Synthesis of 2,2′-Bipyridines: Versatile Building Blocks for Sexy Architectures and Functional Nanomaterials

George R. Newkome,*[a] Anil K. Patri,[b] Elisabeth Holder,[c] and Ulrich S. Schubert*[c]

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The latest synthetic strategies to prepare 2,2′-bipyridine and its mono-substituted, symmetrical and unsymmetrical 3,3′-, 4,4′-, 5,5′-, and 6,6′-disubstituted derivatives are critically discussed and evaluated. Different coupling procedures to achieve new symmetrical and unsymmetrical functionalized 2,2′-bipyridines, such as Stille-type, Negishi-type, and Suzuki-type cross-coupling reactions are discussed in detail. Moreover, condensation procedures that allow further variations are presented. The application of functional group transformations for access to additional groups is examined.

1 Introduction

2,2′-Bipyridine (**1**) (Figure 1) was first synthesized more than 110 years ago by Fritz Blau, who simply dry-distilled the copper salt of picolinic acid.[1] Since then, the preparation of this parent bidentate ligand has been improved dramatically using different synthetic strategies. Moreover, starting in the area of analytical chemistry, an impressive development utilizing bipyridines, as building blocks in supramolecular and macromolecular chemistry as well as nanoscience has been observed [2,2′-bipyridines can also be found in natural products like caerulomycins or collismycins[2−4] (Figure 2)]. However, the corresponding synthetic progress has been scattered over a large variety of journals in very different spheres, which significantly hampers the further application of the ligand. Although the field has been reviewed several times,[5−7] the last comprehensive review (including the extensive historical refer-

[a] Departments of Polymer Science and Chemistry,
The University of Akron, Akron, OH 44325-4717, USA
Fax: (internat.) + 1-330/972-2413
E-Mail: newkome@uakron.edu
[b] Department of Chemistry, University of South Florida,
Tampa, FL 33620 USA
[c] Laboratory of Macromolecular Chemistry and Nanoscience,
Eindhoven University of Technology and
Dutch Polymer Institute,
P. O. Box 513, 5600 MB Eindhoven, The Netherlands
Fax: (internat.) + 31-40/247-4186
E-mail: u.s.schubert@tue.nl

George R. Newkome was born in Akron, Ohio and obtained his PhD from Kent State University under Professor D. L. Fishel, moving onto Princeton University for a postdoctoral position with Professor R. K. Hill, then to Louisiana State University, and subsequently University of South Florida. In 2001, he returned to Akron, specifically The University of Akron, where he is the Oelschlager Professor of Science & Technology in the Departments of Chemistry and Polymer Science. Administratively, he is the Vice President for Research and Dean of the Graduate School as well as the President of The University of Akron Research Foundation. After his initial discovery of arborols/dendrimers in 1985, his major research synthetic initiatives are in the area of new molecular fractals and the design of supramacromolecular materials leading to futuristic nanoconstructs affording novel routes to molecular energy storage, compasses, and nanomotors.

Anil Kumar Patri obtained his Bachelor of Science degree from Osmania University and Master of Science in Organic Chemistry from Aligarh Muslim University, India. After working for two years as a lecturer in Chemistry in Hyderabad, India, he joined the University of South Florida and earned his Ph.D. degree under the guidance of Prof. George R. Newkome in 1999. His dissertation focused on the synthesis of bipyridine derivatives, functional dendritic building blocks, and dendrimers with precise modifications of the surface and the internal structure with the goal of achieving self-assembly and dendritic networks. After his post-doctoral training under the supervision of Dr. Don Tomalia working on the synthesis of tecto(dendrimers) and the surface functionalization on PAMAM dendrimers, he joined the Center for Biologic Nanotechnology at the University of Michigan Medical School as a staff scientist where he is currently working on projects involving dendrimers for targeted drug delivery to cancer tissue. His research interests include the synthesis of new dendritic nanomaterials for biomedical and material science applications.

Elisabeth Holder was born in Lonsingen, Germany. She studied chemistry at the Eberhard-Karls University of Tübingen, Germany where she also received her Ph.D. with Prof. E. Lindner in 2001. After postdoctoral studies in the group of Prof. Joseph R. Lakowicz at the UMAB, Baltimore, USA in 2002 she joined the group of Prof. Dr. Ulrich S. Schubert at the Eindhoven University of Technology, the Netherlands.

Ulrich S. Schubert was born in Tübingen in 1969. He studied chemistry at the Universities of Frankfurt and Bayreuth (both Germany) and the Virginia Commonwealth University, Richmond (USA). His Ph.D. work was performed under the supervision of Professor Eisenbach (Bayreuth, Germany) and Professor Newkome (Florida, USA). In 1995 he obtained his doctorate with Prof. Eisenbach. After a postdoctoral training with Professor Lehn at the Université Strasbourg (France) he moved to the Technische Universität München (Germany) to obtain his habilitation in 1999 (with Professor Nuyken). From 1999 to spring 2000 he held a temporal position as a professor at the Center for Nano Science at the Universität München (Germany). Since Summer 2000 he is Full Professor at the Eindhoven University of Technology (Chair for Macromolecular Chemistry and Nanoscience). His awards include the Bayerischen Habilitations-Förderpreis, the Habilitandenpreis of the GDCh (Makromolekulare Chemie), the Heisenberg-Stipendium of the DFG, and the Dozenten-Stipendium of the Fonds der Chemischen Industrie. The major focus of his research interests relates to organic heterocyclic chemistry, supramolecular materials, combinatorial material research, nanoscience, and tailor-made macromolecules.

MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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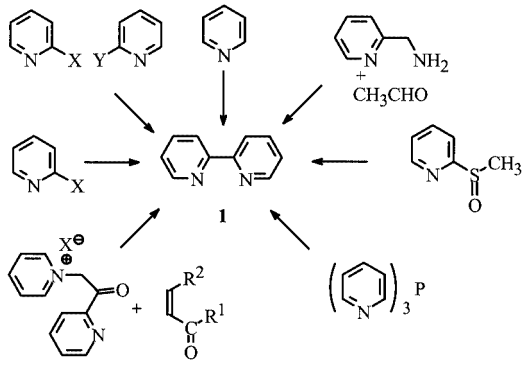


Figure 1. Synthetic strategies towards 2,2′-bipyridine (**1**)

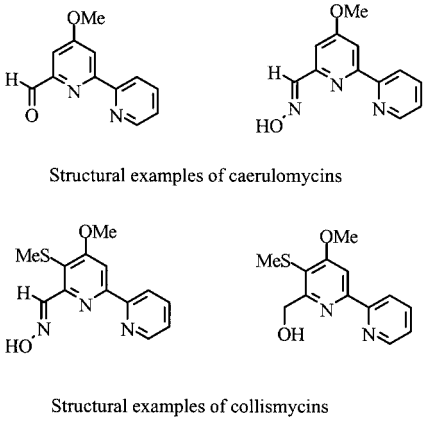


Figure 2. Exemplified caerulomycins and collismycins

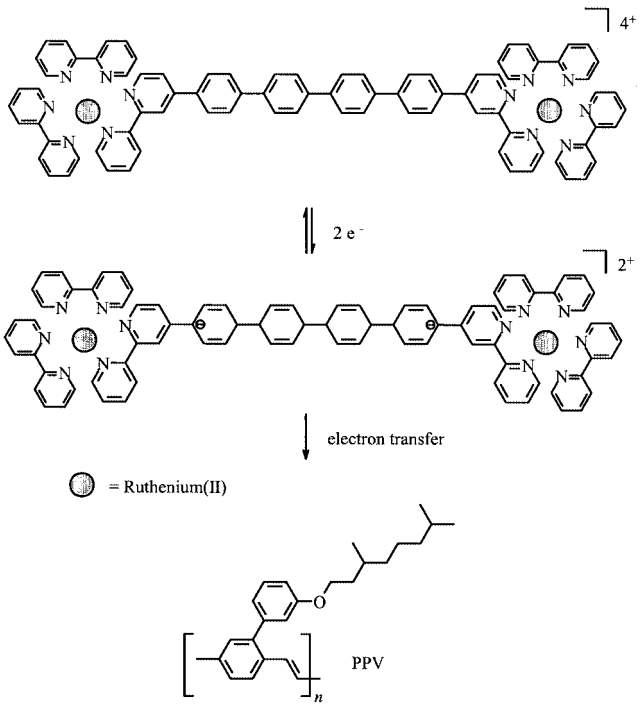


Figure 3. De Cola's red-green emissive device

ences)[7] on bipyridines dates back to the mid 1980s. Therefore, in view of its critical role in supramolecular chemistry an updated overview on substituted and functionalized derivatives is timely for the efficient further development of bipyridine-containing systems (for a recent review concerning macromolecules, see ref.[8]). This review highlights the synthetic efforts published after 1985 as well as a few earlier relevant references on mono- and symmetrical disubstituted 2,2′-bipyridines. A review concerning the chiral bipyridine derivatives and their use in asymmetric homogeneous catalysis has just appeared.[9] We herein critique various improved as well as modern synthetic methodologies for the preparation of these bidentate ligands. The tables of substituted bipyridine derivatives give easy access to timely preparative procedures. A summary of the metal complexes is beyond the scope of this investigation; a comprehensive historical survey, possessing nearly 11000 references, has appeared[10,11] and other appropriate reviews on that subject should be considered.[12–15]

Besides the well-known supramolecular applications, some very selected examples about recently published highlights for new applications of 2,2-bipyridines should be mentioned. De Cola et al. described dinuclear $[Ru(bpy)_3^{2+}]$ systems where phenylene units were used as the connecting backbone (Figure 3).[16] These dinuclear ruthenium units (triplet emitter and electron-transfer mediator) were mixed together with polyphenylenevinylene (PPV) in order to construct a simple efficient electron-transfer device. The usual red emission of the ruthenium dyes is observed. While reversing the device (reverse bias), the lowest excited singlet state of the polymer host is populated with subsequent emission of green light. Moreover, material science has been strongly moving forward on the field of nanomaterials through nanotubes and nanoparticles. Very recently, Panhuis et al. described amino-functionalized multiwalled carbon nanotubes, which could be connected via a modified $[Ru(bpy)_3^{2+}]$ complex.[17]

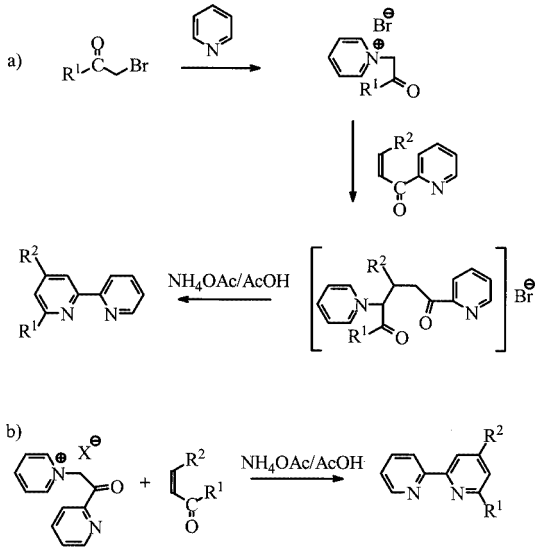
Several synthetic strategies (Figure 1) have been devised over the years to improve the formation of bipyridine derivatives. The most widely used method is the metal-catalyzed coupling of pyridine, substituted pyridines, or 2-halopyridines to form the desired 2,2′-bipyridines; Ni and Pd/C catalysts have been extensively utilized. Several improvements to the Ni-catalyzed homocoupling of aryl halides led to better yields of bipyridines under milder conditions than the traditional Ullmann coupling.[18] Recently, the utilization of directed cross-coupling procedures, such as Stille-type[19,20] and Negishi-type[21] has been described in several cases allowing a high-yield synthesis of symmetrically as well as unsymmetrically substituted and functionalized bipyridines.[22–27] Extrusion procedures involving organophosphorus[28] and -sulfur compounds[29,30] were investigated to prepare simple bipyridines. Ring assembly with the Kröhnke procedure[5] is useful, in particular to synthesize monosubstituted bipyridines; whereas, condensation between aldehydes and amines by a ring-assembly methodology has also given rise to bipyridines.[31] The different routes will be discussed in the following paragraphs followed by an overview of accessible mono- and disubstituted

bipyridines as well as important functional group transformations.[32,33]

2 Cyclization Reactions

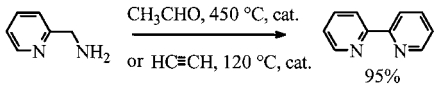
Various routes have been developed wherein one of the pyridine rings is formed directly from simpler entities. Using Kröhnke's method,[5] 2,2′-bipyridines can be prepared by the reaction of pyridinium salt with an unsaturated ketone.

In general, a generic bromomethyl ketone reacts with pyridine to yield the corresponding pyridinium salt (Scheme 1, a). The unsaturated ketone can be obtained by condensation of an aldehyde and 2-acetylpyridine. Treatment of pyridinium salt with the unsaturated ketone yielded, by a Michael addition, the 1,5-diketone intermediate, which cyclizes in the presence of the NH_4OAc to result in the 2,2′-bipyridine derivatives (Scheme 1, a). Another Kröhnke method was the reaction of the pyridacylpyridinium salt, in which the methylene hydrogen atoms are more acidic than those in the previous procedure, with an α,β-unsaturated ketone to produce the 2,2′-bipyridine derivative (Scheme 1, b).[5]



Scheme 1. Kröhnke's ring-assembly methodology

Alternate routes for the formation of bipyridines by the ring-assembly methodology have been developed, e.g. the condensation of 2-(aminomethyl)pyridine with acetaldehyde or acetylene in the presence of a silicon/alumina catalyst at 450 °C, or the reaction of 2-cyanopyridine with acetylene at 120 °C in the presence of a cobalt catalyst in 95% yield (Scheme 2).[34] Further co-cyclotrimerization utilizing Co catalysts and Kröhnke procedures can also be found in section 5.1. Improved cyclisation procedures can be found in section 5 where synthetic examples are discussed in detail.



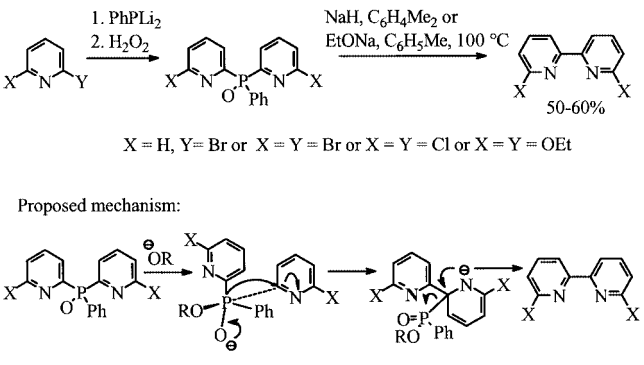
Scheme 2. Ring assembly by condensation

3 Unusual Coupling Methods

3.1 Extrusion Procedure Involving Organophosphorus Reagents

While investigating P-macrocycles, the first synthetically useful expulsion (cheletropic) reaction from bis(2-pyridyl)-phosphane *P*-oxides to form a new (hetero)aryl−(hetero)aryl bond was utilized by Newkome et al.[28] to construct macrocycles with bipyridine from 2-halopyridine precursors.

As shown in Scheme 3, the bipyridines were prepared from the 2-bromo or -chloro derivatives by treatment with $PhPLi_2$; oxidation of the resulting phosphane with H_2O_2 afforded the *P*-oxide, which with EtONa in toluene at 100 °C resulted in the desired extrusion. The mechanism of this P-expulsion was further investigated indicating an intramolecular pathway. Such contractions are to be expected when the atom(s) between the two electron-poor heteroaromatic compounds possess(es) enhanced positive character, similar to the loss of the central carbonyl moiety of 1,2,3-tricarbonyl systems. Thus, bis(2-pyridyl) ketone under basic conditions generated the desired bipyridine through this type of expulsion.[28] Uchida and Oae further investigated this reaction[35−37] when tris(2-pyridyl)phosphane *P*-oxide was treated with an organolithium or an organometallic reagent: 2,2′-bipyridyl derivatives were the major products in the ligand coupling reactions on the phosphorus atom, that occurred during the reactions of phosphonium salts and phosphane oxides with nucleophiles under neutral or acidic conditions. Thus, phosphonium salts and phosphane oxides, bearing at least two 2-pyridyl or substituted 2-pyridyl groups, gave the corresponding 2,2′-bipyridine upon treatment with acid (diluted HCl) or neutral solvents in 26−87% yields.[35] These reactions were considered to proceed via pentacoordinate P-intermediates by nucleophilic attack on the phosphorus atom. A similar coupling was postulated to occur by the nucleophilic attack on a positively charged phosphorus atom bearing 2-pyridyl groups.[37] Treatment of tris(2-pyridyl)phosphane with excess chlorine followed by

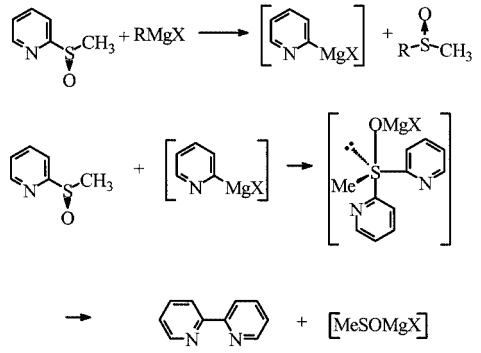


Scheme 3. Extrusion of organophosphorus reagents and proposed mechanism for phosphorus extrusion

treatment with dilute HCl led to the formation of **1** in 51% yield.

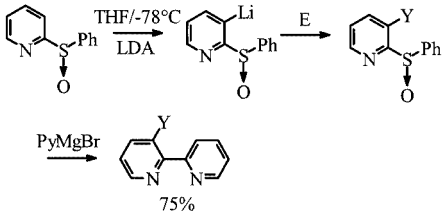
3.2 Ligand Coupling Involving Organosulfur Compounds

Along with the investigation of coupling processes involving *P*-oxides, Furukawa and Oae studied the formation of biaryls from a σ-sulfurane upon nucleophilic attack of organometallic species.[30] They prepared 2,2′-bipyridine derivatives from a σ-sulfurane intermediate, which was formed in moderate yields by treatment of methyl 2-pyridyl sulfoxide with Grignard reagents (Scheme 4).[29] The mechanism proposed involves the initial ligand exchange between 2-pyridyl and phenyl Grignard compounds to form methyl phenyl sulfoxide and 2-pyridylmagnesium bromide, which immediately attacks the sulfinyl sulfur atom of the starting sulfoxide to generate the σ-sulfurane intermediate (Scheme 4). The ligand coupling within the σ-sulfurane results in 2,2′-bipyridine (**1**).



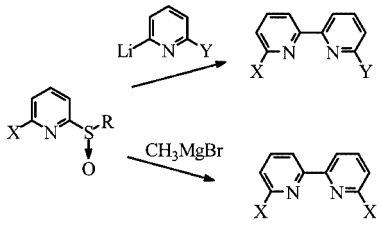
Scheme 4. Ligand coupling with Grignard reagent

Later Furukawa et al. reported the conversion of phenyl pyridyl sulfoxide to monosubstituted bipyridine derivatives by regioselective lithiation, substitution with electrophiles, and cross-coupling reactions with Grignard reagent in overall > 75% yields (Scheme 5).[38]



Scheme 5. Cross-coupling with Grignard reagent; E = a) Me_3SiCl; b) PhCHO; c) PhCOMe; d) PhSSPh; Y = a) $SiMe_3$; b) CH(OH)Ph; c) PhCH(OH)Me; d) SPh

In 1990, Oae et al. (Scheme 6)[39] prepared monosubstituted and symmetrical and unsymmetrical 6,6′-disubstituted 2,2′-bipyridines starting from 2-(alkylsulfinyl)pyridines by treatment with methylmagnesium bromide or 2-pyridyllithium in moderate to high yields; this procedure was also extended to prepare larger functionalized oligopyridines.[39,40]

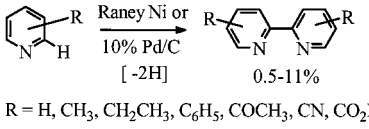


Scheme 6. Reaction of (alkylsulfinyl)pyridines

4 Metal-Catalyzed Coupling Procedures

4.1 Homo-Coupling of Pyridine

Most of the earlier work in the preparation of 2,2′-bipyridine and its derivatives used coupling procedures with diverse metal catalysis.[7] Applications of coupling routes to biaryl formation have been developed amongst others notably by Badger and Sasse,[41−43] who used the Raney nickel catalyst[44] to prepare 2,2′-bipyridine as well as its symmetrically disubstituted derivatives (Scheme 7). A key advantage of this coupling procedure is that the unchanged starting material can be easily recovered and recycled. In these simple procedures, the major disadvantage is that the conversion is generally poor for each synthetic cycle. To exemplify this process, 2,2′-bipyridine was prepared by simply heating neat pyridine in the presence of active W7 Raney nickel catalyst.[41] Traces of an insoluble organonickel compound were also reported, as a side product; its subsequent pyrolysis gave 2,2′-bipyridine. 4-Methylpyridine was coupled with degassed Raney nickel to yield 11% of 4,4′-dimethyl-2,2′-bipyridine;[45,46] whereas, the conversion using 10% Pd/C gave only 2−3% yield.[47,48]



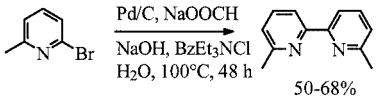
Scheme 7. Coupling of pyridines

Under similar thermal conditions, in the presence of Raney nickel[49] or 10% Pd/C,[48] coupling of 3-methylpyridine gave 5,5′-dimethyl-2,2′-bipyridine in 15 or 0.5% yield, respectively. Although Raney nickel is marginally effective for these primitive thermal reactions, Rh/C was found to be ineffective and failed to generate the coupled products from either pyridine or 3-methylpyridine.[50] However, ethyl nicotinate with 10% Pd/C under elevated temperatures (120 °C at 16 Torr) gave the desired coupled product (35%).[51] Although varying yields have been reported, enhanced conversions were derived by using freshly distilled pyridine derivative, aqueous-free catalysts, and elevated reaction temperatures. When 10% Pd/C was used as catalyst under reduced

pressure, 4,4′-diacetyl-, 5,5′-diacetyl-, 5,5′-bis(ethoxycarbonyl)-, 5,5′-dicyano-, and 5,5′-dimethyl-2,2′-bipyridines were successfully generated from the corresponding precursors.[52,53] Further coupling procedures can be found in section 5 where synthetic examples are discussed in detail.

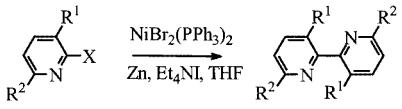
4.2 Homo-Coupling of 2-Halopyridines

Homo-coupling of 2-halopyridines is currently the desired method for the high-yield preparation of symmetrical 2,2′-bipyridine derivatives. The classic Ullmann reaction[18] has been used to generate 3,3′-dimethyl-2,2′-bipyridine by coupling 2-bromo-3-methylpyridine in high-boiling solvents, e.g. *p*-cymene (ca. 177 °C) utilizing Cu powder.[54] The basic disadvantages of this method are the drastic experimental conditions and normally low conversions, even though the unchanged reagents can be readily recovered and recycled. An improvement was achieved when phase-transfer conditions were utilized,[55] e.g., 2-bromo-6-picoline with 5% Pd/C afforded pure 6,6′-dimethyl-2,2′-bipyridine in 50−68% yield (Scheme 8).[56,57] This reaction can also be performed in a multi-hundred-gram scale.



Scheme 8. Coupling of halopyridines utilizing phase-transfer catalysts

The Ni-catalyzed homocoupling of aryl halides[58−60] has received considerable attention. These reactions can be conducted in the presence of diverse functional groups, e.g., an aldehyde or ketone, resulting in good yields (> 75%) and under milder conditions relative to the Ullmann reaction.[61,62] Because of the wide applicability of such coupling procedures, numerous improvements have been reported. Thus, 2-bromo-6-methylpyridine was treated with a stoichiometric amount of degassed Raney nickel[63,64] in refluxing toluene (dried) to afford (6,6′-dimethyl-2,2′-bipyridine-*N*,*N*′)nickel(II) dibromide, which on hydrolysis gave the free bidentate ligand (65%). Starting from 2-chloro-*x*-trifluoromethylpyridine (*x* = 4, 5, or 6), Chan et al. prepared[65] *x*,*x*-bis(trifluoromethyl)-2,2′-bipyridine by an Ni-or Pd-catalyzed homocoupling reaction. Tiecco et al.[61] have used the in situ generation of $Ni(PPh_3)_4$ derived from $NiCl_2$, triphenylphosphane, and zinc dust in DMF with substituted 2-halopyridines (X = Br or Cl) at 50 °C affording the 2,2′-bipyridines in 68−86% yield; the 3,3′-dihydroxy-,[66,67] 3,3′-dimethoxy-,[68] and 4,4′-ditolyl-2,2′-bipyridine[69] derivatives have been similarly prepared. Another improved procedure by Iyoda and co-workers[62] utilized Et_4NI, which allows the Ni-catalyzed reaction to be conducted in THF, acetonitrile or acetone. This coupling procedure is also applicable to substituted halopyridines in which 0.3 equiv. of $[NiBr_2(PPh_3)_2]$ in the presence of excess zinc, (as the reducing metal) and Et_4NI, which has a remarkable effect on the transformation,[62] are used. The iodide ion has been shown to accelerate these Ni-catalyzed coupling reactions.[70] Thus, 2,2′-bipyridine was obtained (Scheme 9) from 2-bromo- and 2-chloropyridine in 72 and 60% yield, respectively, when an equimolar amount of Et_4NI was used, but in only 3% yield with 10 mol % of Et_4NI. Recently, Kira et al.[71] coupled silyl group containing bromopyridines to generate 5,5′-disilylbipyridines using the described method. Methyl 2-chloronicotinate and 2-chloro-6-methoxypyridine gave the corresponding bipyridines in 53 and 90% yields,[71] respectively. Zhang and Breslow[72] coupled 5-amino-*N*-benzylidene-2-chloropyridine to result in the corresponding product using this technique.



X	R^1	R^2	Yield
Br, Cl	H	H	60-86%
Cl	$COOCH_3$	H	53%
Cl	H	OCH_3	90%

Scheme 9. Coupling of halopyridines using nickel catalysts

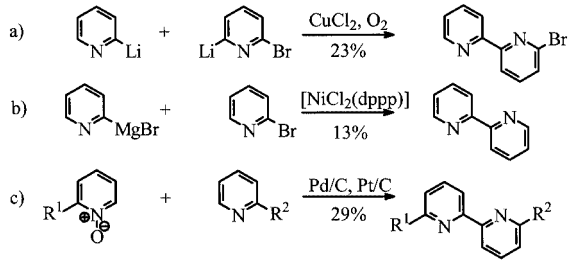
2,2′-Bipyridine derivatives were also prepared from the appropriate 2-halopyridine in 1,2-dimethoxyethane (DME) using *tert*-BuONa/NiCRA/PPh_3 [NiCRA = *Ni*ckel-containing *C*omplex *R*educing *A*gent];[73,74] in this way, unsubstituted, 5,5′-bis(trifluoromethyl)-, 6,6′-dimethyl-, and 6,6′-dimethoxy-2,2′-bipyridines were formed in 70−80% from 2-bromo-, 2-chloro-5-(trifluoromethyl)-, 2-bromo-6-methyl-, and 2-bromo-6-methoxypyridine, respectively. NiCRA is also useful to couple quinolines in 65−90% yield.[74]

Lemaire et al.[75] introduced a catalytic alternative to the Ullmann reaction. 2,2′-Bipyridines and their symmetrical 5,5′-dimethyl derivatives were prepared in very high yields (> 90%) by using $Pd(OAc)_2$ as the catalyst with nBu_4NBr and a base (trialkylamine) in 2-propanol. Using K_2CO_3 as base, Chujo et al.[76] obtained a 70% yield of the 5,5′-dimethyl homocoupling product. Further coupling procedures can be found in section 5 where synthetic examples are discussed in detail.

4.3 Cross-Coupling of 2-Halopyridines

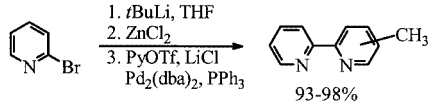
In the last few years a very successful development of directed cross-coupling methods for the synthesis of 2,2′-bipyridines was observed, motivated by the need for unsymmetrically substituted and functionalized ligands. Former approaches used the cross-coupling of lithiated pyridines resulting in functionalized bipyridines (Scheme 10, a, 23% yield),[77] the Ni-catalyzed coupling of Grignard reagents (Scheme 10, b, 13% yield)[78] or the coupling of pyridine *N*-oxides (Scheme 10, c, 29% yield).[79] These methods are also

rather restricted in the functionalities that can be tolerated (see also section 3.2 for the pyridyl sulfoxide approach).



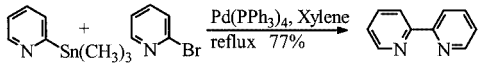
Scheme 10. Traditional cross-coupling methods

Recently, Fraser et al. reported[24] an efficient synthesis of 4-, 5-, and 6-methyl-2,2′-bipyridine by a Negishi cross-coupling strategy.[21] In a one-pot synthesis, lithium/halogen exchange was effected by treatment of 2-bromopyridine with *tert*-butyllithium followed by Li → Zn transmetallation (Scheme 11). Subsequent addition of (methyl)pyridyl triflate and in situ generated $Pd(PPh_3)_4$ yielded 93−98% of the desired methyl-2,2′-bipyridines. Due to the halogen/lithium exchange, this reaction is restricted to bromo- or iodo-functionalized pyridines. The required 2-(trifluoromethylsulfonyl)oxypyridines can be prepared in very high yields by treating the corresponding 2-hydroxypyridines with triflic anhydride. Siegel et al.[25] used a similar procedure by coupling two halopyridines by means of different substituted organozinc precursors to form an array of new heteroaryl compounds.



Scheme 11. Negishi-type cross-cross-coupling procedures

The second now widely used methodology for the preparation of bipyridines is the Stille-type cross-coupling procedure utilizing organotin compounds and palladium catalysts. The first example was published in 1986 by Yamamoto et al. in which (trimethylstannyl)pyridine was cross-coupled with bromopyridines in the presence of a catalytic amount of $Pd[P(PPh_3)_4]$ to afford 2,2′-bipyridine (77%) (Scheme 12).[80] Later, this method was used for the preparation of symmetrical and unsymmetrical methyl-substituted bipyridines,[23,81] bromo-, trimethyltin-, nitro-, ester-, and hydroxymethyl-functionalized bipyridines.[72,82−86] This method presently offers the most general approach towards functionalized bipyridines. Different functional groups are compatible with this coupling procedure, such as protected esters and hydroxy groups. The required organotin functionality (trimethyltin or tributyltin) can be introduced starting from 2-bromo-, -chloro- as well as -iodopyridine derivatives. The halogen → tin exchange can be utilized using organolithium derivatives (e.g. *n*-butyllithium) or the reaction with sodium/stannanes or hexamethylbis(stannane). Further coupling procedures can be found in chapter 5 where synthetic examples are discussed in detail.



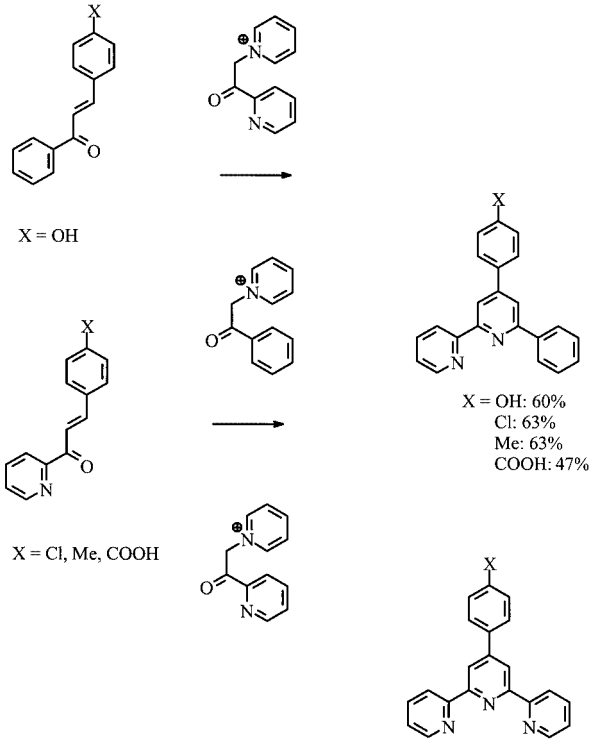
Scheme 12. Stille-type cross-coupling of halopyridines

5 Examples of Substituted Bipyridines

5.1 Monosubstituted Bipyridines

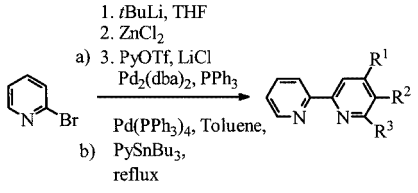
Monosubstituted bipyridines can be easily prepared by the traditional Kröhnke procedure, directed cross-coupling of halopyridine derivatives utilizing Negishi-type or Stille-type, monosubstitution on bipyridine or by ligand-coupling methodologies like Suzuki-type[87] reactions. Most functionalizations on bipyridine start from the methyl precursor, which can be oxidized, brominated or halogenated, lithiated and modified under diverse conditions. These monofunctionalized precursors attract increasing interest as building blocks in supramolecular and macromolecular chemistry as well as nanoscience. As an alternative, the selective monofunctionalization of disubstituted bipyridines is discussed below.

Several valuable unsymmetrical phenyl-derivatized 2,2′-bipyridines have been introduced by Neve et al.[88−91] by applying a classical Kröhnke protocol using the appropriate enone and *N*-(phenylacyl)pyridinium bromide in the presence of a large excess of ammonium acetate (Scheme 13). These 2,2′-bipyridines contain one phenyl substituent in the 6-position and a *p*-substituted phenyl ligand in the 4-position. The functionalities vary from methyl-, chloro-, hydroxy- to carboxylic acid moieties. The same synthetic procedure opens new entries to phenyl-derivatized terpyridines.



Scheme 13. 2,2′-Bipyridines containing one phenyl substituent in 6-position and a derivatized phenyl ligand in 4-position

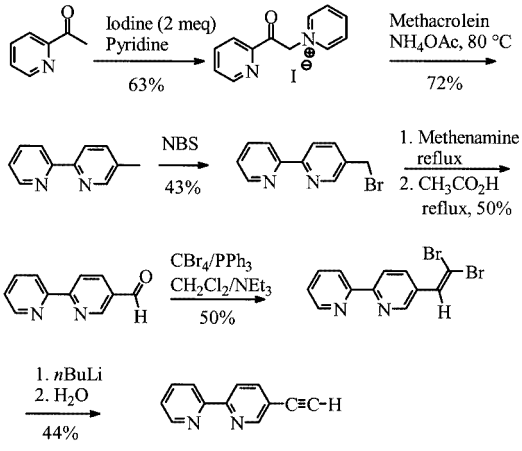
The most general preparation of monomethyl-substituted 2,2′-bipyridines can be realized with the application of Negishi-type couplings of the corresponding bromopyridines with pyridinyl triflates (Scheme 14, a, see also chapter 4.3). In this way, the 4-, 5-, and 6-methylbipyridines could be obtained in 98, 94, and 93% yields, respectively.[24] Alternatively, the Stille-type cross-coupling can be utilized (Scheme 14, b, see also 4.3). In this case, the 4-, 5- and 6-methylbipyridines can be obtained in 56, 64, and 75% yields, respectively.[23] Using Stille-type chemistry and organotin derivatives, 6-bromo- and 6-tributylorganotin and 6-trimethylorganotin substituted bipyridines have been prepared, mostly as intermediates in the synthesis of more complex ligand systems, e.g. leading to [$n \times n$] grid-like systems.[83,84]



	R^1	R^2	R^3	a (Yield)	b (Yield)
	Me	H	H	98%	56%
	H	Me	H	94%	64%
	H	H	Me	93%	75%

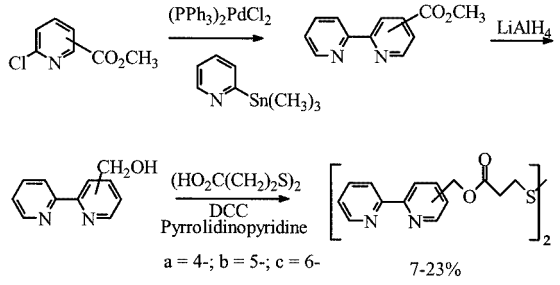
Scheme 14. Preparation of monomethyl-substituted bipyridines: a) Negishi-type; b) Stille-type

Polin et al. have reported the synthesis of interesting ethynyl-substituted bipyridines. Using the Kröhnke procedure, 5-methyl-2,2′-bipyridine was prepared in 72% yield by treating 2-acetylpyridine with iodine and pyridine affording the pyridinium salt, which was then treated with methacrolein and NH_4OAc (Scheme 15).[48] Attempted oxidation of the heteroaryl methyl group to the corresponding aldehyde using SeO_2 failed; however, treatment with NBS under free-radical conditions gave the bromomethyl derivative (43%). Reaction with hexamethylenetetraamine and subsequent hydrolysis with boiling AcOH afforded the desired aldehyde (50%). The formyl → ethynyl conversion was effected by bromination ($CBr_4/PPh_3/Et_3N$) in order to generate the geminal dibromide in 50% yield, which upon treatment with *n*BuLi and hydrolysis resulted in the corresponding 5-ethynyl-2,2′-bipyridine (44%). Ziessel et al. also prepared the 5-ethynyl-2,2′-bipyridine by Pd-catalyzed coupling of (trimethylsilyl)acetylene with 5-bromo-2,2′-bipyridine in the presence of CuI and subsequent deprotection with KF in methanol (overall yield of 64%).[92]



Scheme 15. Preparation of ethynylbipyridines

Using a modified cross-coupling procedure, Panetta et al. reported the synthesis of 4-, 5-, and 6-disulfide-functionalized 2,2′-bipyridines and their ruthenium complexes (Scheme 16).[93] Thus, methyl 6-chloropyridine-2-carboxylate was coupled with 2-(trimethylstannyl)pyridine to afford methyl 2,2′-bipyridine-6-carboxylate, which was then reduced with $LiAlH_4$. Esterification with 3,3′-dithiodipropanoic acid afforded the bis(bipyridinyl) disulfide diester in 18% yield. The related 4- and 5-substituted esters were prepared in a similar way in 23 and 7% yields, respectively.

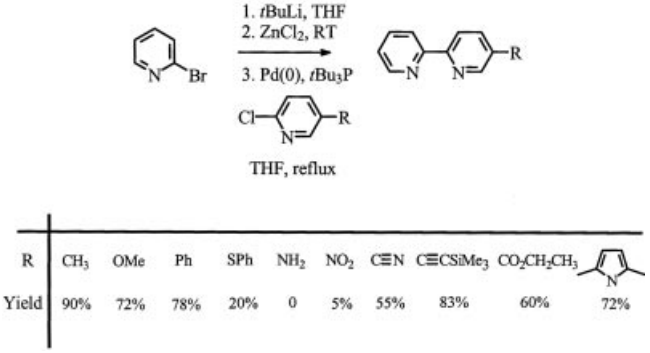


Scheme 16. Synthesis of 6-disulfide-functionalized bipyridines

Additional monosubstituted derivatives have been prepared by direct electrophilic substitution of the bipyridine. For example, bromination of bipyridine with HBr/Br_2 gave (46%) 5-bromo-2,2′-bipyridine[94] and sulfonation with concd. H_2SO_4 resulted (50%) in 2,2′-bipyridine-5-sulfonic acid.[47] Treatment of tris(2-pyridyl)phosphane with bromine or chlorine in methanol gave the corresponding 5-halobipyridines.[37]

Using a modified Negishi cross-coupling procedure, Lützen et al.[26] obtained 5-monosubstituted 2,2′-bipyridines in high yields. Addition of 2-bromopyridine to a *t*BuLi solution in THF forms the lithiated derivative and, in a second step, $ZnCl_2$ was added to build the respective organozinc derivatives. Cross-coupling reactions were performed and catalyzed by Pd_2dba_3 $CHCl_3$ with the respective monoderivatized chloropyridine (Scheme 17). The observed yields greatly depend on the functional group on the chloropyridine but can reach 90%.

5-Nitrobipyridine was prepared in 76% yield by the cross-coupling between 2-(trimethylstannyl)pyridine and 2-chloro-5-nitropyridine catalyzed by $[Pd(PPh_3)_2Cl_2]$; its subsequent $NaBH_4$ reduction catalyzed by 10% Pd/C gave 5-amino-2,2′-bipyridine in 98% yield.[72]



R	CH_3	OMe	Ph	SPh	NH_2	NO_2	C≡N	C≡CSiMe$_3$	$CO_2CH_2CH_3$	
Yield	90%	72%	78%	20%	0	5%	55%	83%	60%	72%

Scheme 17. Modified Negishi cross-coupling procedure

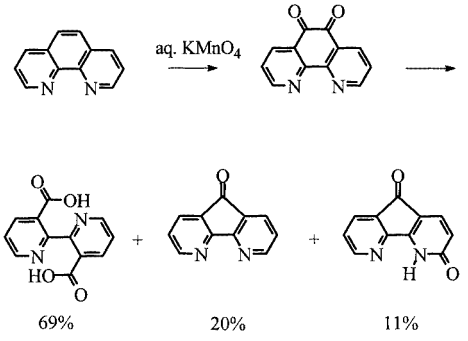
Alkylbipyridines were also prepared starting with the oxidation of (*S*)-2-(1-alkylbenzyl)pyridine with 3-chloroperbenzoic acid yielding the corresponding *N*-oxide, which was treated with dimethyl sulfate, followed by aqueous KCN to give the nitrile isolated in 58% yield. The co-cyclotrimerization of the latter compound with acetylene and a cobalt catalyst yielded the respective alkylbipyridine in 80% yield.[95,96]

5.2 Disubstituted Bipyridines

Most symmetrical disubstituted derivatives have been prepared by homocoupling of substituted pyridine or halopyridine precursors. Oxidations of methylbipyridines generate the corresponding carboxylic acids, which, on esterification and subsequent traditional transformations, gave rise to various functional groups. Another way to functionalize the methyl group is by free radical halogenation, followed by substitution or halogen/metal exchange, and the subsequent treatment with an appropriate electrophile.[31,32] In addition, the Boekelheide arrangement (see section 6)[97] as well as the preparation of *tert*-butyl derivatives with subsequent treatment with electrophiles can be utilized (see section 6).[98] The unsymmetrical bipyridines have been prepared by the heterocoupling of different pyridine precursors or from symmetrical disubstituted precursors by selective conversions, thus taking advantage of equilibrium or solubility properties. Ziessel et al. built unsymmetrically substituted bipyridines by using the Kröhnke condensation.[33] At present, disubstituted derivatives represent the most important class of bipyridines used in supramolecular and macromolecular chemistry.

5.2.1 3,3′-Disubstituted 2,2′-Bipyridines (Table 1)

There are only a few 3,3′-disubstituted 2,2′-bipyridines known largely due to the steric hindrance of the substituents resulting in a twisted, noncoplanar conformation of the 3,3′-bipyridines, which cannot be used for tetrahedral or octahedral coordination. The simplest route to 3,3′-disubstituted 2,2′-bipyridine is through the corresponding dicarboxylic acid, which was prepared in 69% yield,[99] by the oxidation[100] of the readily available 1,10-phenanthroline via the dione intermediate with aqueous $KMnO_4$; diazafluorenone (20%)[101] and dione (11%)[99] were obtained as major byproducts (Scheme 18). The 3,3′-diester was prepared either by the coupling of methyl 2-chloronicotinate[62] or by perbenzoic acid oxidation of 1,10-phenanthroline-5,6-quinone.[102] Furthermore, 3,3′-dimethyl-2,2′-bipyridine can be prepared in 19% yield by homocoupling of 2-bromo-3-methylpyridine with Cu powder in *p*-cymene at 200 °C.[54] 3,3′-Dihydroxy-[66−68,103] and 3,3′-dimethoxy-2,2′-bipyridine[27,61,68,103] were prepared by coupling the corresponding 2-bromopyridines with Ni/Ph_3P/Zn catalysis. The alkylation in the 6,6′-position of the 3,3′-diols was recently described by Grabowska et al.[104]



Scheme 18. Oxidation of 1,10-phenantroline

5.2.2 4,4′-Disubstituted 2,2′-Bipyridines (Table 2)

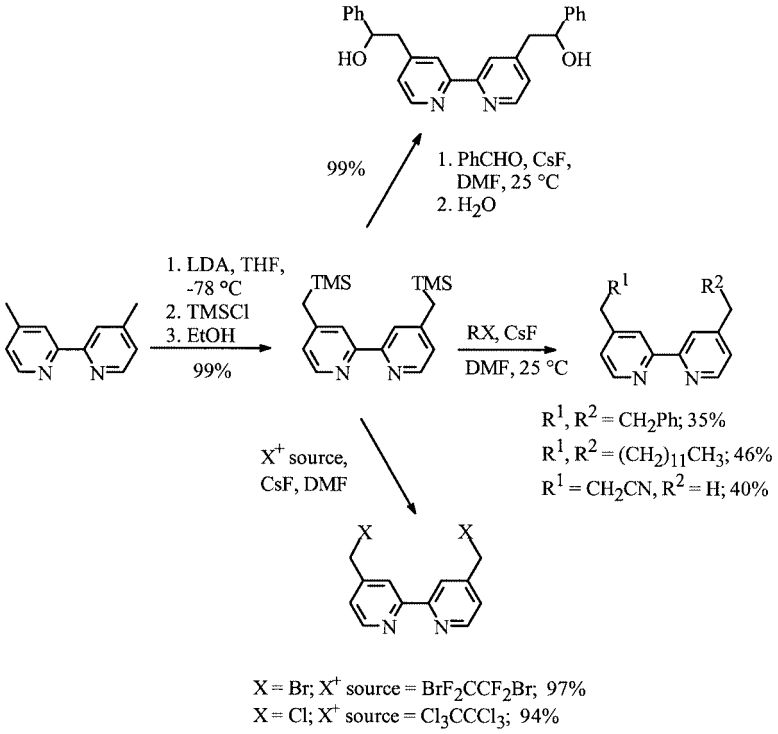
Using 4,4′-dimethyl-2,2′-bipyridine as starting material, Fraser et al. synthesized[98] halomethyl derivatives in very high overall yields (93−96%) as shown in Scheme 19. Tra-

Table 1. 3,3′-Disubstituted 2,2′-bipyridines

R^1	R^2	Starting material	Reagent	Ref.
CH_3	CH_3	2-bromo-3-methylpyridine	Cu	[54]
OH	OH	2-bromo-3-hydroxypyridine	Zn/Ni^0/Ph_3P	[66,67,103,104]
OCH_3	OCH_3	2-bromo-3-methoxypyridine	$NiCl_2$/Ph_3P/Zn	[61,103,104]
OCH_3	OCH_3	2-stannylated pyridines, 2-halopyridine	$Pd(PPh_3)_4$	[27]
OCH_3	OCH_3	alkoxy-2-iodopyridine	$ZnCl_2$/ $Pd(PPh_3)_4$	[27]
CO_2H	CO_2H	1,10-phenanthroline	$KMnO_4$	[99]
CO_2CH_3	CO_2CH_3	methyl 2-chloronicotinate	$NiBr_2(PPh_3)_2$/Zn	[62]
CO_2H	CO_2CH_3	1,10-phenanthroline-5,6-quinone	MCPBA/MeOH	[102]

Table 2. 4,4′-Disubstituted 2,2′-bipyridines

R^1	R^2	Starting material	Reagent	Ref.
CH_3	CH_3	4-methylpyridine	10% Pd/C	[47,48]
			Raney nickel	[45]
C_9H_{19}	C_9H_{19}	4,4′-dimethyl-2,2′-bipyridine	LDA/1-bromooctane	[45]
$(CH_2)_{10-12,14,18}CH_3$	$(CH_2)_{10-12,14,18}CH_3$	4,4′-dimethyl-2,2′-bipyridine	LDA, TMSCl, RBr, CsF	[98,108]
CH_3	$CH_2CH_2OCH_3$	4,4′-dimethyl-2,2′-bipyridine	LDA, $ClCH_2OCH_3$	[117]
CH_3	$CH{=}CH_2$	4,4′-dimethyl-2,2′-bipyridine	2 steps	[117]
$CH{=}CH_2$	$CH{=}CH_2$	4,4′-dimethyl-2,2′-bipyridine	5 steps	[116]
C≡CH	H	4-bromo-2,2′-bipyridine	$HC{\equiv}CSi(CH_3)_3$, $Pd(PPh_3)_2Cl_2$, CuI, KF, MeOH/THF	[92]
C≡CH	C≡CH	4,4′-dibromo-2,2′-bipyridine	$HC{\equiv}CSi(CH_3)_3$,$Pd(Ph_3)_2Cl_2$, CuI, $(iPr)_2NH$, K_2CO_3	[110,111]
CH_2CH_2Ph	CH_2CH_2Ph	4,4′-dimethyl-2,2′-bipyridine	$NaNH_2$, $PhCH_2Cl$	[109]
			LDA, TMSCl, $PhCH_2Br$, CsF	[98]
$PhCH_3$	$PhCH_3$	2-bromo-4-*p*-tolylpyridine	$Ni(PPh_3)_2Cl_2$, PPh_3, Zn	[69]
PhOH, PhMe, PhCl	PhOH, PhMe, PhCl	butane-2,3-dione, 4-methoxybenzaldehyde or 4-chlorobenzaldehyde, 1-pyridiniopropan-2-one bromide	piperidine	[32]
			ammonium acetate	[32]
PhMe	PhMe	4,4′-dibromo-2,2′-bipyridine, 4-methoxyphenylboronic acid	$Pd(PPh_3)_4$	[32,87]
Br	H	4-nitro-2,2′-bipyridyl *N*-oxide	AcBr, PBr_3	[48]
Br	Br	4,4′-dinitro-2,2′-bipyridine *N*,*N*′-dioxide	AcBr, PBr_3	[110]
CH_3	CH_2Br	4-methyl-4′-(hydroxymethyl)-2,2′-bipyridine	HBr	[148]
CH_3	CH_2CH_2Br			[148]
CH_3	$(CH_2)_nBr$ (n = 3−7)	4,4′-dimethyl-2,2′-bipyridine + dibromoalkane	LDA	[149]
$PhCH_2Br$	$PhCH_2Br$	4,4′-bis(*p*-tolyl)2,2′-bipyridine	NBS	[69]
CH_2Br	CH_2Br	4,4′-bis[(trimethylsilyl)methyl]-2,2′-bipyridine	BrF_2CCF_2Br/CsF	[98]
C_4H_8Br	C_4H_8Br	4,4′-dimethyl-2,2′-bipyridine	3-steps	[69]
CH_3	CH_2CH_2Cl			[148]
CH_2Cl	CH_2Cl	4,4′-bis[(trimethylsilyl)methyl]-2,2′-bipyridine	Cl_3CCCl_3/CsF	[98]
CH_2TMS	CH_2TMS	4,4′-dimethyl-2,2′-bipyridine	LDA, TMSCl	[98]
CF_3	CF_3	2-chloro-4-(trifluoromethyl)pyridine	$Ni(Ph_3P)_2Cl_2$/Zn/Et_4NI	[65]
CH_2I	CH_2I	4,4′-bis(chloromethyl)-2,2′-bipyridine (Ru complex)	NaI	[98]
CH_3	$(CH_2)_3OH$	4,4′-dimethyl-2,2′-bipyridine	LDA, ethylene oxide	[149]
CH_3	CH_2OH	4,4′-dimethyl-2,2′-bipyridine	Ac_2O, $NaOH/H_2O$	[148]
CH_3	$(CH_2)_4OH$	corresponding aldehyde	$NaBH_4$	[148]
CH_2OH	CH_2OH	corresponding diester	$NaBH_4$	[112,116]
C_4H_8OH	C_4H_8OH	4,4′-dimethyl-2,2′-bipyridine	LDA, $Br(CH_2)_3OTHP$, H^+	[69]
OH	OH	4,4′-dimethoxy-2,2′-bipyridine	pyridinium chloride	[103]
OCH_3	OCH_3	2-chloro-4-methoxypyridine	$NiCl_2$, PPh_3, Zn	[103]
SCH_3	SCH_3	4,4′-dichloro-2,2′-bipyridine	$NaSCH_3$	[47]
SCH_2CH_3	SCH_2CH_3	4,4′-dichloro-2,2′-bipyridine	KSH, CH_3CH_2I	[47]
CH_3	CHO	corresponding alcohol	MnO_2	[148]
		4,4′-dimethyl-2,2′-bipyridine	SeO_2	[48,113]
CH_3	$(CH_2)_3CHO$			[148]
CHO	CHO	corresponding diol	MnO_2	[112]
		corresponding diol	SeO_2	[116]
		4,4′-dienamine-2,2′-bipyridine	$NaIO_4$	[115]
CH_3	CN	4-methyl-2,2′-bipyridine-4′-carboxaldehyde	NH_2OH. HCl,	[118]
CH_3	CH_2CH_2CN	4,4′-dimethyl-2,2′-bipyridine	$ClCH_2CN$	[98]
CN	CN	2,2′-bipyridine-4,4′-biscarboxamide	$POCl_3$	[46]
CH_3	CH_2CO_2H	4,4′-dimethyl-2,2′-bipyridine	*n*BuLi/CO_2	[148]
CH_3	$(CH_2)_3CO_2H$	corresponding aldehyde	$KMnO_4$	[148]
CO_2H	CO_2H	4,4′-dimethyl-2,2′-bipyridine	$KMnO_4$	[47,113,116]
			CrO_3, H_2SO_4	[112]
			$K_2Cr_2O_7$, H_2SO_4	[114]
CO_2H, CO_2Cl, CO_2NHS	CO_2H, CO_2Cl, CO_2NHS	4,4′-dimethyl-2,2′-bipyridine	$KMnO_4$, $SOCl_2$, *N*-hydroxysuccinimide	[123]
SO_3H	SO_3H	2,2′-bipyridine	5 steps	[47]
CH_3	COCl	4′-methyl-2,2′-bipyridine-4-carboxylic acid.	$SOCl_2$	[120]
COCl	$CO_2CH_2CH_3$	4′-ethoxycarbonyl-2,2′-bipyridine-4-carboxylic acid	$SOCl_2$	[120]
H	CO_2CH_3	methyl 2-chloropyridine-4-carboxylate	2-(trimethylstannyl)pyridine, $(PPh_3)PdCl_2$	[93]
CH_3	$CH_2CO_2CH_3$	corresponding acid	CH_3OH-BF_3	[148]
CO_2H	CO_2CH_3	dimethyl ester	KOH	[113]
CO_2CH_3	CO_2CH_3	2,2′-bipyridine-4,4′-dicarboxylic acid	CH_3OH/H^+	[112,116]
CH_3	$(CH_2)_4NH_2$	4,4′-dimethyl-2,2′-bipyridine	4 steps	[148]
CH_3	CH=NOH	4-formyl-4′-methyl-2,2′-bipyridine oxime	$NH_2OH{\cdot}HCl$	[148]
CH_3	CH_2NH_2	4-(bromomethyl)-4′-methyl-2,2′-bipyridine	10% Pd/C, H_2, potassium phthalimide	[119,148]

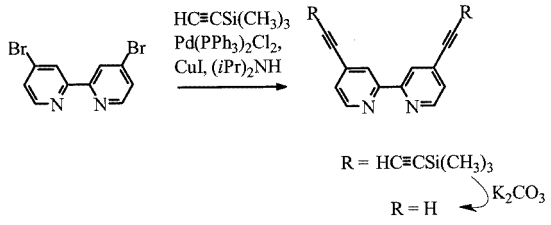


Scheme 19. Fraser's preparation of halomethyl derivatives

ditionally, 4,4′-di(halomethyl) derivatives are prepared from the corresponding methylbipyridines by free-radical halogenation[49,55,64,105] and are normally isolated in poor yields (10−40%) due, in part, to polyhalogenation.[105] The respective TMS derivative was prepared by deprotonation of 4,4′-dimethyl-2,2′-bipyridine with 2 equiv. of LDA, followed by trapping the resulting dianion with TMSCl.[106] This symmetrical bis(TMS) intermediate of 4,4′-dimethyl-2,2′-bipyridine was then treated with CsF and $(CF_2Br)_2$ or $(CCl_3)_2$ in dry DMF as solvent to give 94−97% of the halomethyl derivatives with chloro and bromo functionalities. Treatment of the symmetrical bis(TMS) intermediate with benzaldehyde produced 99% of the diol derivative. This methodology was extended to the reaction of the symmetrical bis(TMS) intermediate with alkyl halides resulting in the formation of dialkylated bipyridines. Moreover, an improved approach to obtain diols was reported recently.[107] Perfluoroalkylated bipyridines could be obtained in 40% yield by treating 4,4′-dimethylbipyridine with LDA and adding the respective perfluoroiodine.[106]

In order to introduce long alkyl chains, Smith et al.[108] deprotonated 4,4′-dimethyl-2,2′-bipyridine by the use of LDA in THF. Subsequently, the resulting dilithiobipyridines were treated with the respective alkyl bromides to yield the corresponding products in 56−88% yield.[108] Alkylphenyl chains were obtained in 14% yield by addition of the respective chloroalkylbenzenes to 4,4′-dimethylbipyridine.[109]

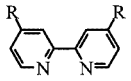
Suffert and Ziessel prepared 4,4′-ethynyl-2,2′-bipyridines by treating the corresponding 4,4′-dibromo-2,2′-bipyridine with trimethylsilylacetylene using $[Pd(PPh_3)_2Cl_2]$ as catalyst, CuI as reducing agent, and diisopropylamine as base (Scheme 20).[110] Deprotection of the respective silyl derivatives was effected by treatment with aqueous K_2CO_3; this method was utilized to prepare new polypyridine building blocks with ethynyl substitution at different positions. 4,4′-Ethynyl-substituted 2,2′-bipyridines are also of interest as building block forming sexipyridines.[111]



Scheme 20. Ethynyl-substituted bipyridines

Kocian et al. have synthesized 4,4′-diformyl-2,2′-bipyridine in four steps starting from 4,4′-dimethyl-2,2′-bipyridine in 34% overall yield (Figure 4).[112] Thus, 4,4′-dimethyl-2,2′-bipyridine was oxidized to the diacid with CrO_3 in sulfuric acid (90%), $KMnO_4$ [47,113] or $K_2Cr_2O_7$ [114] (94% yield). In acidic MeOH, the diacid gave the dimethyl ester derivative, which was then reduced in 72% yield with $NaBH_4$ to the corresponding 4,4′-diol derivative. This diol was oxidized with MnO_2 in dioxane to the 4,4′-dialdehyde in 60% yield; using a modified Bedereck's reagent gave the formyl derivative in 52−71%.[115] Finally, the dinitrile derivative was prepared[46] in 88% yield from the corresponding dicarboxamide upon treatment with $POCl_3$. Zelewsky et al. used the Wittig reaction with Ph_3PMeBr to convert the

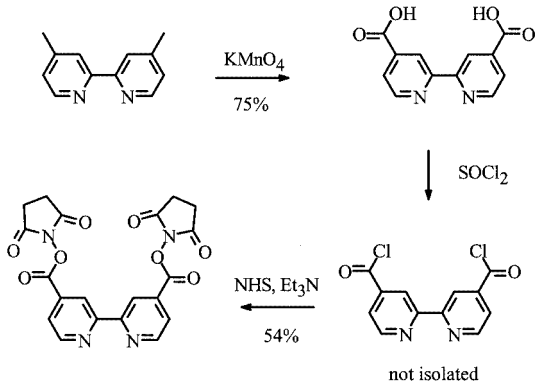
4,4′-dialdehyde into 4,4′-divinyl-2,2′-bipyridine in 54% yield.[116,117] The carboxaldehyde moiety can also be converted into the nitrile functionality in 80% yield by the treatment with hydroxylamine hydrochloride.[118] (Aminomethyl)bipyridine was synthesized from (bromomethyl)bipyridine and potassium phthalimide followed by hydrazinolysis in 90% yield.[119] Carboxy groups afforded after treatment with $SOCl_2$ quantitative yields of the corresponding acyl chlorides.[120]



	a	b	c	d	e	f	g
R	CH_3	CO_2H	CO_2CH_3	CH_2OH	CHO	CN	$CONH_2$

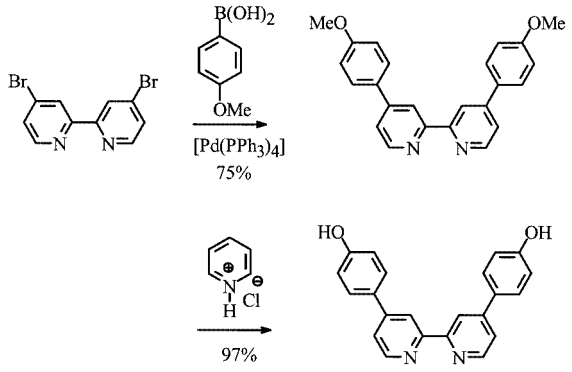
Figure 4. 4,4′-Disubstituted 2,2′-bipyridines

Nolte et al.[121−123] synthesized 2,2′-bipyridines with amino-reactive 4,4′-(*N*-hydroxysuccinimide esters), which represent very versatile building blocks for supramolecular and macromolecular chemistry. 4,4′-Dimethyl-2,2′-bipyridine was converted into the diacid in 75% by using $KMnO_4$ as the oxidant. After chlorination with $SOCl_2$, *N*-hydroxysuccinimide was added in the presence of Et_3N to form the respective esters in 54% (Scheme 21).



Scheme 21. 2,2′-Bipyridines with amino-reactive 4,4′-(*N*-hydroxysuccinimide esters)

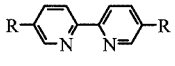
Suzuki-type reactions[87] using bromo-2,2′-bipyridines and phenylboronic acid derivatives under phase reaction conditions with $[Pd(PPh_3)]_4$ as a cross-coupling catalyst and addition of Na_2CO_3 as base yielded (75%) the corresponding 4-(methoxyphenyl)-2,2′-bipyridine (Scheme 22).[31] Constable et al. described the synthesis of similar compounds by Stille-type reactions but obtained only 18% yield utilizing this method.[32] Using a Kröhnke protocol, the 4-(methoxyphenyl)-2,2′-bipyridine was formed in 35% yield.[32] The respective alcohol functionalities were prepared in 97% yield by treating the latter with pyridinium chloride.



Scheme 22. Suzuki-type reactions using bromo-2,2′-bipyridines and phenylboronic acid derivatives

5.2.3 5,5′-Disubstituted 2,2′-Bipyridines (Table 3)

5,5′-Dimethyl-2,2′-bipyridine was prepared by coupling of 3-picoline with Raney Ni[49] (15% yield) or Pd/C (0.5% yield) (Figure 5).[48] Treatment of 2,2′-bipyridine with HBr/Br_2 afforded 5,5′-dibromo-2,2′-bipyridine,[94,124] which was converted into the 5,5′-ethynyl-substituted bipyridine[110,124] in 76% yield with (trimethylsilyl)acetylene catalyzed by $[Pd(PPh_3)_2Cl_2]$ and CuI, followed by deprotection with K_2CO_3 (91% yield). 5,5′-Bis(bromomethyl)-2,2′-bipyridine was prepared by free radical bromination of 5,5′-dimethyl-2,2′-bipyridine with NBS (74[125] and 36%[49]). Whittle described[126] various symmetrically 5,5′-disubstituted-2,2′-bipyridines; thus, 5,5′-dimethyl-2,2′-bipyridine was oxidized with $KMnO_4$ to the respective 5,5′-diacid. Reaction with $SOCl_2$ afforded 5,5′-bis(chlorocarbonyl)-2,2′-bipyridine, which upon condensation with 2-methoxyethylamine, *n*-butylamine, and *n*-dodecylamine gave the respective 2,2′-bipyridine-5,5′-diamides in yields of 61−85%. 5,5′-Bis(chlorocarbonyl)-2,2′-bipyridine also serves as a potent linking molecular host for amino acids in basic methanol. The amino acid moiety could induce stereoselectivity.[127] Subsequently, the acid was converted with EtOH and sulfuric acid into the 5,5′-diethyl ester. Alternatively, this compound was also prepared by direct coupling of ethyl nicotinate with 10% Pd/C.[51]



	a	b	c	d	e	f	g	h
R	CH_3	C≡CH	Br	CH_2Br	CO_2H	CO_2Et	CH_2OH	$CONH_2$

	i	j	k	l	m	n	o
R	CN	$CONHNH_2$	CON_3	$NHCO_2Et$	NH_2	$NHCOCH_3$	$N(CH_3)_3$

Figure 5. 5,5′-Disubstituted 2,2′-bipyridines

The 5,5′-diester was converted into the 5,5′-diol by $LiAlH_4$ reduction or to the dicarboxamide derivative by treatment with ammonia in a 1:1 mixture of EtOH and ethylene

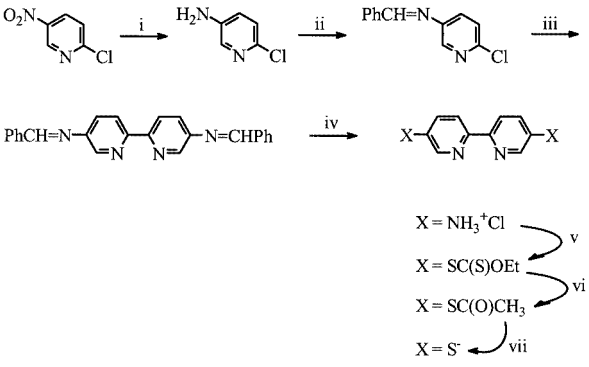
Table 3. 5,5′-Disubstituted 2,2′-bipyridines

R^1	R^2	Starting material	Reagent	Ref.
CH_3	H	2-acetylpyridine	I_2, methacrolein, NH_4OAc	[48]
CH_3	CH_3	3-picoline	Raney nickel	[49]
			Pd/C	[48]
C≡CH	H	5-(2,2-dibromovinyl)-2,2′-bipyridine	*n*BuLi	[48]
		5-bromo-2,2′-bipyridine	$HC{\equiv}CSi(CH_3)_3$, $Pd(PPh_3)_2Cl_2$, CuI, KF, MeOH	[92,110]
C≡CH	C≡CH	5,5′-dibromo-2,2′-bipyridine	$HC{\equiv}CSi(CH_3)_3$, $Pd(PPh_3)_2Cl_2$, CuI, KF, MeOH.	[92,110]
$C{\equiv}CSi(CH_3)_3$	$C{\equiv}CSi(CH_3)_3$	5,5′-dibromo-2,2′-bipyridine	$HC{\equiv}CSi(CH_3)_3$, $Pd(PPh_3)_2Cl_2$, CuI	[110]
$SiMe_3$, Si_2Me_5	$SiMe_3$, Si_2Me_5	2,5-dibromopyridine, corresponding silyl chloride	BuLi, Ni^0 catalyst, Et_4NI	[71]
CH_3	CH_2Br	5,5′-dimethyl-2,2′-bipyridine	LDA, TMSCl, $(CBrF_2)_2$	[22]
CH_2Br	H	5-methyl-2,2′-bipyridine	NBS	[48]
CH_2Br	CH_2Br	5,5′-dimethyl-2,2′-bipyridine	NBS	[49,125]
CF_3	CF_3	2-chloro-5-(trifluoromethyl)pyridine	$Ni(PPh_3)_2Cl_2/Zn/Et_4NI$ or	[65]
			5% Pd/C *t*BuONa-NiCRA PPh_3	[73]
Br	H	2,2′-bipyridine	HBr, Br_2, OH^-	[94]
		$(pyridyl)_3P$	Br_2/MeOH	[37]
Br	Br	2,2′-bipyridine	HBr, Br_2, OH^-	[94,124]
Cl	H	$(pyridyl)_3P$	Cl_2/MeOH	[37]
$CH(CH_3)OH$	$COCH_3$	5,5′-diacetyl-2,2′-bipyridine	$NaBH_4$	[133]
$CH(CH_3)OTBDMS$	$COCH_3$	5-acetyl-5′-(1-hydroxyethyl)-2,2′-bipyridine	TBDMS-Cl	[133]
SH	SH	2,2′-bipyridine-5,5′-bis(thioacetate)	NH_3	[129]
CHO	H	5-bromomethyl-2,2′-bipyridine	Methenamine, AcOH	[48]
$COCH_3$	$COCH_3$	3-acetylpyridine	10% Pd/C	[133]
CN	CN	2,2′-bipyridine-5,5′-dicarboxamide	$POCl_3$	[46]
H	SO_3H	2,2′-bipyridine	H_2SO_4	[47]
SO_3H	SO_3H	2,2′-bipyridine	H_2SO_4	[47]
H	CO_2CH_3	methyl 2-chloropyridine-5-carboxylate	2-Trimethylstannylpyridine, $(PPh_3)PdCl_2$	[93]
CO_2Et	CO_2Et	ethyl nicotinate	10% Pd/C	[51,127]
$SCOCH_3$	H	2,2′-bipyridine-5-ethyldithiocarbonate	KOH, CH_3COCl	[72]
$SCOCH_3$	$SCOCH_3$	2,2′-bipyridine-5,5′-bis(ethyldithiocarbonate)	KOH, CH_3COCl	[72]
SC(S)OEt	H	5-amino-2,2′-bipyridine	$NaNO_2/H^+$, KSC(S)OEt	[72]
SC(S)OEt	SC(S)OEt	5,5′-diamino-2,2′-bipyridine	$NaNO_2/H^+$, KSC(S)OEt	[72]
NH_2	CO_2H	5′-[(ethoxycarbonyl)amino]-2,2′-bipyridine-5-carboxylate	EtOH, NaOH	[51]
NH_2	CO_2Me	nitro precursor	Pd/C	[131]
NH_2	CO_2Et	5′-amino-2,2′-bipyridine-5-carboxylic acid	EtOH, H_2SO_4	[51]
NO_2	CO_2Me	2-(trimethylstannyl)-5-nitropyridine	LiCl, $Pd(PPh_3)_4$	[131]
$NHCO_2Et$	CO_2Et	ethyl 5′-carbazido-2,2′-bipyridine-5-carboxylate	EtOH, Xylene	[51]
CON_3	CO_2Et	5-(ethoxycarbonyl)-5′-carbohydrazido-2,2′-bipyridine	$HCl/NaNO_2$	[51]
$CONHNH_2$	CO_2Et	diethyl 2,2′-bipyridine-5,5′-dicarboxylate	NH_2NH_2	[51]
$CONHNH_2$	$CONHNH_2$	diethyl 2,2′-bipyridine-5,5′-dicarboxylate	NH_2NH_2	[51]
NH_2	H	5-nitro-2,2′-bipyridine	10% Pd/C	[72]
NH_3Cl	NH_3Cl	5-amino-*N*-benzylidene-2-chloropyridine	Steps	[72]
CH_2NEt_2	CH_2NEt_2	5,5′-bis(bromomethyl)-2,2′-bipyridine	Et_2NH/K_2CO_3	[130]
CH_2NMePh	CH_2NMePh	5,5′-bis(bromomethyl)-2,2′-bipyridine	$PhNHCH_3/K_2CO_3$	[130]
$CH_2N(CH_2CH_2OH)_2$	$CH_2N(CH_2CH_2OH)_2$	5,5′-bis(bromomethyl)-2,2′-bipyridine	$(CH_2CH_2OH)_2NH/K_2CO_3$	[130]
N=CHPh	N=CHPh	5-amino-*N*-benzylidene-2-chloropyridine	$NiBr_2(PPh_3)_2$, Zn/Et_4NI	[72]
NO_2	H	2-(trimethylstannyl)pyridine, 2-chloro-5-nitropyridine	$Pd(PPh_3)_2Cl_2$	[72]
NO_2	NO_2	2-bromo-5-nitropyridine	$Pd(OAc)_2/nBu_4NBr$	[75]

glycol in a sealed tube at 90 °C. Interestingly, the sole use of EtOH resulted in the formation of the monocarboxamide as the major product.[126] The 5,5′-diamide derivative was dehydrated using P_2O_5 to generate the corresponding 5,5′-dinitrile (59%), which was previously prepared by coupling 3-cyanopyridine with 10% Pd/C in a meager 7% yield. The conversion of the 5,5′-diamide to the 5,5′-diamine derivative by the Hoffmann rearrangement was reported to be unsuccessful;[126] however, the diamine can be prepared by reduction of the corresponding dinitro derivative albeit in poor yield (9%). An improved procedure utilized the 5,5′-diethyl ester, which with hydrazine hydrate in EtOH gave

the 5,5′-dicarbohydrazide in 62% yield.[51,126] Treatment of this dicarbohydrazide with HCl/$NaNO_2$ yielded the 5,5′-dicarbazide, which underwent a Curtius rearrangement[128] on heating in an EtOH/xylene mixture to result in the respective bis(ethoxycarbonylamine). Subsequent hydrolysis to the corresponding 5,5′-diamine was accomplished both in either acidic or basic media. Moreover, reaction with Ac_2O gave the respective bis(acetamide). The bis(dimethylamino)-2,2′-bipyridine was also prepared starting from 5,5′-diamino-2,2′-bipyridine by treatment with formaldehyde and formic acid in 92% yield. Finally, 5,5′-diamino-2,2′-bipyridine was converted into 5,5′-dibromo-2,2′-bipyridine on treatment with $NaNO_2$ and hydrobromic acid.

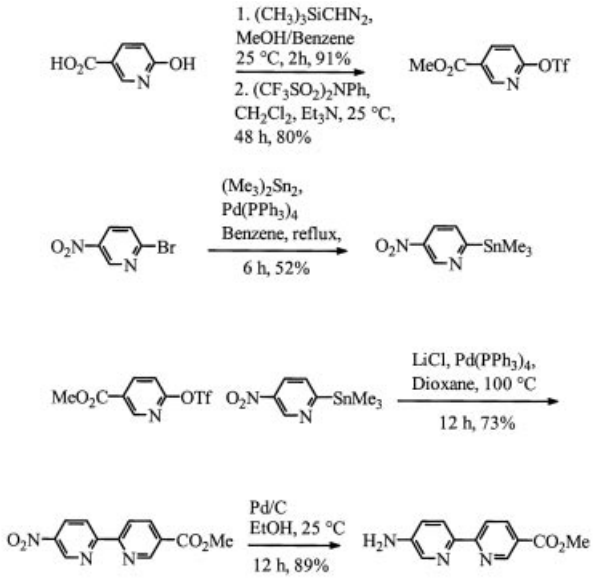
The 5,5′-diamine hydrochloride was prepared by coupling 5-amino-*N*-benzylidene-2-chloropyridine (obtained by the reduction of 2-chloro-5-nitropyridine and subsequent protection of the 5-amino-2-chloropyridine with benzaldehyde) in the presence of Ni^{II}/Zn catalyst, followed by deprotection with 1 N HCl (Scheme 23).[72] Conversion of the 5,5′-diamine hydrochloride to the corresponding bis(diazonium) salt was followed by treatment with potassium ethyl xanthate to yield the corresponding diethyl 2,2′-bipyridine-5,5′-dixanthate. The latter compound could be transformed into the respective bis(thioacetate) by treatment with ethanolic KOH and acetyl chloride. Finally, a complete deprotection afforded the corresponding dianion of the 5,5′-thiol derivative.[129] Grigg et al. introduced a general procedure to synthesize 5,5′-bis(aminoalkyl)-2,2′-bipyridines utilizing the respective 5,5′-bis(bromomethyl)-2,2′-bipyridine and the respective amines in benzene containing potassium carbonate.[130]



Scheme 23. Preparation of 2,2′-bipyridine-5,5′-dithiol: i) Fe/NH_4Cl, MeOH, H_2O, room temp.; ii) PhCHO, $MgSO_4$, Et_3N, CH_2Cl_2, room temp., 24 h; iii) [$NiBr_2(PPh_3)_2$], Zn/$Et_4N^+I^-$/THF, 50−80 °C, 20 h; iv) 1 N HCl, reflux; v) 1. $NaNO_2/H_3O^+$, 2. KSC(S)OEt, H_2O, 65−70 °C; vi) 1. 20% KOH/EtOH, reflux, 2. CH_3COCl, 0−5 °C; vii) NH_3/MeOH, room temp., 1 h

Kira et al.[71] reported the synthesis of 5,5′-disilyl-substituted-2,2′-bipyridines by cross-coupling (bromosilyl)pyridines utilizing an in situ generated Ni^0 catalyst in the presence of Et_4NI and freshly activated zinc. Depending on the silyl ligand, utilized yields up to 55% were observed.

The methyl 5′-amino-2,2′-bipyridine-5-carboxylate was prepared[131] by Stille coupling[20,132] of methyl 2-(trifluoromethylsulfonyl)pyridine-5-carboxylate and 2-trimethyltin-5-nitropyridine (Scheme 24). Methyl 2-(trifluoromethylsulfonyl)pyridine-5-carboxylate was synthesized in 72% yield by methylation of 2-hydroxypyridine-5-carboxylic acid with (trimethylsilyl)diazomethane and subsequent treatment with *N*-phenyltrifluoromethanesulfonamide. Refluxing 2-bromo-5-nitropyridine with Sn_2Me_6 in benzene for 6 h gave the desired tin derivative. The Stille coupling of methyl 2-(trifluoromethylsulfonyl)pyridine-5-carboxylate and the tin derivative utilized LiCl and $Pd(PPh_3)_4$ in dioxane afforded methyl 5′-nitro-2,2′-bipyridine-5-carboxylate (73%), which was reduced by catalytic hydrogenation with Pd/C in EtOH to give methyl 5′-amino-2,2′-bipyridine-5-carboxylate (89%). The 5-acetyl-5′-(1-hydroxyethyl)-2,2′-bipyridine was achieved by reduction of the 5,5′-diacetyl-2,2′-bipyridine, synthesized by coupling of 3-acetylpyridine, with sodium borohydride in 44% yield.[52,133]

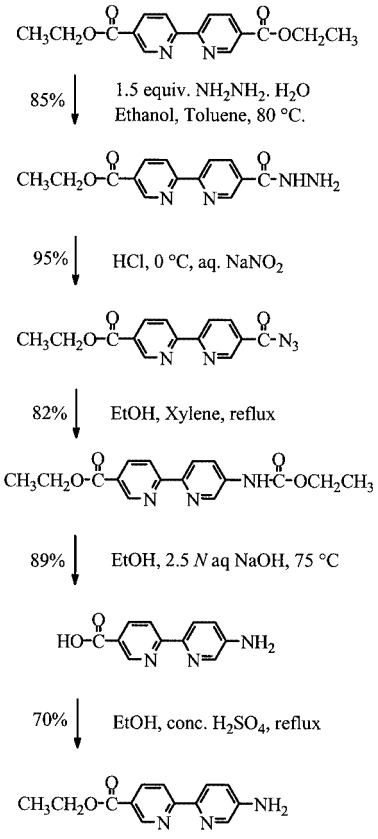


Scheme 24. Cross-coupling strategy for unsymmetrical 2,2′-bipyridines

The synthesis of 5,5′-dinitrobipyridine was improved by Lemaire et al. using a catalytic alternative to the Ullmann reaction.[75] The respective bromo-nitropyridines were coupled by using $Pd(OAc)_2$ to afford the 5,5′-dinitrobipyridine in 20% yield. 2,2′-Bipyridines and their symmetrical 5,5′-dimethyl derivatives were prepared in very high yields (> 90%) by utilizing the same procedure using K_2CO_3, as base, in DMF/water mixtures.

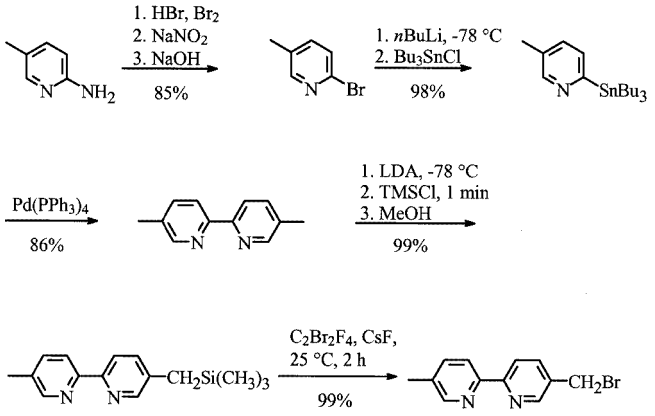
Taking advantage of the solubility differences of synthetic intermediates offers a tremendous opportunity to selectively direct multiple reactions on a specific polyfunctional level. To demonstrate this concept, unsymmetrical 5,5′-disubstituted 2,2′-bipyridines were prepared;[51] thus, starting from diethyl 2,2′-bipyridine-5,5′-dicarboxylate, the

exclusive formation of the respective monocarbohydrazide was achieved in 85% yield using 1.5 equiv. of hydrazine hydrate and adjusting the polarity of the solvent system with an EtOH/toluene mixture (Scheme 25). The monocarbohydrazide, which precipitated under these tailored conditions, was converted in 95% into the corresponding 5,5′-carbazide upon treatment with $NaNO_2$ in concentrated HCl. The Curtius rearrangement of the monocarbazide was achieved upon refluxing in xylene/ethanol to afford the (ethoxycarbonyl)amine derivative (82%), which was hydrolyzed to give 5′-amino-2,2′-bipyridine-5-carboxylic acid hydrochloride in 89% yield. In order to enhance the solubility characteristics, the amino acid was subjected to Fischer esterification conditions affording 70% of the non-zwitterionic ethyl 5′-amino-2,2′-bipyridine-5-carboxylate.



Scheme 25. Unsymmetrical 5,5′-disubstituted 2,2′-bipyridines

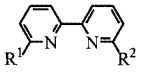
Another example of the application of limited solubilities was shown by Schubert et al., in which 5,5′-dimethylbipyridine, synthesized in a convenient and straightforward way utilizing the Stille-type coupling procedure in 86% yield, was selectively monofunctionalized (Scheme 26).[22,134] Reaction of the starting material with LDA at low temperatures resulted in an exclusive monolithiated intermediate, which was trapped with TMSCl. Reaction with $C_2Br_2F_4$ and CsF afforded the 5′-bromomethyl-5-methyl-2,2′-bipyridine in 99% yield.[22]



Scheme 26. Straightforward Stille-type coupling procedure

5.2.4 6,6′-Disubstituted 2,2′-Bipyridines (Table 4)

6,6′-Dimethyl-2,2′-bipyridine (Figure 6) was typically obtained by coupling 2-bromo-6-methylpyridine with Pd/C,[55–57,135] Raney nickel,[63,64] or *tert*-BuONa/NiCRA/PPh_3,[73] as described previously. 6,6′-Divinyl-2,2′-bipyridine was prepared by a Wittig reaction, using methyltriphenylphosphonium bromide and the corresponding 6,6′-dialdehyde, which was generated by SeO_2 oxidation of 6,6′-dimethyl-2,2′-bipyridine in refluxing acetic acid.[135]



	a	b	c	d	e	f	g	h	i	j
R^1	CH_3	$CH=CH_2$	CH_2Br	CH_2Cl	Br	CH_2OH	CH_2OAc	CH_2OAc	CH_2OH	CHO
R^2	CH_3	$CH=CH_2$	CH_2Br	CH_2Cl	Br	CH_2OH	CH_2OAc	CH_3	CH_3	CHO

Figure 6. 6,6′-Disubstituted 2,2′-bipyridines

Free-radical bromination of 6,6′-dimethyl-2,2′-bipyridine using NBS afforded 6,6′-bis(bromomethyl)-2,2′-bipyridine[56,57,64] in poor yields as well as other polybrominated materials.[136] 6,6′-Dibromo-2,2′-bipyridine was synthesized in 72% yield[137] by air oxidation of bis(6-bromo-2-pyridinyl)cuprate, obtained by Br → Li exchange of 2,6-dibromopyridine, followed by Li → Cu transmetallation, and subsequent quenching. The use of 2,6-dibromopyridine has some disadvantages such as high cost, immense net molecular weight loss, large-scale lithiations, and potentially hazardous coupling procedures. To circumvent at least some of these problems the cheap and commercially available 2,6-dichloropyridine can be easily transformed into the corresponding diiodo derivative in 73% yield.[55] 6,6′-Difunctionalized bipyridines have been derived from 6,6′-dibromo-2,2′-bipyridine by a Br → Li exchange, followed by addition of suitable electrophiles, (e.g. *N*,*N*-dimethylformamide), to give the respective dialdehyde.[55] Halomethyl de-

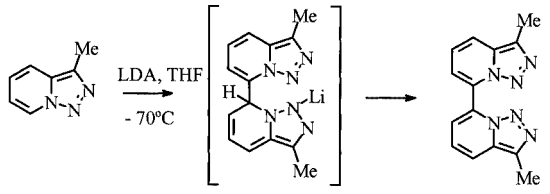
Table 4. 6,6′-Disubstituted 2,2′-bipyridines

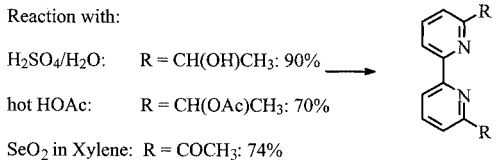
R^1	R^2	Starting material	Reagent	Ref.
CH_3	CH_3	2-bromo-6-methylpyridine	*t*BuONa-NiCRA-PPh_3	[73]
			Pd/C	[55−57]
			Raney nickel	[63,64]
CH_3		2-methylsulfinylpyridine	6-Methyl-2-pyridyllithium	[39]
CH_2CH_3	H			[96]
$CH{=}CH_2$	$CH{=}CH_2$	6,6′-diformyl-2,2′-bipyridine	BuLi, CH_3PPh_3Br	[135]
C≡CH	C≡CH	6,6′-dibromo-2,2′-bipyridine	2 steps	[110]
chiral diterpene	chiral diterpene	corresponding chiral 2-chloropyridine	$(PPh_3)_2NiCl_2$, triphenylphosphane, Zn	[142]
$C{\equiv}CSi(CH_3)_3$	$C{\equiv}CSi(CH_3)_3$	6,6′-dibromo-2,2′-bipyridine	$HC{\equiv}CSi(CH_3)_3$, $Pd(PPh_3)_2Cl_2$, CuI, $(i\text{Pr})_2NH$	[110]
CH_2Br	CH_3	6-hydroxymethyl-6′-methyl-2,2′-bipyridine	PBr_3	[146]
CH_2Br	CH_2Br	6,6′-dimethyl-2,2′-bipyridine	NBS	[56,64,136]
CH_2Cl	H	6-methyl-2,2′-bipyridine	NCS	[55]
CH_2Cl	CH_2Cl	6,6′-dimethyl-2,2′-bipyridine	NCS	[55]
			LDA, TMSCl, $(CFCl_2)_2$	[106]
		6,6′-bis(hydroxymethyl)-2,2′-bipyridine	$SOCl_2$	[55]
CF_3	CF_3	2-chloro-6-trifluoromethylpyridine	$Ni(PPh_3)_2Cl_2$/Zn/Et_4NI or Pd/C	[65]
Br	CH_3	6-methyl-2-ethylsulfinylpyridine	6-bromo-2-pyridyllithium	[39]
Cl	CH_3	6,6′-dichloro-2,2′-bipyridine	NaSMe	[47]
Br	H	2,2′-bipyridine-2-methylsulfinylpyridine	3-steps 6-bromo-2-pyridyllithium	[39,40]
Br	Br	2,6-dibromopyridine	*n*BuLi, CuBr	[137]
Br	OC_6H_{13}	6,6′-dibromo-2,2′-bipyridine	n-$C_6H_{13}OH$/KOH	[141]
CH_2OTBS	H	2-ethylsulfinylpyridine reagent	2-Pyridyllithium	[39]
CH_2Cl	CH_2OH	6,6′-bis(hydroxymethyl)-2,2′-bipyridine		[145]
CH_2OH	CH_2OH	6,6′-bis(acetoxymethyl)-2,2′-bipyridine	K_2CO_3	[55]
CH_2OAc	CH_2OAc	6,6′-dimethyl-2,2′-bipyridine *N*,*N*′-dioxide	Ac_2O	[55]
OCH_3	OCH_3	2-chloro-6-methoxypyridine	*t*BuONa-NiCRA-PPh_3 $NiCl_2$,	[73,74]
			PPh_3, Zn	[61]
OC_6H_{13}	OC_6H_{13}	6,6′-dibromo-2,2′-bipyridine	*n*-$C_6H_{13}OH$/KOH	[141]
OR	OR	MEC-31, ROH (R = Me, Et, Pr, Bu, Hex)		[141]
manisyl	manisyl	4-methoxy-2,6-dimethylbromobenzene, halopyridine	$ZnCl_2$	[25]
$CH(OH)CH_3$	$CH(OH)CH_3$	7-methyltriazolopyridine	H_2SO_4	[143]
$CH(OAc)CH_3$	$CH(OAc)CH_3$	7-methyltriazolopyridine	HOAc	[143]
$CHOCH_3$	$CHOCH_3$	7-methyltriazolopyridine	SeO_2, xylene	[143]
SEt	H	6-ethylthio-2-ethylsulfinylpyridine	2-Pyridyllithium	[39]
CHO	CHO	6,6′-dimethyl-2,2′-bipyridine	SeO_2	[135]
		6,6′-bis(bromomethyl)-2,2′-bipyridine	DMSO	[64]
$COCH_3$	$COCH_3$			[143]
CO_2H	CO_2H	6,6′-dimethyl-2,2′-bipyridine	SeO_2	[136]
H	CO_2CH_3	methyl 2-chloropyridine-6-carboxylate	2-(trimethylstannyl)pyridine, $(PPh_3)_2PdCl_2$	[93]
CN	CN	2,2′-bipyridine	MCPBA, $(CH_3)_3SiCN$, PhCOCl	[136]
CH_2NH_2	CH_2NH_2	6,6′-dicyano-2,2′-bipyridine	BH_3·THF	[56,136]
NH_2	NH_2	6,6′-dibromo-2,2′-bipyridine	Liq. NH_3	[141]
NH_2	$NHC_{12}H_{25}$	6,6′-diamino-2,2′-bipyridine	KOH, *n*-dodecyl bromide	[141]
$NHC_{12}H_{25}$	$NHC_{12}H_{25}$	6,6′-diamino-2,2′-bipyridine	NaH, *n*-dodecyl bromide	[141]

rivatives are the starting material for the incorporation of bipyridine into macrocycles[138] and can be prepared either by free-radical halogenation[55] or by treating the corresponding alcohols with thionyl halide.[139] Thus, the reduction of the 6,6′-dialdehyde gave the corresponding 6,6′-bis(carbinol), which could also be prepared by treating bis(*N*-oxide) with Ac_2O to afford the corresponding bis(acetate), followed by saponification with K_2CO_3 in EtOH. Treatment of the bis(carbinol) with redistilled $SOCl_2$[139] yielded the bis(chloromethyl) derivative.[55] 6,6′-Diamino-2,2′-bipyridine was synthesized from 6,6′-dibromo-2,2′-bipyridine (see above-described procedure)[137] in three steps by hydrazinolysis of the bromo functionalities in 95% yield. The resulting hydrazide groups were treated with HCl/$NaNO_2$ and yielded the bis(azide) (92%). Phase-transfer-catalyzed reduction of the azide groups with $NaBH_4$ afforded the diamino derivative (59%).[140,141]

The already described procedures of Siegel[25] and Constable[31,32] afford access to 6,6′-disubstituted 2,2′-bipyridines with new aromatic ligands. Recently, Kocovsky et al.[142] presented a coupling procedure, which uses a [$(PPh_3)_2NiCl_2$] catalyst, triphenylphosphane, and zinc to generate chiral diterpene-substituted 2,2′-bipyridines in yields up to 90%. Thummel et al. described in a recently published review chiral 2,2′-bipyridines, 1,10-phenanthrolines, and 2,2′:6′,2′′-terpyridines.[9]

Triazolopyridines react upon treatment with lithium reagents at −70 °C to form a 7-lithio dimer intermediate, which further gave rise to the 7,7′-bis(triazolo)pyridine (50%). Simple triazolopyridines gave free pyridines when treated with electrophiles, thus these 6−5 ring systems can be used to produce 2,2′-bipyridines. Treatment of 7,7′-bis-(triazolo)pyridine with aqueous sulfuric acid afforded a bis-(alcohol) derivative in 90% yield. While treatment of the dimer with hot glacial acid yielded a bis(acid) derivative in 70% yield and reaction with selenium dioxide in boiling xylene gave the bis(aldehyde) derivative in 74% yield (Scheme 27).[143]

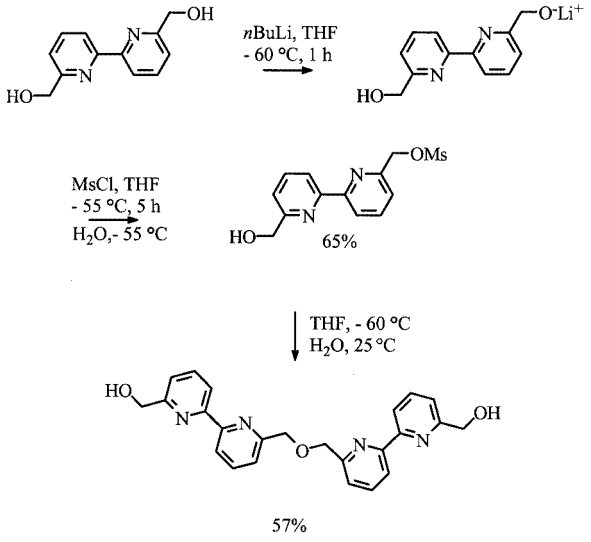




Scheme 27. Triazolopyridines, source for 2,2′-bipyridines

Reaction of 6,6′-dimethyl-2,2′-bipyridine with 1 equiv. of *m*-chloroperbenzoic acid gave the corresponding mono(*N*-oxide), which, when refluxed in Ac_2O, gave the monoacetate, which was hydrolyzed, affording the corresponding hydroxymethyl derivative.[55]

Newkome et al. described further selective derivatization of the 6,6′-bis(hydroxymethyl)-2,2′-bipyridine (Scheme 28).[144,145] The monolithiated intermediate could be selectively



Scheme 28. Selective derivatization of the 6,6′-bis(hydroxymethyl)-2,2′-bipyridine

precipitated under certain solvent/temperature/concentration conditions. Subsequent treatment with methanesulfonyl chloride gave the 6′-hydroxymethyl-6-[(methylsulfonyl)methyl]-2,2′-bipyridine (65%). If the monolithium salt was treated with LiBr, 6-bromomethyl-6′-hydroxymethyl-2,2′-bipyridine was isolated in 88% yield. Moreover, oligopyridines could be achieved by reaction of the bipyridine monolithium salt with the bipyridine mesylate in 52% yield.[144,145] The procedure of coupling 6-lithiomethyl-2,2′-bipyridine with 5,5′-bis(bromomethyl)-2,2′-bipyridine afforded oligopyridines (40%).[146]

A general route to synthesize 6,6′-alkoxy-2,2′-bipyridines was introduced by Shreeve et al. Reaction of MEC-31 [bis(*N*-fluoro)-2,2′-bipyridine tetrafluoroborate] with various non-fluorinated alcohols at 60 °C forms the respective 6,6′-alkoxy-2,2′-bipyridines in yields of 88−95%.[147]

6 Transformations of Functionalized Groups

Meyer et al. have synthesized[148] side-chain derivatives by functionalization of 4,4′-dimethyl-2,2′-bipyridine with *n*-butyllithium (Figure 7). The resulting equilibrium mixture of the respective mono- and dilithiated bipyridines was treated with a variety of electrophiles. It should be noted that less than 1 equiv. of *n*-butyllithium was used to minimize polymetalation. Reaction of the 4-(lithiomethyl)-4′-methylbipyridine with dry ice gave 4′-methyl-2,2′-bipyridine-4-acetic acid (66%), which is stable at 25 °C but has been shown to undergo facile decarboxylation upon warming.[148] This facile decarboxylation can be easily prevented by esterification using a BF_3·MeOH complex at 0 °C in order to form the methyl ester. The monolithiated bipyridine was also treated with 2-(2-bromoethyl)-1,3-dioxolane to generate the respective dioxolane derivative, which on acidic deprotection gave the 4-(3-formylpropyl)-4′-methyl-2,2′-bipyridine. Moreover, the latter compound could be transformed into different end groups by standard procedures. Oxidation of the aldehyde with $KMnO_4$ gave the corresponding carboxylic acid; whereas, reduction with $NaBH_4$ afforded the alcohol, which on further treatment with HBr was converted into the bromobutyl derivative. This lengthy route was reported to be of advantage for the preparation of bromobutyl derivatives,[148] compared to the treatment of the lithiated derivative of 4,4′-dimethyl-2,2′-bipyridine with 1,3-dibromopropane,[149] since purification was easier in the former. The two-step Gabriel synthesis[150] with the bromobutyl derivative gave the corresponding butylamine (90%). Further amino derivatives were accessible according to a Gabriel protocol utilizing potassium phthalimide, followed by hydrazinolysis in 90% yield.[119] Several other bromination methods of the side chains or methyl substituents of respective 2,2′-bipyridines were described by Sullivan et al.,[151] Balzani et al.,[152] and Kamachi et al.[153,154] by using *N*-bromosuccinimide or radical bromination applying different radical starters. Using the Boekelheide[97] rearrangement, 4,4′-dimethyl-2,2′-bipyridine was treated with MCPBA to form the mono(*N*-oxide) (section

5.2). Subsequent treatment with Ac_2O, followed by a hydrolysis with ethanolic sodium hydroxide resulted in 41% of 4-methyl-4′-hydroxymethyl-2,2′-bipyridine. Oxidation of the latter with MnO_2 gave the corresponding aldehyde (58%), previously synthesized in 32% yield by the SeO_2 oxidation of 4,4′-dimethyl-2,2′-bipyridine.[48,113] 4′-Aminomethyl-4-methyl-2,2′-bipyridine dihydrochloride was prepared (90%) by treatment of the aldehyde composition with $NH_2OH{\cdot}HCl$ and subsequent reduction (73%) of the oxime with Pd/C. 4′-Hydroxymethyl-4-methyl-2,2′-bipyridine can be easily transformed into the respective bromo derivative in 92% yield by treatment with aqueous HBr.

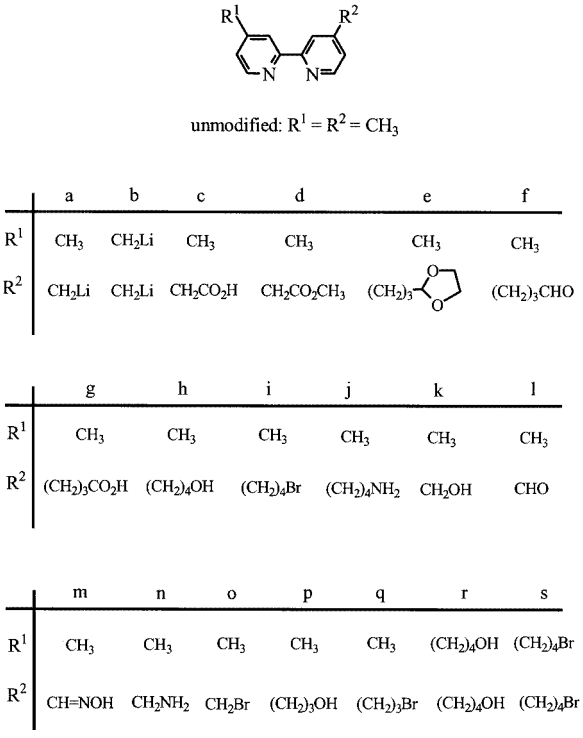
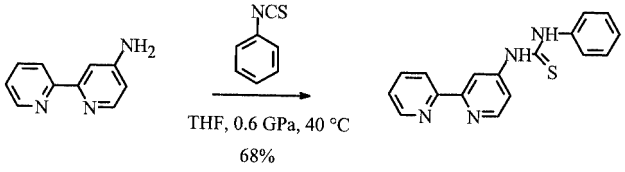


Figure 7. Side-chain derivatives

In distance-dependency studies on electron-transfer rates within tris(bipyridine)ruthenium(II) complexes, Mallouk et al. prepared several bromoalkyl derivatives with alkyl spacers from 4,4′-dimethyl-2,2′-bipyridine.[149] Thus, subjecting 4,4′-dimethyl-2,2′-bipyridine to ca. 1 equiv. of $LiN(iPr)_2$, followed by addition of ethylene oxide gave the 4-(3-hydroxypropyl)-4′-methyl-2,2′-bipyridine (78%). Subsequent treatment with HBr/acetic acid afforded the corresponding mono(bromopropyl) derivative (55%). Other bromoalkyl derivatives were directly prepared from 4,4′-dimethyl-2,2′-bipyridine by this selective monolithiation, followed by addition of dibromoalkanes in good yields (79−87%).[149] Sauvage et al.[69] converted 4,4′-bis(lithiomethyl)-2,2′-bipyridine into the corresponding bis(bromoalkyl) derivative via the diol derivative by treatment with HBr.

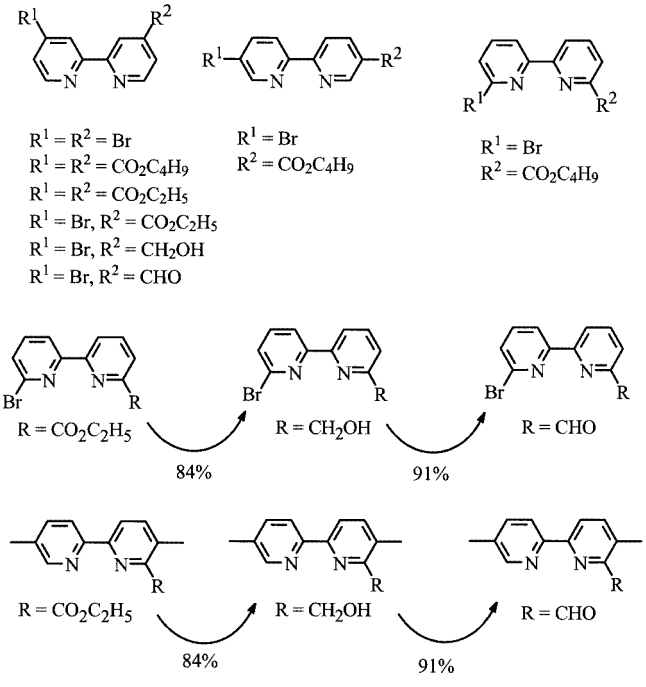
Amino acids of 2,2′-bipyridine are available by further derivatization of the bromomethyl derivative. Bowler et al. introduced a 2,2′-bipyridine amino acid synthesis[155] as well as a further derivatization to create metalloamino acids.[156] The respective bromobipyridine is coupled to *N*-(diphenylmethylene)glycin-*tert*-butyl ester. According to classical amino acid chemistry, the ligand was further derivatized to a BOC-protected amino acid that could be used as a chelating ligand in organometallic chemistry.

Using a high-pressure-promoted condensation with isothiocyanates, Kotsuki et al.[157] generated the thiourea derivatives in good yields. Starting with the 4-amino-2,2′-bipyridine and phenyl isothiocyanate, the thiourea was isolated in 68% yield. The reaction was performed in THF applying 0.6 GPa (Scheme 29).



Scheme 29. High-pressure-promoted condensation

Ziessel et al.[158] reported a general way to form polypyridine esters and their subsequent transformation to hydroxy and aldehyde groups as well as a convenient way to insert additional ester, hydroxy, and aldehyde functional groups into 5,5′-dimethyl-2,2′-bipyridine (Scheme 30). Reaction of 6-bromo-5′-dibromomethyl-2,2′-bipyridine with *n*-propylamine or *n*-decylamine and further conversion afforded 5′-alkylaminomethyl-2,2′-bipyridine derivatives in 30−85% yield.[159] Constable et al.[160] presented a Suzuki-type reac-



Scheme 30. Additional groups within 5,5′-dimethyl-2,2′-bipyridine

tion to prepare a 5,5′-bis(hydroxyphenyl)-2,2′-bipyridine from 5,5′-dibromo-2,2′-bipyridine[94] and 3-methoxyphenylboronic acid. Stille-type conditions are also very valuable to synthesize new modified 2,2′-bipyridines (section 4.2). 2,2′-Bipyridylstannane[83] was coupled to the respective chlorides with $Pd(PPh_3)_4$ in good yields (42 and 60%).[161,162] Utilizing dichloropyrimidine[129] or tetrachloronaphthyridine[130] derivatives, as new building units for grid-forming ligands could be obtained. 5-Bromomethyl-5′-methyl-2,2′-bipyridine serves as the chelating portion in podands as tripodal ligands; the reaction was conducted in DMF utilizing Cs_2CO_3 in 30−83% yield.[163] Other oligobipyridines of this type possessing a carboxylate and at least one bromoethyl group are synthesized by Ulrich et al.[164] As calixarenes are known to be good candidates for complexing neutral or organic guests in their cavities, or, when modified by incorporation of chelating arms, of various metal species, new bifunctional calix[4]arenes were obtained in 90% yield by coupling 6-bromomethyl-6′-methyl-2,2′-bipyridine and *p-tert*-butylcalix[4]arene utilizing BaO/$Ba(OH)_2$ in DMF.[165,166]

7 Conclusion

The growing interest in the field of supramolecular and macromolecular chemistry as well as nanoscience has led to the development of new strategies for the synthesis of various 2,2′-bipyridine derivatives. The main synthetic efforts were directed towards selective monofunctionalized and symmetrical and unsymmetrical bis(functionalized) 2,2′-bipyridine derivatives. Major synthetic success was made by applying coupling procedures such as Stille-type, Negishi-type, Suzuki-type reactions as well as using ring-assembling reactions like the Kröhne-type condensations. These reactions allow access to diverse 2,2′-bipyridines in high yields and controlled reaction conditions. The new and very versatile "library" of compounds presents the basis for a straightforward design of innovative materials, which bridge the organic/inorganic divide. The utility of this well-known bidentate in various branches of chemistry is currently expressed in new applications for photo-induced electron- and energy-transfer processes, dendrimer construction through connectivity, branching and self-assembly of supramolecular systems, functional polymers, molecular recognition systems, and new catalytic species. Several interesting new routes for bipyridine-containing nanodevices, nanoparticles, and novel metallopolymers with new favorable characteristics were described recently.[138,166−178]

Acknowledgments

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