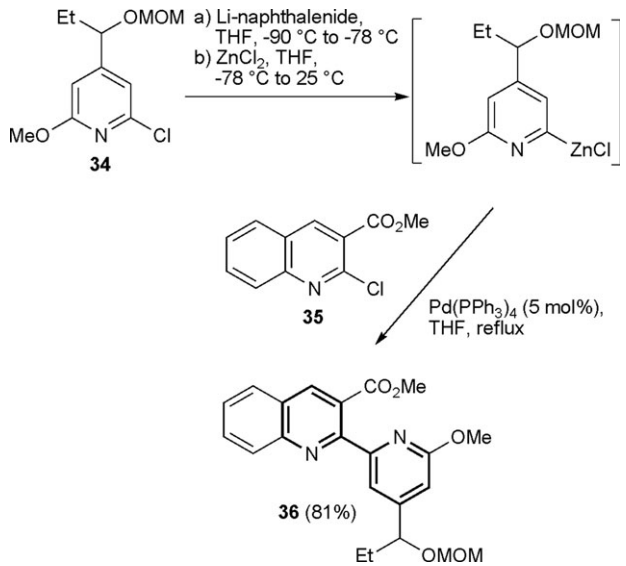
Like the Stille and the Suzuki–Miyaura reaction the Negishi cross-coupling reaction has seen a large body of applications since its discovery.[73–75] Next to the use in biaryl couplings of benzene derivatives and alkylations, alkenylations as well as alkynylations of aryl halides and sulfonates, the Negishi coupling is frequently used in heterocyclic chemistry.[48] Although, nowadays a number of organozinc compounds are commercially available as solutions in THF, *e.g.* 2-pyridylzinc bromide and related compounds, it is usually necessary or at least advisable to freshly prepare the required organozinc reagents either from the appropriate heteroaryl iodide or bromide by reaction with organolithium compounds or Grignard reagents, followed by transmetallation with a zinc salt, or by direct oxidative addition of the heteroaryl halide to extremely fine-powdered zinc or Rieke zinc.[76,77] This might seem to be a disadvantage, compared to the Stille and Suzuki coupling with in most cases stable organometallic precursors. However, the Negishi coupling can compensate this seeming disadvantage because the reaction combines the tolerance of a large number of functional groups with a higher transmetallation activity, the latter being more comparable with that of the Grignard reagents in the Kumada coupling. These observations can be attributed to the zinc–carbon bond containing a higher portion of covalent bonding, leading to a higher chemoselectivity compared to the Kumada coupling, but on the other hand inorganic zinc salts are resulting from the successful coupling, donating the (exothermic) driving force for the reaction. In the catalytic cycle the transmetallation can be rate-determining in cases where the oxidative addition is fast. Furthermore, the addition of additives, which is necessary for the Suzuki–Miyaura coupling, and in many cases also for the Stille coupling, is not required for the Negishi coupling. Unfortunately, much less detailed mechanistic information on the transmetallation step of the Negishi coupling is known, compared to the Stille or Suzuki coupling and preliminary mechanistic studies have been published only recently.[78]



Scheme 11 Early example for the synthesis of a 2,2′-bipyridine using the Negishi reaction.

A number of examples for the synthesis of bipyridines by the Negishi protocol have already been compiled,[19] while some earlier examples have been unmentioned.[79–85] Two cases should be exemplified here. One of the earliest examples for a successful 2,2′-bipyridine synthesis following the Negishi protocol was published by Bolm *et al.* (Scheme 11).[79] They prepared the 6-monosubstituted bipyridyl alcohol **33** from the appropriate 2-bromopyridine **32** and 2-pyridylzinc chloride (**31**) as coupling components. The reaction was run at room temperature and furnished the desired bipyridine **33** with 56% yield, which is slightly better than the comparable Stille coupling, while the latter needed more drastic conditions (95 °C, 29 h). The free hydroxyl group did not need protection, but a second equivalent of the organozinc reagent was required.

In another synthetic study the bipyridine core of camptothecin precursor **36** has been synthesised by applying the reaction with an organozinc reagent as the key step for connecting the two heteroaromatic fragments in a remarkable coupling reaction (Scheme 12).[82]

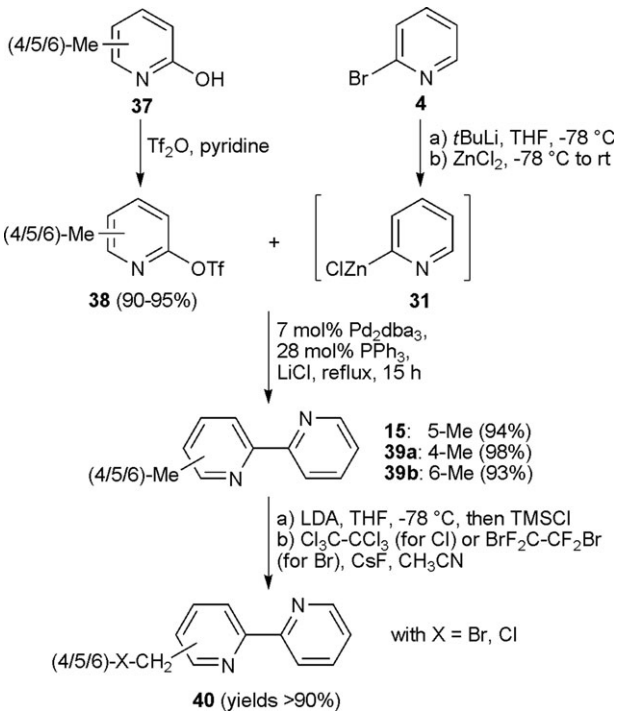


Scheme 12 Synthesis of the bipyridine fragment of camptothecin precursor **36** by the Negishi coupling.

In this transformation the preparation of the organozinc reagents is particularly interesting, because it started from 2-pyridyl chloride **34** and was accomplished by using lithium naphthalenide and subsequent transmetallation with $ZnCl_2$. The consecutive coupling with the chloroquinoline derivative **35** proceeded smoothly and furnished the product **36** in an excellent yield of 81% using standard catalytic conditions. These two examples already demonstrated that Negishi couplings usually proceed smoothly even under relatively mild conditions.

A major improvement and the first systematic investigation into the selective synthesis of functionalised 2,2′-bipyridines by the Negishi protocol was carried out by the end of the 1990s by Fraser and co-workers.[86,87]

In their investigation they first prepared 2-pyridyl triflates **38**, which were then reacted with $Pd(PPh_3)_4$ and organozinc reagent **31** in THF to furnish the monomethylated 2,2′-bipyridines **15**

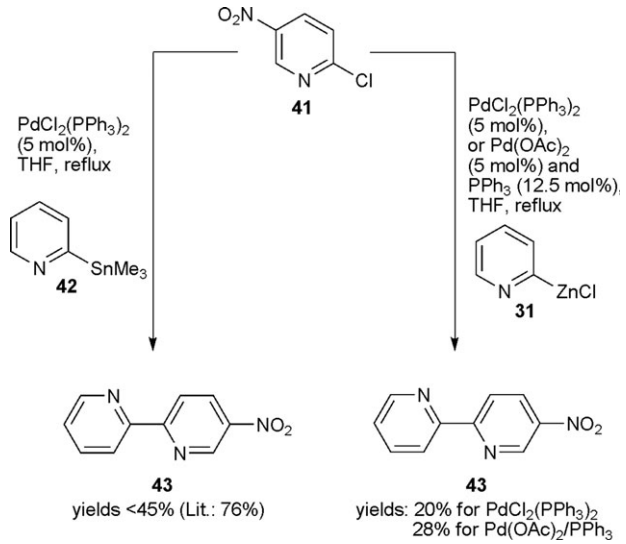


Scheme 13 Synthesis of functionalised 2,2′-bipyridines **15**, **39** and **40** by Fraser and co-workers.

and **39** in excellent yields (Scheme 13). Subsequent functionalisations of the methyl groups such as silylations and halodesilylations led to further functionalised derivatives **40**, again with yields exceeding 90%. The authors already discovered that an excess of $ZnCl_2$ and EDTA work-up to decomplex the bipyridine products were necessary to furnish high isolated yields of the 2,2′-bipyridines.

Our initial interest in bipyridine chemistry came from the requirement of functionalised 2,2′-bipyridines for the construction of supramolecular entities by the self-assembly of transition metal complexes.[88–91] The required compound was a 2,2′-bipyridine carrying either a halide or an alkynyl substituent in the 5-position. Our first approach started from a published Stille coupling procedure to give 5-nitro-2,2′-bipyridine (**43**) from commercially available 2-chloro-5-nitropyridine (**41**) and **42**, followed by reduction to the amine and Sandmeyer reaction to give the required 5-iodo-2,2′-bipyridine.[92] Unfortunately, this procedure did not work well in our hands. We therefore investigated the Negishi coupling approach with the same substrate, however, with unsatisfying results (Scheme 14),[36] even though Negishi *et al.* already reported on the successful coupling with nitro arenes.[93,94]

Despite these largely ineffective experiments, we decided to investigate another approach to the required bipyridine building block based on the Negishi reaction. Our aim was also, to evaluate the conditions for successful cross-couplings of pyridyl precursor molecules in terms of a modular concept for the synthesis of functionalised 2,2′-bipyridines. Several points should be addressed or needed to be kept in mind. In the synthesis of the organozinc reagent, the use of two equivalents of *t*BuLi proved to be essential to exclusively generate the corresponding lithiopyridyl species. The excess of added $ZnCl_2$ plays an important role not only for the transmetallation and



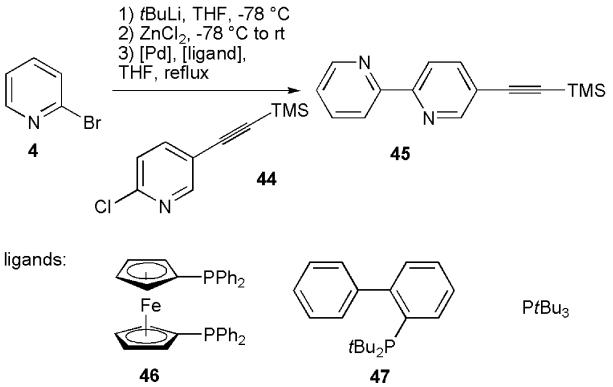
Scheme 14 Stille and Negishi couplings with 2-chloro-5-nitropyridine (**41**).

therefore coupling reaction but also for the coordination of the resulting 2,2′-bipyridine to prevent it from coordinating to the palladium catalyst, which could lead to catalyst poisoning.[95,96] However, we also checked for the necessary catalyst amount and did find out that catalyst loadings well below 3 mol% of palladium gave lower yields.

With this knowledge in mind lower catalyst loadings when turning to highly active catalytic systems should, in principle, be possible. Finally, the nature of the functionalised pyridyl compound used for coupling to the pyridylzinc species is vitally important. The need *e.g.* to synthesise pyridyl triflates can negatively influence the existence of other functional groups at the pyridine ring or could interfere with their elaboration. With the recent development of highly active catalyst systems that are able to allow cross-coupling reactions with the formerly often unreactive aryl chlorides under mild conditions, the possibilities were remarkably broadened.[97] We decided to take advantage of these developments and use 2-pyridyl chlorides as coupling reagents for the organozinc component. There are several advantages: a significant number of the chloro compounds is commercially available and they allow a wide array of transformations at the pyridine ring system to be feasible without getting involved, *e.g.* by substitution, because the 2-position of the pyridine ring can be rather prone especially to nucleophilic substitution in case of the bromides and iodides.

It was quite convenient that at the time of our synthetic considerations for bipyridine **45** Baxter had published a work, where he described the synthesis of different ethynylated pyridines.[98] Especially the 2-chloro-5-({trimethylsilyl}ethynyl)-pyridine (**44**) attracted our interest. Its synthesis is an excellent example for the advantage of a chloro substituent in the 2-position.[99] After the preparation of **44** we turned our attention to the Negishi cross-coupling with this 2-pyridyl chloride derivative.[100] As shown in Table 1 electron-rich trialkylphosphane P*t*Bu$_3$[101] gave superior yields (entry 4) compared to the standard catalyst $PdCl_2(PPh_3)_2$ (entry 1), chelating phosphanes such as dppf (**46**), or the biphenyl backbone-based Buchwald ligand **47** (entries 1–3).[102–104]

Table 1 Initial screening experiments for the modified Negishi cross-coupling reaction

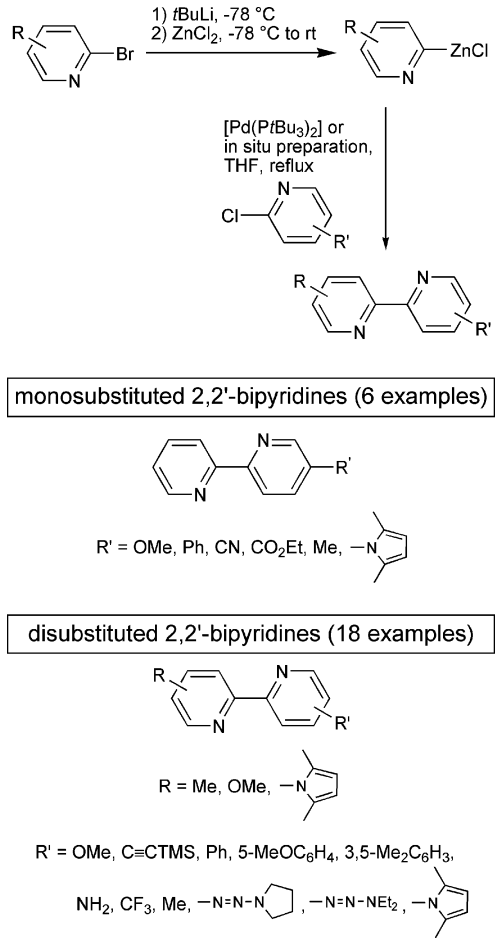


Entry	[Pd], [ligand]	Yield (%)
1	$PdCl_2(PPh_3)_2$ (8 mol% Pd)	44
2	$Pd_2dba_3{\cdot}CHCl_3$ (8 mol% Pd), dppf (**46**)	72
3	$Pd_2dba_3{\cdot}CHCl_3$ (3 mol% Pd), *t*Bu$_2$(2-biph)P (**47**)[a]	58
4	$Pd_2dba_3{\cdot}CHCl_3$ (3 mol% Pd), P*t*Bu$_3$[b]	83

[a] Here also 35% of the homo-coupling product 5,5′-bis[(trimethylsilyl)-ethynyl]-2,2′-bipyridine (**48**) were isolated. [b] The yield was exactly the same regardless if 3 or 6 mol% of the phosphane were used.[105]

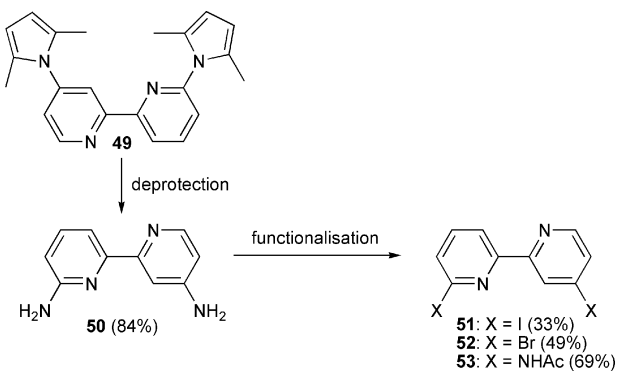
While in the beginning we used $Pd_2dba_3{\cdot}CHCl_3$ and solutions of P*t*Bu$_3$ for the *in situ* generation of the actual catalyst, this was replaced later by the more stable complex Pd(P*t*Bu$_3$)$_2$][101] and also the nowadays commercially available and stable ligand precursor [HP*t*Bu$_3$]BF$_4$.[106] The Pd(0)/PtBu$_3$ catalytic system was therefore systematically investigated in terms of the broadness and scope for the synthesis of six 5-monosubstituted 2,2′-bipyridines (yields ranging from 55–90%) and as much as eighteen differently disubstituted examples (yields ranging from 50–85% and somewhat lower yields if an additional deprotection step of the amino group was done directly after the cross-coupling step without isolating the respective pyrrole) carrying a wide array of different functional groups useful for subsequent manipulations.[100,107,108] An overview on the synthesised mono- and difunctionalised 2,2′-bipyridines is presented in Scheme 15. We evaluated a number of functionalised bromopyridines suitable for the preparation of the organozinc compound, especially with methyl, methoxy and the pyrrole-protected amines. The coupling reaction also tolerates a wide range of substituents in the substrate chloropyridines as coupling components. Low or no yields, however, were observed with nitro, free amino, boronic acid ester and thiophenyl substituents, presumably because they interfere with the organozinc reagent or the catalyst system.

However, we could solve the problem for the amino group by transforming the free amine in high yields into the stable dimethylpyrrole derivative that can easily and with, in most cases, very good yields be deprotected to furnish the free amine afterwards, *e.g.* the deprotection of **49** to **50** shown in Scheme 16. Interestingly, the pyrrole function can act as a chemical all-rounder, since it can be utilised as a precursor for the introduction of other functional groups. A number of



Scheme 15 Overview of 5-monosubstituted and differentially disubstituted 2,2′-bipyridines synthesised by the modified Negishi cross-coupling reaction.

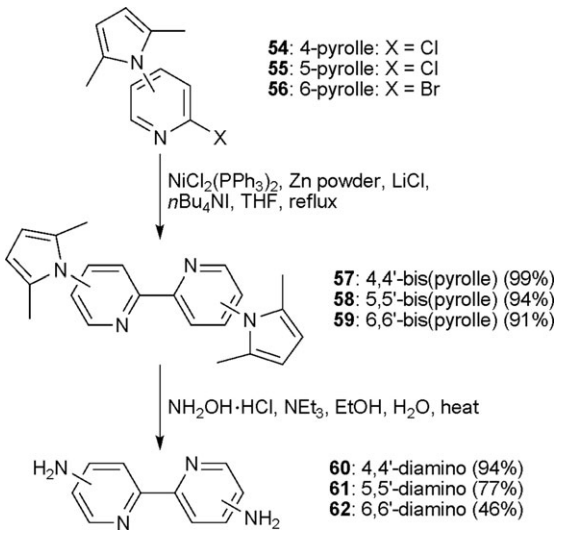
interesting subsequent transformations to variously functionalised bipyridine building blocks such as **51–53** (Scheme 16) have been achieved starting from the pyrrole/amino functionalised 2,2′-bipyridines,[100,107,108] demonstrating the potential of this cross-coupling methodology not only for the synthesis of non-symmetrical diamino-2,2′-bipyridines.



Scheme 16 Transformation of pyrrole-protected 2,2′-bipyridine **49**.

The accessibility of the symmetrically substituted diamino compounds by different methods has been investigated earlier and especially nickel-catalysed homo-coupling reactions have found application.[92,109] However, in many cases the free amines such as 2-chloro-5-aminopyridine were coupled, but the reaction proved to be troublesome.[110] Therefore, we decided to take advantage of the pyrrole-protected derivatives and investigated the synthesis of 4,4′-, 5,5′- and 6,6′-diamino-2,2′-bipyridine (**60**, **61** and **62**), respectively (Scheme 17). The homo-coupling reaction of easily available pyrrole-protected 2-chloro- (**54** and **55**) or 2-bromo-5-aminopyridine (**56**) using the nickel catalyst $NiCl_2(PPh_3)_2$ and elemental zinc as reducing agent gave excellent >90% yield in each case.

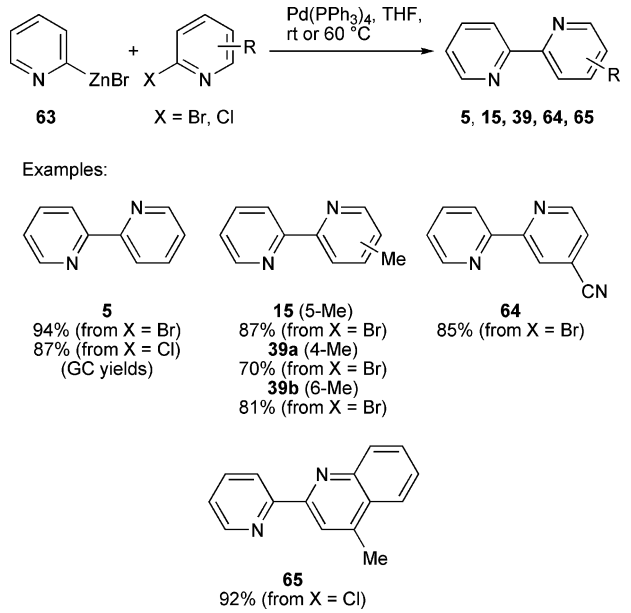
The coupling reaction of the pyrrole-protected 2-chloro-5-aminopyridine (**55**) was also investigated using the $Pd(OAc)_2$/tBu_2(2-biph)P catalyst system described for other homo-coupling reactions and especially for an alkynyl-substituted system.[111] However, the coupling yield for the synthesis of **58** did not exceed 58%.



Scheme 17 Synthesis of symmetrical diamino-2,2′-bipyridines **60–62** by homo-coupling of the protected derivatives.

Beside the use of the [Pd(0)]/P*t*Bu$_3$-system, recent work by Hanan *et al.* and also by us pointed out the potential of "old-fashioned" catalyst $Pd(PPh_3)_4$ for the use in Negishi cross-coupling reactions between 2-pyridylzinc reagents such as **63** and 2-pyridyl chlorides and bromides.[112,113] Although nowadays the [Pd(0)]/P*t*Bu$_3$ complex is easily generated from stable precursors or commercially available, the $Pd(PPh_3)_4$ complex is still interesting in terms of its relatively low costs and easy availability, especially for large scale applications.

Fang and Hanan first investigated the reactivity of 2-pyridyl bromides with the organozinc reagents under $Pd(PPh_3)_4$ catalysis at room temperature and found that the reactions were completed within 24 h, yielding the appropriate 2,2′-bipyridines **5**, **15**, **39a**, **39b**, **64** and **65** in good to excellent yields.[112] They extended this study to 2-pyridyl chlorides, where they disclosed the feasibility of the coupling reaction under elevated temperatures and longer reaction times (Scheme 18). The reactivity of the 2-pyridyl chlorides is expectedly higher when the heteroaromatic ring systems carries electron-withdrawing substituents. Therefore, reactions with chloropyridines

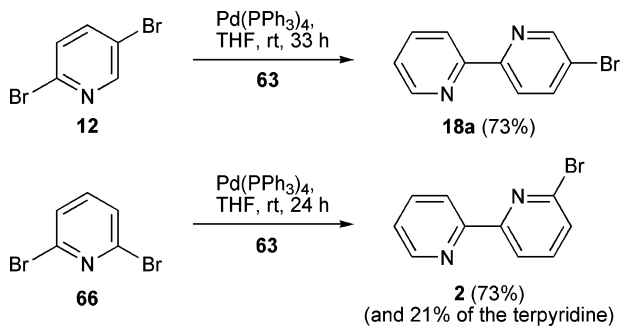


Scheme 18 Synthetic work by Fang and Hanan towards the synthesis of functionalised 2,2′-bipyridines with $Pd(PPh_3)_4$ as the catalyst.

carrying electron-donating groups were slow or appeared not feasible with this catalyst.

Fang and Hanan were also able to synthesise the highly desirable brominated 2,2′-bipyridines **18a** and **2** from the appropriate dibrominated pyridines, in most cases with the formation of only insignificant or even without the formation of the dicoupled product (Scheme 19). The reaction benefited from the observation mentioned earlier, that the newly formed bipyridine zinc salts precipitate and therefore were removed from the reaction system.[96]

The selective monofunctionalisation was used for the synthesis of binding sites in ligands and metal complexes. In particular the assembly of the bipyridine ligand by Negishi cross-coupling reaction with a ruthenium complex bearing an pyridyl bromide for the stepwise assembly of a heterobimetallic complex is worth mentioning.[114]



Scheme 19 Selective synthesis of brominated 2,2′-bipyridines **18a** and **2** by the Negishi reaction.

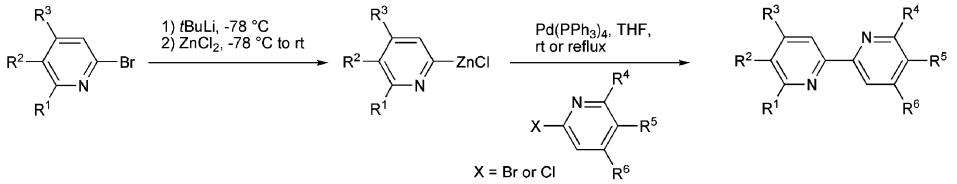
We acted on the suggestion of Hanan's work and investigated the use of $Pd(PPh_3)_4$ in coupling reactions with functionalised 2-pyridyl chlorides and bromides. Our results showed that $Pd(PPh_3)_4$ is an efficient catalyst for the highly selective synthesis of mono- and difunctionalised 2,2′-bipyridines in excellent yields accepting a wide variety of functional groups (Scheme 20).[113] The strategy again included the preparation of the organozinc reagents from the 2-bromopyridines and *t*Bu-Li/$ZnCl_2$ due to a high flexibility of the approach allowing diverse pyridyl bromides as precursors. The excess of the zinc reagents was varied in the range 1.1 to 1.5 equiv., however, this had no influence on the yield of the cross-coupling reaction.

As already reported in the work of Fang and Hanan the reactivity of the pyridyl bromides used as coupling partners is much higher than that of the comparable chlorides and the coupling reactions occurred smoothly at room temperature, giving yields from 55% to quantitative. The corresponding chlorides, however, required considerably higher temperatures, such as *e.g.* refluxing THF to yield the bipyridine products with 51–90% yield depending on the substitution pattern. The development of this methodology revealed some interesting results. In general, the yields for monosubstituted 2,2′-bipyridines were very good to excellent (see caption of Scheme 20), especially for the sensitive ester **69** (monosubstituted bipyridines, entry 5). The yield for the 5-ethynylated biypridine **45** (monosubstituted bipyridines, entry 1) is slightly higher than in the previous examples (see Table 1). The 5-methyl-2,2′-bipyridine (**15**) was obtained quantitatively, still exceeding the already excellent yield obtained when we used P*t*Bu_3 as ligand and significantly improving the yield compared to the Stille coupling reaction (Scheme 6). The disubstituted bipyridines display again a great diversity of functional groups, that can hardly be installed in another effective manner in such a low number of steps. Subsequent transformations can even increase this molecular versatility easily.[113]

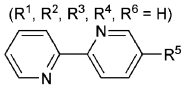
Some single examples for the synthesis of 2,2′-bipyridines for different purposes utilising the Negishi cross-coupling approach have been recorded during the last couple years and should be cited here.[115–118] The use of heterogeneous catalysts and microwave heating in the Negishi coupling was investigated very recently and interestingly found to proceed within short reaction times.[119] However, the investigation of the functionalised 2,2′-bipyridines was limited to methyl substitution. Ley and co-workers reported a single example of a microwave-assisted Negishi coupling using the $Pd(PPh_3)_4$ catalyst furnishing a nitrile substituted 2,2′-bipyridine with 85% yield.[116]

2.4 The Suzuki–Miyaura reaction: a late comeback in 2,2′-bipyridine synthesis

The Suzuki–Miyaura cross-coupling reaction can certainly be considered the most widely used cross-coupling reaction in synthetic organic chemistry. Like the other cross-coupling reactions it has found widespread application also in heterocyclic chemistry.[48,120,121] Usually, one of the biggest advantages is the ease of preparation and in many cases commercial availability of a large number of boronic acids and esters, that are usually shelf-stable compounds, insensitive to air and moisture.[122] However, the synthetic utilisation for the joining of two pyridine fragments in the synthesis of 2,2′-bipyridines was scarce until very recently. Unfortunately, unlike for the Stille, Negishi and even Hiyama coupling, where rather stable

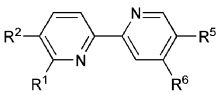


monosubstituted 2,2'-bipyridines (R^1, R^2, R^3, R^4, R^6 = H)



entry	X	R^5	product	yield (%)
1	Cl	C≡CTMS	**45**	90*
2	Br	OMe	**67**	98*
3	Br	Me	**15**	quant.*
4	Br		**68**	73*
5	Cl	CO_2Me	**69**	80
6	Cl	4-$MeOC_6H_4$	**70**	76

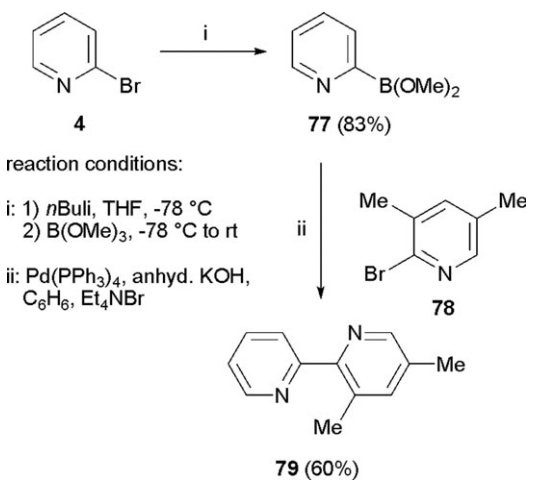
disubstituted 2,2'-bipyridines (R^3, R^4 = H)



entry	X	R^1	R^2	R^5	R^6	product	yield (%)
1	Cl	H	Me	4-$MeOC_6H_4$	H	**71**	66*
2	Br	H	*n*heptyl	Br	H	**72**	85
3	Cl	H	C≡CTMS	CO_2Me	H	**73**	70
4	Br		H	H	CO_2Me	**74**	55
5	Cl	Me	H	H	Me	**75**	84
6	Cl	OMe	H	H		**76**	88

Scheme 20 Synthesis of various non-symmetrical functionalised 2,2′-bipyridines using a Negishi reaction with $Pd(PPh_3)_4$ as the catalyst (*yields were 83% (**45**), 72% (**67**), 90% (**15**), 72% (**68**) and 46% (**71**) when we employed P*t*Bu_3 as ligand).

organometallic 2-pyridyl derivatives are well known, this has not been the case for the corresponding 2-pyridylboronic acids (and their derivatives) required for the Suzuki–Miyaura reaction for a long time. This is especially interesting in view of the fact that the 3-pyridyl and 4-pyridyl boronic acids are well known and even commercially available substances for quite some time already.[120,123,124]

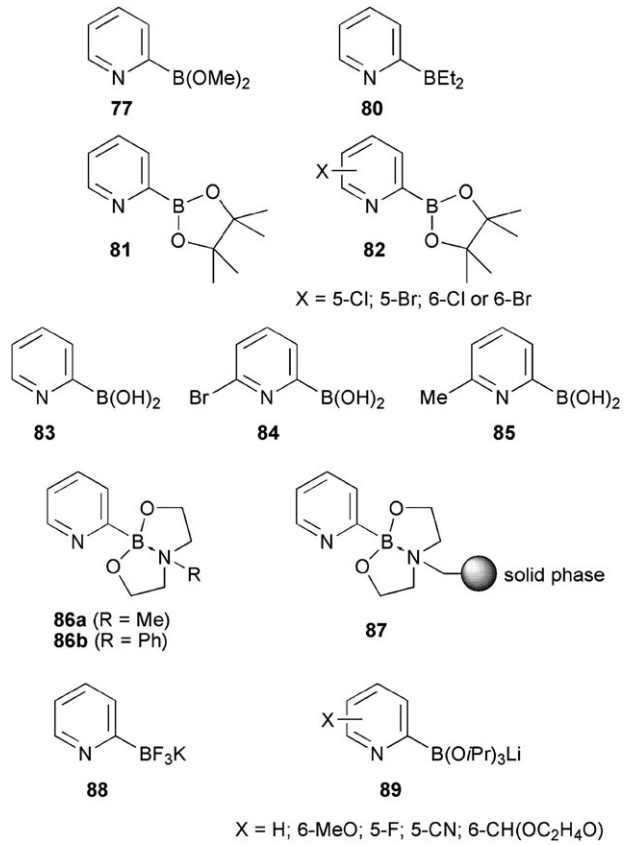


Scheme 21 Synthesis of the 2-pyridylboronate **77** and the subsequent Suzuki–Miyaura coupling with the 2-pyridyl bromide **78**.

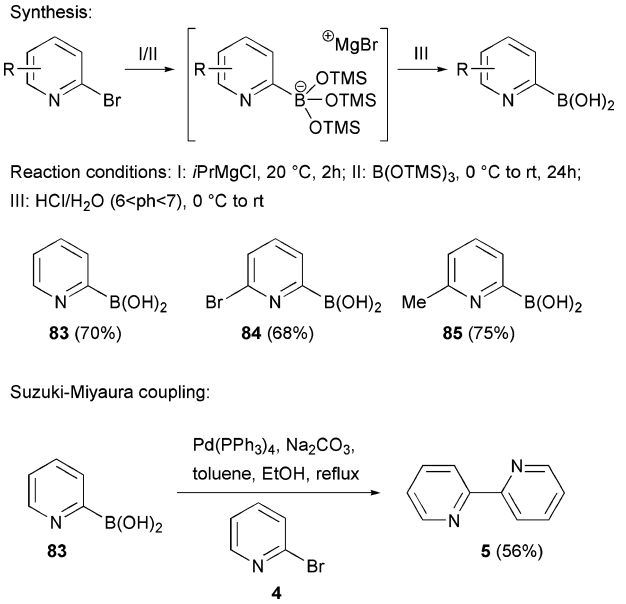
This lack of suitable 2-pyridylboron compounds can be traced back to the fact, that boryl substituents in α-position to the nitrogen atom are rather susceptible to protodeboration, especially under acidic and protic conditions.[125] The earliest example for the successful use of a stable 2-pyridylboronate in a Suzuki–Miyaura coupling yielding a 2,2′-bipyridine core have been reported from Diederich and co-workers in 1991.[126] Interestingly, the synthesis of the sensitive dimethyl 2-pyridylboronate **77** was not described in detail until five years later, followed by the application in a cross-coupling reaction with **78** giving the disubstituted 2,2′-bipyridine **79** (Scheme 21).[127]

Until the turn of the millennium only few investigations into the synthesis of 2-pyridylboron compounds have been reported. Terashima *et al*. reported synthetic investigations on dialkylpyridylboranes, including the diethyl(2-pyridyl)borane (**80**).[128,129] However, the yields of **80** and also some derivatives turned out to be troublesome and they failed to react in cross-coupling reactions with aryl halides, presumably due to the formation of a very stable dimer even in solution.[130] Interestingly, the situation is different for dialkyl-2-quinolylboranes, where successful cross-coupling reactions have been observed albeit with yields of the products rarely exceeding 50%.[131]

However, the situation has strongly changed in recent years and there are even quite a number of 2-pyridylboronic acid derivatives commercially available from different suppliers now.[132] In 2000 a total synthesis of (±)-cytisine has been reported, where the authors prepared a 2-pyridylboronate *in situ* for a subsequent cross-coupling reaction with a 3-pyridyl bromide, yielding a 2,3′-bipyridine.[133] Since then efforts have been made to prepare significantly more stable 2-pyridylboron precursor compounds that can be efficiently used in cross-coupling reactions. A compilation of synthesised compounds is displayed in Scheme 22. The pinacol boronates such as **81** and **82** often exhibit superior stability compared to the other dialkylboronates. Their synthesis has been thoroughly examined by Rault and co-workers, who also investigated their cross-coupling reaction with aryl bromides and iodides.[134–139] The procedure is rather general and included the reaction of the 2-lithiopyridines with B(O*i*Pr)$_3$ and



Scheme 22 Overview of known 2-pyridylboron compounds **77** and **80–89**.



Scheme 23 Synthesis of 2-pyridylboronic acids and their use in the synthesis of 2,2′-bipyridines by Matondo *et al.*

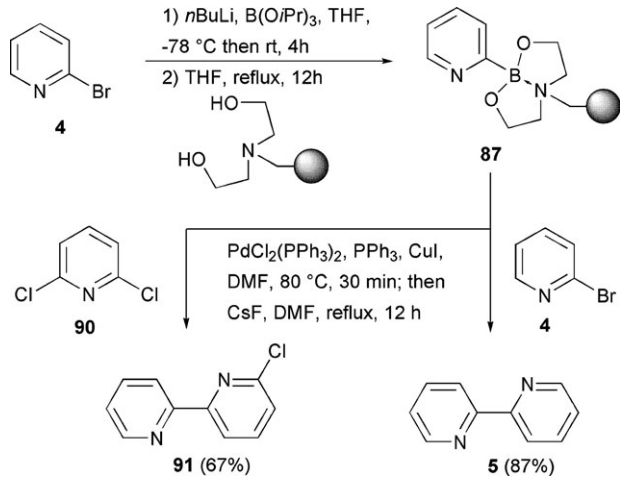
subsequent transesterification with pinacol to furnish the pinacol boronates **81** or **82** or hydrolysis to give the free boronic acid analogs (*e.g.* **83**, **84** or **85**). Attempted synthesis with the palladium-catalysed coupling of 2-pyridyl chlorides with bis(pinacolato)diboron or the iridium-catalysed C–H functionalisation with the same diboron reagent have not been met with success.[140,141] However, the successful and selective borylation of 2,2′-bipyridines in *ortho*-position to the nitrogen *via* Ir-catalysed C–H functionalisation was observed.[142]

A palladium-catalysed *in situ* coupling method of 2-pyridyl bromides with bis(pinacolato)diboron comparable to the one discussed for the Stille coupling with hexaalkyl distannane (see Scheme 7) has been described, yielding 2,2′-bipyridines presumably *via* the formation of 2-pyridylboronates.[143]

The efficient synthetic access to the elusive 2-pyridylboronic acids such as **83–85** has finally been evaluated by Matondo *et al.*, using tris(trimethylsilyl)borate for the quenching of the organometallic 2-pyridyl compound (Scheme 23).[144] While in most cases a bromine–lithium exchange was preferred, they made use of a bromine–magnesium exchange using the Grignard reagent *i*PrMgCl. Two important features for the success of the synthesis were noted: first, the application of tris(trimethylsilyl)borate as the efficient quenching electrophile, and the second is the compliance of the work-up conditions with a pH of $6 < pH < 7$. A more acidic pH promotes the protodeboration of the sensitive 2-pyridylboronic acids. The pure boronic acids **83–85** were obtained in excellent yields of 68–75%. This procedure was used to prepare amphiphilic 2-pyridylboronic acids bearing an alkoxy ligand in the 3-position.[145] The same group examined the potential of the prepared boronic acids such as **83** and **84** for the Suzuki–Miyaura reaction with other pyridyl halides, as exemplified for the synthesis of 2,2′-bipyridine (**5**) with 56% yield using $Pd(PPh_3)_4$ as the catalyst (Scheme 23 below).[146]

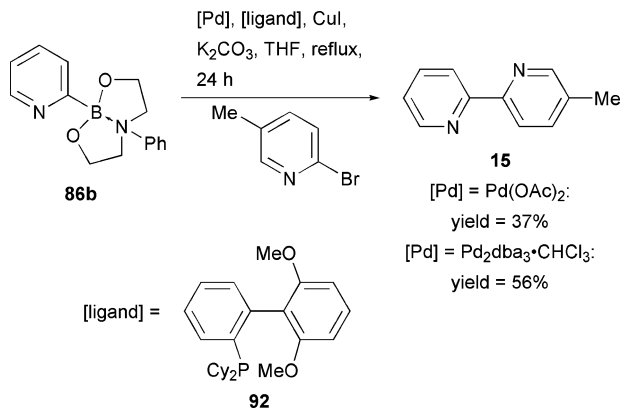
The derivatisation of free boronic acids, however, is still an attractive goal for the provision of a reliable and stable source of the crucial 2-pyridylboron fragment. The synthesis of the diol-derivatives **81** and **82** revealed the stabilising influence of the protection of the free hydroxy groups. An even better stabilisation was found for the use of *N*-aryl or -alkyldiethanolamine as the "protecting group".[122] This diol affords the dioxazaborocanes such as **86a**, **86b** and **87**, possessing a ring structure, where the nitrogen of the former diol can undergo internal B←N dative bonding, leading to a tetracoordinated B atom.[147] These boron derivatives possess a higher stability against deboration and are easier to purify. The first example related to 2-pyridylboronates was reported by Hodgson and Salingue in 2004.[148] They prepared **86b** on a large scale and found it to be a rather stable compound. The published results include a reactivity study with several aryl iodides and bromides using $Pd(OAc)_2/PPh_3/CuI/K_2CO_3$ in THF as the catalyst system. While for the iodides the yields can be as high as 89%, for the bromides the presence of electron-withdrawing groups are necessary to obtain high yields.

In a combined effort of stabilising the 2-pyridylboron fragment and immobilisation for combinatorial chemistry purposes, Gros *et al.* reported the first polystyrene-supported 2-pyridylboronate **87** (Scheme 24).[149] The investigations included the optimisation of Suzuki–Miyaura cross-coupling conditions for this system and the screening of a number of different coupling substrates, namely aryl iodides and bromides and interestingly the cross-coupling reaction with 2-pyridyl bromide (**4**) and 2,6-dichloropyridine (**90**). The yield obtained for 2,2′-bipyridine (**5**) was excellent 87%, which is



Scheme 24 Preparation of solid-phase bound 2-pyridyldioxazaborocane **87** and its use in the synthesis of 2,2′-bipyridines.

better than in the example mentioned above (Scheme 23) and for the so far unknown coupling with 2,6-dichloropyridine (**90**), still a very good yield of 67% was observed for the synthesis of the 6-chlorinated 2,2′-bipyridine **91**, making this approach promising for future applications.

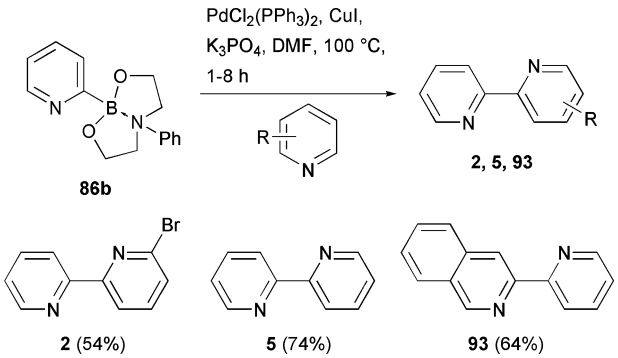


Scheme 25 Study on the synthesis of 5-methyl-2,2′-bipyridine (**15**) by the Suzuki–Miyaura reaction of **86b**.

We have also investigated the Suzuki–Miyaura coupling of **77** and **86b** with different 2-pyridyl bromides and iodides.[150] Using boronate **77** we could in no case obtain any bipyridine product using $Pd(PPh_3)_4$ as the catalyst with different additives and solvents. Instead, nucleophilic substitution of the halide with methoxide (originating obviously from the boronate) in 2-position was observed, especially with electron-withdrawing substituted pyridines such as 2-chloro-5-nitropyridine (**41**).

We then turned our attention to the use of **86b** for the screening with different catalyst systems in cross-coupling reactions. The use of Buchwald-type ligands such as **92** in particular proved to be a promising starting point.[151,152] This approach furnished the desired functionalised 2,2′-bipyridine **15** in acceptable yield (Scheme 25).[153]

A very recent study by Stevens and co-workers investigated the preparation of 2,2′-bipyridine (**5**) and related diazines (*e.g.* **2** and **93**) from **86b** within a broader scope.[154] The yields were useful in general and the reaction required only 1.1 equivalents of **86b** relative to the haloazine instead of 2 equivalents applied in earlier reports. The catalytic system is comparable to the systems used in an earlier report,[149] except that a different base (K_3PO_4) was used (Scheme 26). These screening experiments utilising bromides and chlorides demonstrated the general feasibility of the Suzuki–Miyaura coupling with modified 2-pyridyl boronates for the synthesis of 2,2′-bipyridines.



Scheme 26 Approach to the synthesis of the 2,2′-bipyridines **2**, **5** and **93** and substituted analogues by Stevens and co-workers using **86b**.

Finally, the synthesis of saline 2-pyridylboronates **88** and **89** have been reported. Molander and Biolatto prepared potassium trifluoroboronates such as **88**, however, they reported solubility problems and insufficient stability of the compound and no successful cross-coupling experiments were reported.[155] A thorough study of the coupling of different 2-pyridylboron nucleophiles (such as **81**, **83**, **86b**, **88** and **89** (X = H) was published very recently by Buchwald and Billingsley.[156] They described the synthesis and successful application of several isopropoxy boronates of the type **89** for cross-coupling reactions with aryl halides using [Pd_2dba_3] and different phosphine oxides as suitable ligands, giving the biaryls (however, no 2,2′-bipyridines) in mostly good to very good yield. Several examples were reported, where diazines were synthesised starting from **89** including two cases, in which unfunctionalised 2,3′-bipyridine was obtained with 73% (from 3-pyridyl bromide) and 92% yield (from 3-pyridyl chloride).

3. Conclusions

The 2,2′-bipyridines have found numerous applications as ligands in transition metal-coordination compounds in areas such as catalysis, photochemistry, macromolecular chemistry, supramolecular chemistry and nanosciences. Thus, there is a still growing demand for efficient protocols that allow the selective formation of highly functionalised derivatives. In this review, we wanted to account the recent developments that have been achieved concerning the use of modern cross-coupling reactions for this purpose. While the Stille reaction is an established and longstanding instrument in the toolbox of bipyridine chemistry, especially the Negishi reaction and only very recently also the Suzuki–Miyaura reaction have evolved to similarly powerful tools. The Negishi cross-coupling reaction allows the synthesis of a very broad

spectrum of 2,2′-bipyridines carrying all kinds of functionalised groups in different positions in an efficient and often high-yielding manner. The systematic development of this methodology makes it an attractive approach for the efficient preparation of very different 2,2′-bipyridines. The remarkable development of the Suzuki–Miyaura coupling especially in terms of the discovery of stable 2-pyridylboron precursors required for the evaluation of successful coupling strategies can have a deep impact and will help to further improve this approach towards reliable and broadly applicable synthetic methods for the preparation of 2,2′-bipyridines. Some potential in this aspect can also be expected from the cross-coupling of stable organosilicon compounds of the 2-pyridyl fragment, namely the Hiyama coupling, and also direct arylation reactions.

Acknowledgements

A. L. and M. H. would like to thank the "bipyridine guys" Dr U. Kiehne, J. Bunzen and H. Staats for their creative work and dedication to the project. The authors acknowledge financial support from the DFG (SFB 624) and the Leibniz-Institut für Katalyse e.V. an der Universtät Rostock (LIKAT). M. H. thanks Prof. Uwe Rosenthal for his support and Dr Rosa C. Taboada for proof reading and helpful suggestions.

References

1 A. P. Smith and C. L. Fraser, in *Comprehensive Coordination Chemistry II*, eds. J. A. McCleverty and T. J. Meyer, Elsevier, Oxford, 2004, vol. 1, p. 1.
2 C. Kaes, A. Katz and M. W. Hosseini, *Chem. Rev*., 2000, **100**, 3553.
3 C. A. Schalley, A. Lützen and M. Albrecht, *Chem.–Eur. J*., 2004, **10**, 1072.
4 M. J. Hannon and L. J. Childs, *Supramol. Chem*., 2006, **16**, 7.
5 The photochemistry of transition metal-bipyridine complexes is covered extensively, in *Photochemistry and Photophysics of Coordination Compounds I + II (Topics in Current Chemistry)*, eds. V. Balzani and S. Campagna, Springer Verlag, Berlin, vol. 280 and 281, 2007.
6 Md. K. Nazeeruddin, T. Bessho, Le Cevey, S. Ito, C. Klein, F. De Angelis, S. Fantacci, P. Comte, P. Liska, H. Imai and M. Graetzel, *Photochem. Photobiol. A: Chem*., 2007, **185**, 331, and references therein.
7 Recent review with focus on chiral 2,2′-bipyridines: A. V. Malkov and P. Kočovsý, *Curr. Org. Chem*., 2003, **7**, 1737, and references therein.
8 H.-L. Kwong, H.-L. Yeung, C.-T. Yeung, W.-S. Lee, C.-S. Lee and W.-L. Wong, *Coord. Chem. Rev*., 2007, **251**, 2188.
9 Arene borylation: T. M. Boller, J. M. Murphy, M. Hapke, T. Ishiyama, N. Miyaura and J. F. Hartwig, *J. Am. Chem. Soc*., 2005, **127**, 14263.
10 Negishi cross-coupling reaction: A. Gavryushin, C. Kofink, G. Manolikakes and P. Knochel, *Tetrahedron*, 2006, **62**, 7521.
11 Grubbs' metathesis catalyst analogues: J. A. Wright, A. A. Danopoulos, W. B. Motherwell, R. J. Carroll and S. Ellwood, *J. Organomet. Chem*., 2006, **691**, 5204.
12 Copper-catalysed homo-coupling of aryldiazonium salts: I. Cepanec, M. Litvić, J. Udiković, I. Pogorelić and M. Lovrić, *Tetrahedron*, 2007, **63**, 5614.
13 Nickel-catalysed carbonylative Negishi reaction: Q. Wang and C. Chen, *Tetrahedron Lett*., 2008, **49**, 2916.
14 F. Mongin, F. Trecourt, B. Gervais, O. Mongin and G. Quéguiner, *J. Org. Chem*., 2002, **67**, 3272.
15 T. Sammakia, E. L. Stangeland and M. C. Whitcomb, in *Strategies and Tactics in Organic Synthesis*, ed. M Harmata, Elsevier, New York, 2005, vol. 6, p. 415, and references therein.
16 F. Trecourt, B. Gervais, O. Mongin, C. Le Gal, F. Mongin and G. Quéguiner, *J. Org. Chem*., 1998, **63**, 2892.
17 A recent compilation of synthetic strategies for the assembling of the camptothecin backbone: W. Du, *Tetrahedron*, 2003, **59**, 8649.
18 G. Bringmann, Y. Reichert and V. V. Kane, *Tetrahedron*, 2004, **60**, 3539.
19 G. R. Newkome, A. K. Patri, E. Holder and U. S. Schubert, *Eur. J. Org. Chem*., 2004, 235.
20 F. Kröhnke, *Synthesis*, 1976, 1.
21 L. Anastasia and E. Negishi, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E. Negishi, John Wiley & Sons, New York, 2002, p. 311.
22 30 Years of the Cross-coupling Reaction (Special Issue), eds. K. Tamao, T. Hiyama and E. Negishi, *J. Organomet. Chem*., 2002, **653**, 1.
23 I. Cepanec, *Synthesis of Biaryls*, Elsevier, Oxford, 2004.
24 Extensive overview on aryl–aryl coupling reactions: J. Hassan, M. Sevignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev*., 2002, **102**, 1359.
25 *Metal-catalyzed Cross-coupling Reactions*, eds. F. Diederich and P. J. Stang, Wiley-VCH, Weinheim, 2nd edn, 2004.
26 *Cross-coupling Reactions (Topics in Current Chemistry)*, ed. N. Miyaura, Springer Verlag, Berlin, 2002, vol. 219.
27 For a general account on palladium-catalysed cross-coupling reactions with heteroaromatics, see: K. Undheim, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E. Negishi, John Wiley & Sons, New York, 2002, p. 409.
28 For a compilation of modern synthetic methods for the synthesis of N-containing bisheteroaromatics, see: P. Gros and Y. Fort, *Curr. Org. Chem*., 2003, **7**, 629.
29 A very recent review with focus on the functionalisation of pyridines: L.-C. Campeau and K. Fagnou, *Chem. Soc. Rev*., 2007, **36**, 1058.
30 M. Albrecht, *Chem. Rev*., 2001, **101**, 3457.
31 G. F. Swiegers and T. J. Malefetse, *Coord. Chem. Rev*., 2002, **225**, 91.
32 Recent review: C. R. K. Glasson, L. F. Lindoy and G. V. Meehan, *Coord. Chem. Rev*., 2008, **252**, 940.
33 J. E. Parks, B. E. Wagner and R. H. Holm, *J. Organomet. Chem*., 1973, **56**, 53.
34 K. Tamao, S. Kodama, I. Nakajima and M. Kumada, *Tetrahedron*, 1982, **38**, 3347.
35 H. Ila, O. Baron, A. J. Wagner and P. Knochel, *Chem. Commun*., 2006, 583.
36 We have tried to synthesise a nitro-substituted 2,2′-bipyridine by using a halogen/magnesium exchange at low temperatures and subsequent palladium-catalysed cross-coupling reaction. However, the reactions did not show useful conversions: M. Hapke, Dissertation, Shaker Verlag, Aachen, 2003.
37 Synthesis of bisheterocyclic systems: V. Bonnet, F. Mongin, F. Trécourt, G. Breton, F. Marsais, P. Knochel and G. Quéguiner, *Synlett*, 2002, 1008.
38 Synthesis of bisheterocyclic systems: S. Dumouchel, F. Mongin, F. Trécourt and G. Quéguiner, *Tetrahedron Lett*., 2003, **44**, 3877.
39 For an example of cross-coupling reactions of pyridines with aryl Grignard reagents, see: V. Bonnet, F. Mongin, F. Trécourt, G. Quéguiner and P. Knochel, *Tetrahedron*, 2002, **58**, 4429, and references therein.
40 P. Pierrat, P. Gros and Y. Fort, *Org. Lett*., 2005, **7**, 697.
41 C. J. Handy, A. S. Manoso, W. T. McElroy, W. M. Seganish and P. DeShong, *Tetrahedron*, 2005, **61**, 12201.
42 For the 2-pyridylchlorosilane, see: T. Hiyama, *J. Organomet. Chem*., 2002, **653**, 58.
43 For the 2-pyridyl biscatecholsiloxane, see: W. M. Seganish and P. DeShong, *J. Org. Chem*., 2004, **69**, 1137.
44 This observation has also been described for the carbopalladation step in Heck reactions with alkenylpyridylsilanes: S. E. Denmark and R. F. Sweis, *Chem. Pharm. Bull*., 2002, **50**, 1531.
45 For the application of the 2-pyridylsilyl group for different purposes, see: K. Itami and J. Yoshida, *Synlett*, 2006, 157.
46 For a more general perspective of CIPE, see: M. C. Whisler, S. MacNeil, V. Snieckus and P. Beak, *Angew. Chem., Int. Ed*., 2004, **43**, 2206.

47 T. Kawashima, T. Takao and H. Suzuki, *J. Am. Chem. Soc.*, 2007, **129**, 11006.
48 *Palladium in Heterocyclic Chemistry (Tetrahedron Organic Chemistry Series)*, eds. J. J. Li and G. W. Gribble, Pergamon, Elsevier, Oxford, 2000, vol. 20.
49 A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed.*, 1999, **38**, 2411.
50 W. Su, S. Urgaonkar, P. A. McLaughlin and J. G. Verkade, *J. Am. Chem. Soc.*, 2004, **126**, 16433.
51 A. Godard, P. Rocca, J.-M. Fourquez, J.-C. Rovera, F. Marsais and G. Quéguiner, *Tetrahedron Lett.*, 1993, **34**, 7919.
52 V. Farina, V. Krishnamurthy and W. J. Scott, *Org. React.*, 1997, **50**, 1.
53 J. A. Zoltewicz and M. P. Cruskie, Jr, *Tetrahedron*, 1995, **51**, 11393.
54 J. A. Zoltewizc, M. P. Cruskie, Jr and C. D. Dill, *Tetrahedron*, 1996, **52**, 4239.
55 U. S. Schubert, C. Eschbaumer and G. Hochwimmer, *Synthesis*, 1999, 779.
56 M. Heller and U. S. Schubert, *J. Org. Chem.*, 2002, **67**, 8269, and references therein.
57 For a recent study on the synthesis of brominated 2,2′-bipyridines, see: A. B. Zdravkov and N. N. Khimich, *Russ. J. Org. Chem.*, 2006, **42**, 1200, and references therein.
58 P. F. H. Schwab, F. Fleischer and J. Michl, *J. Org. Chem.*, 2002, **67**, 443.
59 R. García-Lago, J.-L. Alonso-Gómez, C. Sicre and M.-M. Cid, *Heterocycles*, 2008, **75**, 57.
60 D. Martineau, P. Gros and Y. Fort, *J. Org. Chem.*, 2004, **69**, 7914.
61 H. Nierengarten, J. Rojo, E. Leize, J.-M. Lehn and A. Van Dorsselaer, *Eur. J. Inorg. Chem.*, 2002, 573.
62 A. Puglisi, M. Benaglia and G. Roncan, *Eur. J. Org. Chem.*, 2003, 1552.
63 J. Mathieu and A. Marsura, *Synth. Commun.*, 2003, **33**, 409.
64 X.-F. Duan, X.-H. Li, F.-Y. Li and C.-H. Huang, *Synthesis*, 2004, 2614.
65 V. Patroniak, M. Kubicki, A. R. Stefankiewicz and A. M. Grochowska, *Tetrahedron*, 2005, **61**, 5475.
66 Y. D. M. Champouret, R. K. Chaggar, I. Dadhiwala, J. Fawcett and G. A. Solan, *Tetrahedron*, 2006, **62**, 79.
67 A. Bouet, G. Deguest, B. Heller, C. Papamicaël, G. Dupas, S. Oudeyer, F. Marsais and V. Levacher, *Org. Biomol. Chem.*, 2007, **5**, 1397.
68 J. S. Bair and R. G. Harrison, *J. Org. Chem.*, 2007, **72**, 6653.
69 D. N. Lee, B. K. Soh, S. H. Kim, Y. M. Jun, S. H. Yoon, W.-Y. Lee and B. H. Kim, *J. Organomet. Chem.*, 2008, **693**, 655.
70 M. P. A. Lyle, N. D. Draper and P. D. Wilson, *Org. Biomol. Chem.*, 2006, **4**, 877.
71 P. Pierrat, P. C. Gros and Y. Fort, *J. Comb. Chem.*, 2005, **7**, 879.
72 Y. A. Getmanenko and R. J. Twieg, *J. Org. Chem.*, 2008, **73**, 830.
73 Overview on the development of the method: E. Negishi, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E Negishi, John Wiley & Sons, New York, 2002, p. 229.
74 E. Negishi, X. Zeng, Z. Tan, M. Qian, Q. Hu and Z. Huang, in *Metal-Catalyzed Cross-Coupling Reactions*, eds. A. de Meijere and F. Diederich, Wiley-VCH, Weinheim, 2nd edn, 2004, p. 815.
75 E. Negishi, Q. Hu, Z. Huang, G. Wang and N. Yin, in *Chemistry of Organozinc Compounds*, eds. Z. Rappoport and I. Marek, John Wiley & Sons, Chichester, 2006, p. 457.
76 *Organozinc Reagents: A Practical Approach*, eds. P. Knochel and P. Jones, Oxford University Press, Oxford, 1999.
77 E. Nakamura, in *Organometallics in Synthesis—A Manual*, ed. M. Schlosser, John Wiley & Sons, Chichester, 2004, p. 579.
78 J. A. Casares, P. Espinet, B. Fuentes and G. Salas, *J. Am. Chem. Soc.*, 2007, **129**, 3508, and references therein.
79 C. Bolm, M. Ewald, M. Felder and G. Schlingloff, *Chem. Ber.*, 1992, **125**, 1169.
80 T. Sakamoto, Y. Kondo, N. Murata and H. Yamanaka, *Tetrahedron*, 1993, **49**, 9713.
81 F. Trécourt, B. Gervais, M. Mallet and G. Quéguiner, *J. Org. Chem.*, 1996, **61**, 1673.
82 N. Murata, T. Sugihara, Y. Kondo and T. Sakamoto, *Synlett*, 1997, 298.
83 S. L. Hargreaves, B. L. Pilkington, S. E. Russell and P. A. Worthington, *Tetrahedron Lett.*, 2000, **41**, 1653.
84 W.-S. Lee, H.-L. Kwong, H.-L. Chan, W.-W. Choi and L. Y. Ng, *Tetrahedron: Asymmetry*, 2001, **12**, 1007.
85 For the synthesis of an non-symmetrical 2,3′-bipyridine as a key step in the natural product synthesis of (±)-cytisine, see: P. Nshimyumukiza, D. Cahard, J. Rouden, M.-C. Lasne and J.-C. Plaquevent, *Tetrahedron Lett.*, 2001, **42**, 7787.
86 S. A. Savage, A. P. Smith and C. L. Fraser, *J. Org. Chem.*, 1998, **63**, 10048.
87 A. P. Smith, S. A. Savage, J. C. Love and C. L. Fraser, *Org. Synth.*, 2000, **78**, 51.
88 A. Lützen, M. Hapke, J. Griep-Raming, D. Haase and W. Saak, *Angew. Chem., Int. Ed.*, 2002, **41**, 2086.
89 U. Kiehne, T. Weilandt and A. Lützen, *Org. Lett.*, 2007, **9**, 1283.
90 U. Kiehne and A. Lützen, *Org. Lett.*, 2007, **9**, 5333.
91 U. Kiehne, T. Weilandt and A. Lützen, *Eur. J. Org. Chem.*, 2008, 2056.
92 B. Zhang and R. Breslow, *J. Am. Chem. Soc.*, 1997, **119**, 1676.
93 E. Negishi, A. O. King and N. Okukado, *J. Org. Chem.*, 1977, **42**, 1821.
94 E. Negishi, T. Takahashi and A. O. King, *Org. Synth.*, 1988, **66**, 67.
95 The independent synthesis of different substituted 2,2′-bipyridine-zinc complexes has been reported, *e.g.*: S. N. Ghosh, *Inorg. Nucl. Chem. Lett.*, 1969, **5**, 841.
96 The description of low-solubility behaviour of the 2,2′-bipyridine–zinc complexes in THF has been reported: H.-L. Kwong, K.-M. Lau, W.-S. Lee and W.-T. Wong, *New J. Chem.*, 1999, **23**, 629.
97 A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed.*, 2002, **41**, 4176, and references therein.
98 P. N. W. Baxter, *J. Org. Chem.*, 2000, **65**, 1257.
99 **44** can be prepared cleanly by a palladium-catalysed Sonogashira reaction of 2-chloro-5-iodopyridine with trimethylsilylacetylene at room temperature. However, attempts to selectively couple 2-bromo-5-iodopyridine in the same way produced besides the desired 5-ethynylated product also the undesired 2,5-diethynylated product.
100 5-Monosubstituted 2,2′-bipyridines: A. Lützen and M. Hapke, *Eur. J. Org. Chem.*, 2002, 2292.
101 C. Dai and G. C. Fu, *J. Am. Chem. Soc.*, 2001, **123**, 2719.
102 Original work: J. P. Wolfe, R. A. Singer, B. H. Yang and S. L. Buchwald, *J. Am. Chem. Soc.*, 1999, **121**, 9550.
103 This class of ligands was later also used for efficient Negishi cross-coupling reactions: J. E. Milne and S. L. Buchwald, *J. Am. Chem. Soc.*, 2004, **126**, 13028.
104 An interesting aspect came to light with the use of **47**, because not only the cross-coupling product **45** but also the homo-coupling product bis-5,5′-[(trimethylsilyl)ethynyl]-2,2′-bipyridine (**48**) was isolated in rather large amount as, at that time, unwanted byproduct. Nevertheless, inspired by these results, we developed a palladium-based catalyst system for the efficient homo-coupling of **44** later on, that could not be accomplished with the normally used nickel catalysts (see text and ref. 111).
105 This suggests a monophosphane–palladium species as the active catalyst: U. Christmann and R. Vilar, *Angew. Chem., Int. Ed.*, 2005, **44**, 366.
106 M. R. Netherton and G. C. Fu, *Org. Lett.*, 2001, **3**, 4295.
107 Differently disubstituted 2,2′-bipyridines: A. Lützen, M. Hapke, H. Staats and J. Bunzen, *Eur. J. Org. Chem.*, 2003, 3948.
108 Amino-functionalised 2,2′-bipyridines: M. Hapke, H. Staats, I. Wallmann and A. Lützen, *Synthesis*, 2007, 2711.
109 Recent other example: M. E. Thibault, K. L. Luska and M. Schlaf, *Synthesis*, 2007, 791.
110 First modified synthesis of 5,5′-diamino-2,2′-bipyridine (**58**) after experiencing difficulties with other methods: M. Albrecht, I. Janser, A. Lützen, M. Hapke, R. Fröhlich and P. Weis, *Chem.–Eur. J.*, 2005, **11**, 5742.
111 A. Lützen, M. Hapke and S. Meyer, *Synthesis*, 2002, 2289.
112 Y.-Q. Fang and G. S. Hanan, *Synlett*, 2003, 852.
113 U. Kiehne, J. Bunzen, H. Staats and A. Lützen, *Synthesis*, 2007, 1061.

114 Y.-Q. Fang, M. I. J. Polson and G. S. Hanan, *Inorg. Chem.*, 2003, **42**, 5.
115 J. R. Roppe, B. Wang, D. Huang, L. Tehrani T. Kamenecka, E. J. Schweiger, J. J. Anderson, J. Brodkin, X. Jiang, M. Cramer, J. Chung, G. Reyes-Manalo, B. Munoz and N. D. P. Cosford, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3993.
116 J. Siu, I. R. Baxendale, R. A. Lewthwaite and S. V. Ley, *Org. Biomol. Chem.*, 2005, **3**, 3140.
117 D. Jouvenot, E. C. Glazer and Y. Tor, *Org. Lett.*, 2006, **8**, 1987.
118 F. Havas, M. Danel, C. Galaup, P. Tisnès and C. Picard, *Tetrahedron Lett.*, 2007, **48**, 999.
119 L. R. Moore and D. A. Vicic, *Chem.–Asian J.*, 2008, **3**, 1046.
120 Recent overview: E. Tyrrell and P. Brookes, *Synthesis*, 2003, 469.
121 S. Schröter, C. Stock and T. Bach, *Tetrahedron*, 2005, **61**, 2245.
122 D. G. Hall, in *Boronic Acids*, ed. D. G. Hall, Wiley-VCH, Weinheim, 2005, p. 1.
123 F. C. Fischer and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, 1965, **84**, 439.
124 F. C. Fischer and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, 1974, **93**, 21.
125 N. Miyaura, *Adv. Met. Org. Chem.*, 1988, **6**, 187.
126 K. Deshayes, R. D. Broene, I. Chao, C. B. Knobler and F. Diederich, *J. Org. Chem.*, 1991, **56**, 6787.
127 S. R. L. Fernando, U. S. M. Maharoof, K. D. Deshayes, T. H. Kinstle and M. Y. Ogawa, *J. Am. Chem. Soc.*, 1996, **118**, 5783.
128 M. Ishikura, T. Mano, I. Oda and M. Terashima, *Heterocycles*, 1984, **22**, 2471.
129 Overview: M. Terashima and M. Ishikura, *Adv. Heterocycl. Chem.*, 1989, **46**, 143.
130 T. Murafuji, R. Mouri and Y. Sugihara, *Tetrahedron*, 1996, **52**, 13933.
131 M. Ishikura, I. Oda and M. Terashima, *Heterocycles*, 1985, **23**, 2375.
132 A SciFinder inquiry on June 20th, 2008 revealed approx. 30 commercially available 2-pyridylboron compounds from *ca.* 70 different suppliers.
133 B. T. O'Neill, D. Yohannes, M. W. Bundesmann and E. P. Arnold, *Org. Lett.*, 2000, **2**, 4201.
134 Synthesis of the 2-pyridylboronates: A. Bouillon, J.-C. Lancelot, J. S. de Oliveira Santos, V. Collot, P. R. Bovy and S. Rault, *Tetrahedron*, 2003, **59**, 10043.
135 Structural informations on the 2- and 3-pyridylboronates: J. S. de Oliveira Santos, A. Bouillon, J.-C. Lancelot and S. Rault, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 2003, **59**, o596.
136 Synthesis of 6-halopyridin-3-yl boronic acids and esters: A. Bouillon, J.-C. Lancelot, V. Collot, P. R. Bovy and S. Rault, *Tetrahedron*, 2002, **58**, 2885.
137 Synthesis of 2-, 4- or 5-halopyridin-3-yl boronic acids and esters: A. Bouillon, J.-C. Lancelot, V. Collot, P. R. Bovy and S. Rault, *Tetrahedron*, 2002, **58**, 3323.
138 Synthesis of 2- or 3-halopyridin-4-yl boronic acids and esters: A. Bouillon, J.-C. Lancelot, V. Collot, P. R. Bovy and S. Rault, *Tetrahedron*, 2002, **58**, 4369.
139 Structural informations on the 4-pyridylboronate and the free acid analogue: J. S. de Oliveira Santos, J.-C. Lancelot, A. Bouillon and S. Rault, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 2003, **59**, o111.
140 Pd-catalysis: T. Ishiyama, K. Ishida and N. Miyaura, *Tetrahedron*, 2001, **57**, 9813.
141 Ir-catalysis: J. Takagi, K. Sato, J. F. Hartwig, T. Ishiyama and N. Miyaura, *Tetrahedron Lett.*, 2002, **43**, 5649.
142 I. A. I. Mkhalid, D. N. Coventry, D. Albesa-Jove, A. S. Batsanov, J. A. K. Howard, R. N. Perutz and T. B. Marder, *Angew. Chem., Int. Ed.*, 2006, **45**, 489.
143 A. A. Fuller, H. R. Hester, E. V. Salo and E. P. Stevens, *Tetrahedron Lett.*, 2003, **44**, 2935.
144 H. Matondo, S. Souirti and M. Baboulène, *Synth. Commun.*, 2003, **33**, 795.
145 H. Matondo, M. Baboulène and I. Rico-Lattes, *Appl. Organomet. Chem.*, 2003, **17**, 239.
146 H. Matondo, N. Ouhaja, S. Souirti and M. Baboulène, *Main Group Met. Chem.*, 2002, **25**, 163.
147 X-Ray crystal structure study of a 2-pyridyldioxazaborocane derivative: J. S. de Oliveira Santos, A. Bouillon, J.-C. Lancelot and S. Rault, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 2004, **60**, o582.
148 P. B. Hodgson and F. H. Salingue, *Tetrahedron Lett.*, 2004, **45**, 685.
149 P. Gros, A. Doudouh and Y. Fort, *Tetrahedron Lett.*, 2004, **45**, 6239.
150 M. Hapke, L. Brandt, A. Lützen, unpublished results.
151 K. L. Billingsley, K. W. Anderson and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2006, **45**, 3484, and references therein.
152 K. Billingsley and S. L. Buchwald, *J. Am. Chem. Soc.*, 2007, **129**, 3358, and references therein.
153 L. Brandt, Diploma Thesis, University of Oldenburg, Oldenburg, 2005.
154 N. A. Jones, J. W. Antoon, A. L. Bowie, Jr, J. B. Borak and E. P. Stevens, *J. Heterocycl. Chem.*, 2007, **44**, 363.
155 G. A. Molander and B. Biolatto, *J. Org. Chem.*, 2003, **68**, 4302.
156 K. L. Billingsley and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2008, **47**, 4695.