Syntheses of Functionalized 2,2′:6′,2′′-Terpyridines

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Dedicated to Prof. Dr. George R. Newkome on the occasion of his 65th birthday

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2,2′:6′,2′′-Terpyridine compounds are important chelating ligands in a multitude of applications in the fields of supramolecular and macromolecular chemistry as well as electrochemistry. Therefore, a "pool" of functionalized terpyridine derivatives is essential. Classical and modern synthetic strategies towards terpyridine systems and novel functional 2,2′:6′,2′′-terpyridine compounds that originated in the last seven years are reviewed comprehensively.

Introduction

2,2′:6′,2′′-Terpyridine (TPY) has been extensively studied as an outstanding complexing agent for a wide range of transition metal ions. This multitude of potential applications is the result of a great advance in the design of terpyridine derivative in the last decade. The well-known characteristics of terpyridine metal complexes, such as their special redox and photophysical properties, depend on the electronic influence of the substituents. Therefore, terpyridine complexes may be used in photochemistry for the design of luminescent devices[1] or as sensitizers for light-to-electricity conversion.[2,3] Ditopic terpyridyl units may form polymetallic species which can be used to prepare luminescent or electrochemical sensors.[4,5] In clinical applications and

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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 PhD 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 NanoScience 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 Bayerische 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 interest relates to organic heterocyclic chemistry, supramolecular materials, combinatorial material research, nanoscience and tailor-made macromolecules.

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

biochemistry, functionalized terpyridines have found a wide range of potential uses,[6] ranging from colorimetric metal determination[7,8] to DNA binding agents[9−11] and antitumor research.[12−14]

Terpyridines have also been utilized for catalytic[15,16] and asymmetric catalytic[17] purposes. Another interesting topic regarding novel supramolecular architectures is the formation of "mixed complexes", where two differently functionalized terpyridine ligands are coordinated to one transition metal ion.[18−20] One of the most promising fields for new terpyridine compounds is their application in supramolecular chemistry.[21] In this context, the formation of supramolecular terpyridine-containing dendrimers[22−24] should be noted. Layer-by-layer self-assembly of extended terpyridine complexes on graphite surfaces forms grid-like supramolecular structures.[25−28] Self-assembly of terpyridine compounds on gold,[29] CdS,[30] or TiO_2,[31] as well as surface-functionalization with specially functionalized terpyridine ligands,[32] should also be mentioned in this context. Terpyridines incorporated in macromolecules enable the formation of well-defined supramolecular polymer architectures, opening the opportunity of switching the physical and chemical properties of materials.[19,20,33−38]

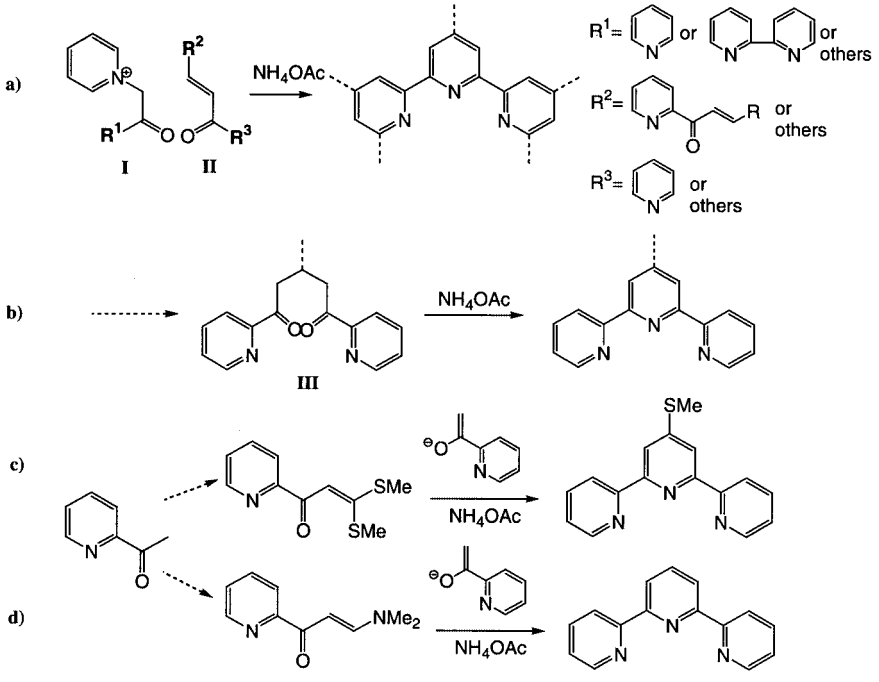
The use of 2,2′:6′,2′′-terpyridines for this wide range of potential applications and research areas requires a large "pool" of differently functionalized terpyridines. Therefore, a highly efficient and simple ligand synthesis is as essential as the well-defined derivatization at every ring position. Functional groups may be introduced directly in the course of the terpyridine preparation or by a variety of functional group conversion reactions. While the number of publications concerning applications or investigations of terpyridine complexes has increased enormously, comparably few preparations of functionalized 2,2′:6′,2′′-terpyridine ligand derivatives have been reported as yet. Cargill-Thompson reviewed the essential synthesis of terpyridine ligands up to 1996.[39] In this article both innovative synthetic strategies and "classical" methods for the synthesis of new 2,2′:6′,2′′-terpyridine derivatives are reported. In this review we do not cover new developments in the preparation of chiral terpyridines[17,40−42] or the synthesis of ditopic terpyridine-containing ligands.[43−50] (Terpyridine)metal complexes and supramolecular applications of the ligands are also outside the scope of this microreview and the reader is referred to corresponding publications.[21,33]

Synthetic Strategies

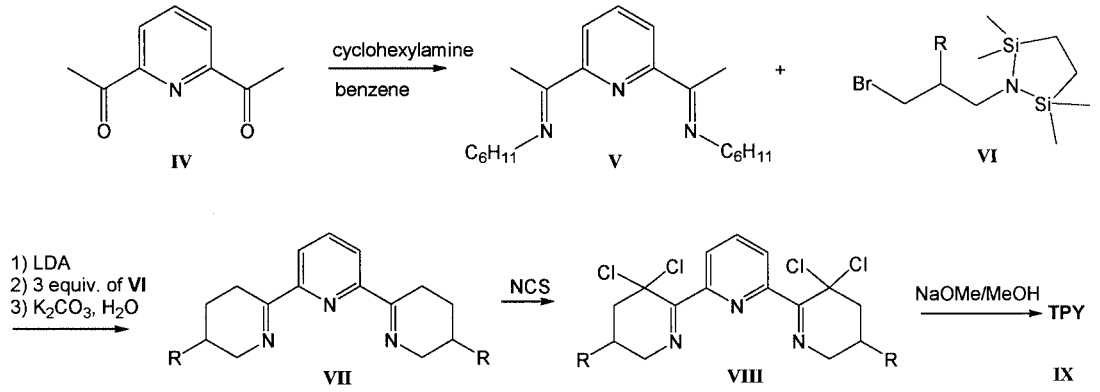
The two basic synthetic approaches to terpyridines are ring assembly and coupling methodologies. Ring assembly is still the most prevalent strategy, although modern palladium-catalyzed cross-coupling procedures have become seriously competitive over the last few years and may eventually supercede ring closure reactions due to their multiplicity and efficiency.

Ring Assembly

A set of terpyridine-forming ring assembly strategies has been developed over the last few decades. Frequently applied routes are displayed in Scheme 1. The most common preparation of terpyridines by ring assembly reaction is the well-known Kröhnke condensation, which involves the synthesis of *N*-heteropyridinium salts **I** and the subsequent ammonia condensation with an enone **II** (Scheme 1, a).[51,52] Further important methods are the construction of



Scheme 1

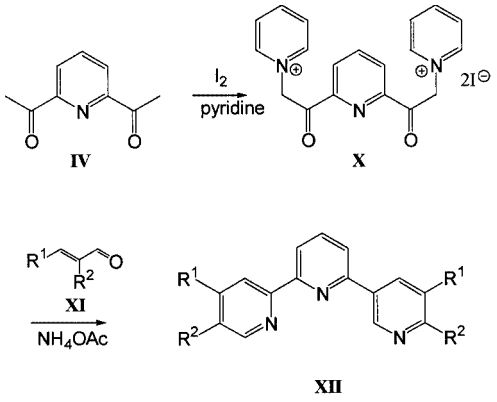


Scheme 2

1,5-diketones **III** and subsequent ring closure (Scheme 1, b),[53−55] the α-oxoketene dithioacetal methodology (Scheme 1, c),[52] and the Jameson method involving the condensation of a (dimethylamino)enone with the enolate of 2-acetylpyridine (Scheme1, d).[56] The common disadvantage of these methods is that the final condensation step usually yields tar-like crude products, which require special efforts in order to isolate and purify the desired terpyridine compounds.

High yields and good crude product purities are obtained by a four-step synthesis starting from the commercially available 2,6-diacetylpyridine (**IV**), which can be converted into 2,6-bis(*N*-cyclohexylacetimidoyl)pyridine (**V**) (multistep preparation described in the reference) by reaction with cyclohexylamine (Scheme 2).[57] Cyclization of **V** with Si-protected 3-bromopropylamines **VI** yields the tetrahydropyridines **VII**. After chlorination, the tetrachloro adducts **VIII** are converted into the terpyridines **IX** with an overall yield of 73−93% starting from **V**.

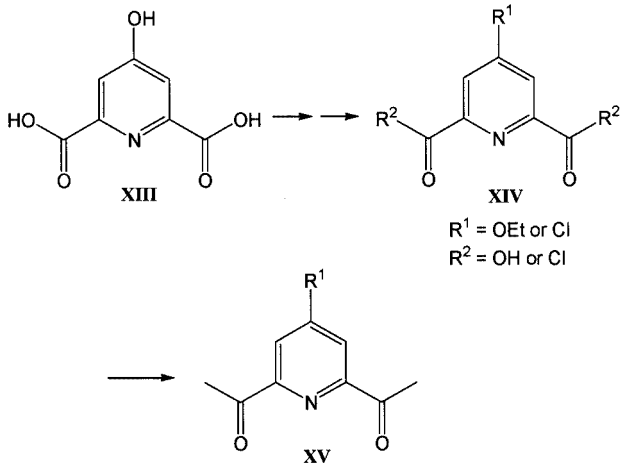
An effective and simple two-step synthesis of polysubstituted symmetric terpyridines including the Kröhnke reaction with 2,6-diacetylpyridine (**IV**) has been described by Sasaki et al. (Scheme 3).[58] Bis(pyridinium) iodide (**X**) was obtained from **IV** in 85% yield and was subsequently reacted with various α,β-unsaturated aldehydes **XI** at 80 °C for 4 h in formamide in the presence of ammonium acetate,



Scheme 3

yielding different symmetric terpyridines **XII** in 80−90% yield.

A novel 4-functionalized 2,6-diacetylpyridine **XV** as key intermediate for the Kröhnke methodology can be prepared from chelidamic acid (**XIII**) as starting material (Scheme 4).[59] Compound **XIII** is esterified to diethyl 4-chloropyridine-2,6-dicarboxylate which yields 4-ethoxypyridine-2,6-dicarbonyl dichloride (**XIV**) upon hydrolysis. The reaction with 2,2-dimethyl-1,3-dioxane-4,6-dione followed by hydrolysis with aqueous acetic acid resulted in the formation of 4-ethoxy-2,6-diacetylpyridine (**XV**) in 36% yield. Subsequent Kröhnke reactions yielded various 4′-substituted terpyridine derivatives.

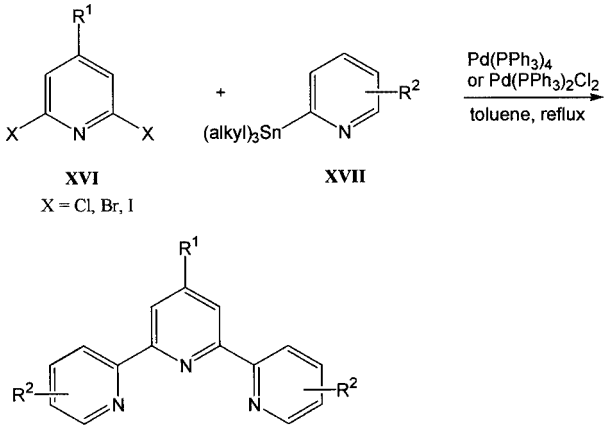


Scheme 4

Cross-Coupling Procedures

Over the last couple of years, appropriate methodologies for the construction of variously functionalized terpyridine ligands have been derived from directed cross-coupling procedures. Old-fashioned examples, like the cross-coupling of organosulfur compounds[60] or lithiated pyridines with $CuCl_2$,[61] have the disadvantage of poor yields. Modern palladium(0)-catalyzed coupling reactions combine the desired efficiency and simplicity with controllable substitution possibilities. Suzuki,[62] Negishi[63] and Stille couplings[64]

are all based on a Pd^0/Pd^{II} catalytic cycle. The Stille cross-coupling, in particular, has become a popular terpyridine preparation route, due to its universal building-block principle, its multigram product accessibility and the well-directed functionalization at almost every desired position of the terpyridine rings (Scheme 5).[65−68] 2,2′:6′,2′′-Terpyridines functionalized at the central and/or at the terminal pyridine rings can be obtained utilizing appropriate 2,6-dihalopyridines **XVI** as central building blocks; they can be treated with 2-(trialkylstannyl)pyridines **XVII** and palladium(0) catalysts in toluene for at least 24 h.



Scheme 5

Terpyridine synthesis by the Stille reaction can also be carried out by utilizing 2,6-bis(trimethylstannyl)pyridines (**XVIII**) as the central ring units and coupling them with the corresponding 2-bromopyridines (**XIX**) (Scheme 6).[69,70] Other palladium-catalyzed cross-coupling procedures have not yet been used for the synthesis of 2,2′:6′,2′′-terpyridines themselves, but also seem to be appropriate methods. A Negishi cross-coupling, for instance, has been used for the synthesis of terpyridine-related compounds[71] and of 2,2′-bipyridines[72] in excellent yields.

Synthesis of 2,2′:6′,2′′-Terpyridine Derivatives

Terpyridines may be functionalized at both the central and the terminal pyridine rings, and therefore the desired groups must be introduced using substituted starting compounds by ring assembly or coupling procedures. In this overview, the terpyridine derivatives are organized regarding their positions in the ring system.

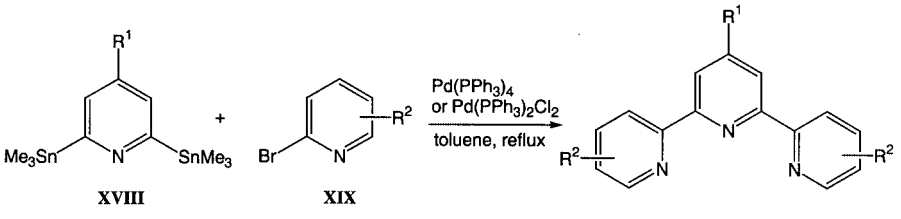
(I) 4′-Substituted 2,2′:6′,2′′-Terpyridinyl Ethers

4′-Terpyridinyl ethers are an important class of terpyridine derivatives due to their convenient accessibility from either nucleophilic aromatic substitution of 4′-haloterpyridines by any primary alcohols (and analogues) or condensation reactions with 4′-hydroxyterpyridines. A large variety of functional terpyridinyl ethers has been synthesised using these methods (Table 1).

Sampath et al. and Schubert et al. have reported a number of linear 4′-terpyridinyl ethers with terminal hydroxy (**1a**−**e**), carboxy (**1f**−**g**) (see also ref.[73]), *tert*-butoxy (**1h**), thio (**1i**) and amino groups (**1j**−**k**).[19,74,75] All these compounds were prepared in high yields (60−90%) by the reaction of an alcohol with a suspension of a base (KOH or NaH) in a polar nonprotic solvent (DMSO or DMF) and the subsequent introduction of 4′-chloro-2,2′:6′,2′′-terpyridine. The same route was utilized in order to synthesize 4′-(3-phenylpropoxy)terpyridine (**1l**).[76] The reaction of 4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl (OH-TEMPO) with 4′-chloro-2,2′:6′,2′′-terpyridine afforded the 4′-*O*-TEMPO-functionalized compound **1m**, a spin-labelled terpyridine.[77]

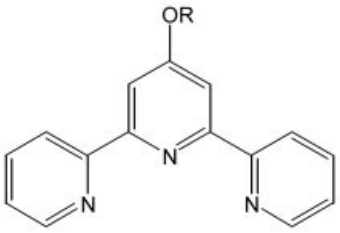
Constable et al. have reported the synthesis of the alkyne-functionalized terpyridine ligand **1n** by the reaction of 2,2′:6′,2′′-terpyridin-4′(1′*H*)-one with 3-bromoprop-1-yne (56% yield).[78,79] This compound was subsequently treated with $B_{10}H_{14}$ in acetonitrile. However, only poor yields of the desired carbaborane-functionalized terpyridine **1o** (n = 1) were reported.[79] A clearly more effective strategy for the preparation of carbaborane-functionalized terpyridine compounds is the reaction of 4′-hydroxy-2,2′:6′,2′′-terpyridine with 1-(3-iodopropyl)-*closo*-1,2-carbaborane in the presence of potassium carbonate. The ether **1o** (n = 3) can be obtained in 53% yield. In order to probe molecular recognition events by the functionalization of biomolecules by metal-binding sites, Constable et al. also presented a new class of terpyridine ligands in which a sugar is covalently linked to a terpyridine ligand.[50] Glucosides have been attached directly or spacer-linked to 4′-hydroxy-2,2′:6′,2′′-terpyridine by the use of α-bromo- or α-(bromoethyl)glucose and their tetraacetyl-protected derivatives. The sugar-functionalized terpyridines **1p** were isolated in 27 and 68% yield, respectively.[50] Furthermore, a protected galactose derivative was attached to the terpyridine unit at the 6-position of the sugar to give **1q** (52% yield).

Another example of sophisticated ether-linked functional groups is represented by the formation of a fullerene-func-

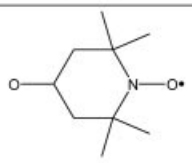
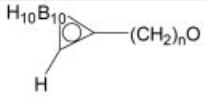
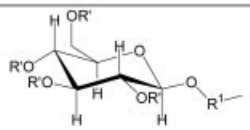
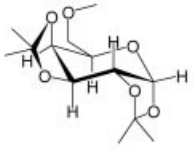
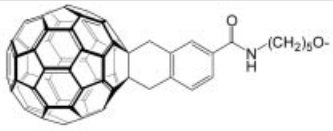
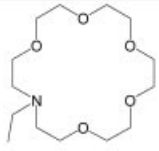
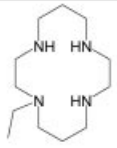
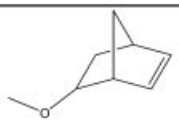


Scheme 6

Table 1. 4′-Terpyridinyl ethers



	R
1a[74]	$O(CH_2)_3OH$
1b[74,75]	$O(CH_2)_4OH$
1c[74, 75]	$O(CH_2)_6OH$
1d[74]	$O(CH_2)_8OH$
1e[74]	$O(CH_2)_{10}OH$
1f[73,74]	$O(CH_2)_3COOH$
1g[19,75]	$O(CH_2)_5COOH$
1h[75]	$O(CH_2)_4O^tBu$
1i[19,75]	$O(CH_2)_6SH$
1j[74]	$O(CH_2)_3NH_2$

	R
1k[19,75]	$O(CH_2)_5NH_2$
1l[76]	$O(CH_2)_3Ph$
1m[77]	
1n[78,79]	
1o[79]	 $n = 1,3$
1p[50]	 R′ = H, CH_3CO; R^1 = nothing or $(CH_2)_2O$.
1q[50]	
1r[75,80,81]	
1s[44]	
1t[45]	
1u[82]	

tionalized 4′-terpyridine **1r**, published by Schubert et al. in order to investigate the special electronic properties of such compounds. This compound was obtained by the reaction of **1k** with a fullerenecarboxylic chloride derivative in 47% yield.[80,81] The 4′-derivatization of terpyridines with aza-crown macrocycles may be important for their use as luminescent or electrochemical sensors[4] and the preparation of di- or multitopic terpyridine ligands.[44,45] Ward et al. have described the preparation of 4′-substituted and 4′-phenyl-substituted 2,2′:6′,2′′-terpyridines (see section II) with aza-18-crown-6 groups (**1s**) from the reaction of 4′-bromo-2,2′:6′,2′′-terpyridine and aza-18-crown-6 in 55% yield.[44] Martinez-Manez et al. have reported similar systems functionalized with 1,4,8,11-tetraazacyclotetradecane (**1t**) from the reaction of 4′-(bromomethyl)-2,2′:6′,2′′-terpyridine (see chapter III, **3bb**) and cyclam in 50% yield.[45]

The norbornene-functionalized 4′-terpyridinyl ether (**1u**) was prepared in 61% yield from 4′-chloro-2,2′:6′,2′′-terpyridine and 5-norbornene-2-methanol by a Williamson ether linkage.[82]

(II) 4′-Aryl-Substituted 2,2′:6′,2′′-Terpyridines

A series of 2,5-disubstituted 4′-arylterpyridines **2a** has been prepared by Colbran et al. starting from 4′-(2,5-dimethoxyphenyl)-2,2′:6′,2′′-terpyridine (see also ref.[83]), which was deprotected with hydrobromic acid to yield the hydroquinonyl ligand (Table 2).[84,85] The following conversions were carried out with the $Ru^{II}(PF_6)_2$ complex of the 2,5-dihydroxy-substituted 4′-aryl-2,2′:6′,2′′-terpyridine: the 2,5-diphenyl diester of **2a** was obtained upon reaction with benzoyl chloride, the 2,5-diethyl diester upon reaction with propionyl chloride in the presence of pyridine and the 2,5-dibenzyl derivative was obtained upon reaction with benzyl chloride.

Lo et al. have described the introduction of a 4′-(*p*-aminoaryl) group, **2b**, from the corresponding nitror compound (see ref.[86]) by reaction with hydrazine monohydrate and palladium on charcoal (see also ref.[87]).[88] In a mixed $Ir^{III}(PF_6)_3$ complex containing **2b**, the amino function was then transformed into an isothiocyanate group, **2c**, by reaction with $CSCl_2$ in the presence of $CaCO_3$ in acetone. 4′-[4-(2,3,4,5-Tetramethylcyclopenta-1,3-dien-1-yl)phenyl]-2,2′:6′,2′′-terpyridine has been prepared by the group of Siemeling[89] in order to transform this compound into the corresponding ferrocene **2d** after lithiation and reaction with iron(II) chloride. The formation of boronic acid functionalized 4′-arylterpyridines has been reported by Williams et al. Bis(pinacolato)diboron was treated with 4′-(4-bromophenyl)-2,2′:6′,2′′-terpyridine to form **2e**.[90] The analogous neopentyl ester **2f** was obtained from the reaction of the (bromophenyl)terpyridine with bis(neopentylglycolato)diboron (as shown in chapter III for the ligand **3w**). Compound **2f** was then hydrolyzed in order to prepare the boronic acid derivative **2g**.

4′-(4-Fluorophenyl)-2,2′:6′,2′′-terpyridine (**2h**), an arylterpyridine with an electron-releasing aryl substituent, has been prepared from a two-step ring-closure reaction with 2-acetylpyridine and 4-fluorobenzaldehyde as starting materials (step 1: 29%; step 2: 64%).[91]

4′-(4-*tert*-Butylphenyl)-2,2′:6′,2′′-terpyridine (**2i**) has been prepared by Constable et al. as an oligopyridine with enhanced solubility properties.[92,93] The authors utilized the same method as described for **2h**, starting with 2-acetylpyridine and 4-*tert*-butylbenzaldehyde (step 1: 40%; step 2: 73%).

Jing et al. have reported the synthesis of 4-(2,2′:6′,2′′-terpyridin-4′-yl-phenyl)phosphonic acid (**2k**). This compound was obtained from 4′-[*p*-$(OEt)_2$OP-phenyl]-2,2′:6′,2′′-terpyridine (**2j**) (see also ref.[94]) by saponification with HCl in 87% yield.[95] The 4′-(dicyanoaryl)-functionalized terpyridine **2m** was synthesized in a seven-step synthesis.[96] The bromo-functionalized terpyridine precursor **2l** was obtained after the sixth step of the Kröhnke methodology. The desired compound **2m** was then synthesized by a Rosenmund-von-Braun reaction of **2l**.

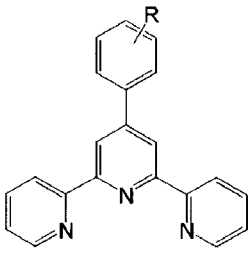
4′-[4-(Bromomethyl)phenyl]-2,2′:6′,2′′-terpyridine is the starting compound for the synthesis of 4′-[4-(hydroxymethyl)phenyl]-2,2′:6′,2′′-terpyridine (**2o**).[97] Because direct substitution of the bromo group turned out to be impracticable, an indirect pathway by an acetolysis of the bromo group with acetic acid and sodium acetate was used to yield 85% of 4′-(4-acetoxymethylphenyl)-2,2′:6′,2′′-terpyridine (**2n**), which was subsequently saponified to form the desired product **2o** (65% yield).[97] 4′-Arylterpyridines functionalized in the *para* position with different alkyne substituents have been descorbed by Constable et al. Different alkynes [HC≡CCH_2OH, HC≡CH, HC≡C(TMS)] were coupled with 4′-(4-bromophenyl)-2,2′:6′,2′′-terpyridine in the presence of $[PdCl_2(PPh_3)_2]$, CuI and NEt_3 to obtain the compounds **2p** with yields between 52 and 78%.[78]

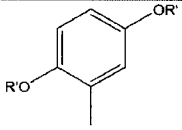
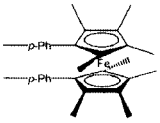
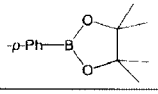
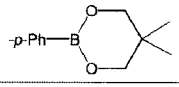
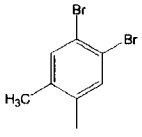
Ether substituents also play an important role for 4′-aryl-substituted terpyridines due to their easy accessibility by substitution and condensation reactions. Hanabusa et al. have reported the synthesis of a series of terpyridine-4′-aryl-*p*-carboxylic acids; *para*-, *meta*- and *ortho*-4′-[(phenyl)(hydroxycarbonyl)pentyloxy]-2,2′:6′,2′′-terpyridines (**2r**−**s**) were obtained from the corresponding 4-, 3- and 2-hydroxy compounds **2q**, respectively,[86,98] with 6-bromohexanoate (and homologues) or by using a modification of Kröhnke's method.[98]

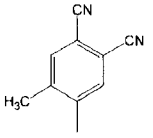
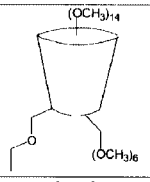
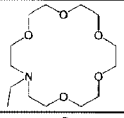
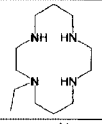
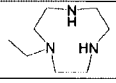
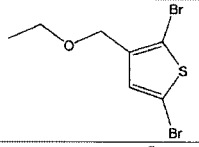
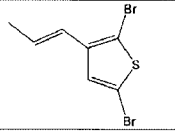
Pikramenou et al. and Haider et al. have investigated the creation of long-lived charge-separated states by the attachment of cyclodextrin receptors to terpyridine ligands that coordinate to metal ions.[99−101] Protection of all but one hydroxy group of the β-cyclodextrin cups by methylation and subsequent reaction with 4′-(4-bromomethylphenyl)-2,2′:6′,2′′-terpyridine in THF in the presence of NaH yielded 71% of the desired 4′-cyclodectrin-functionalized terpyridine **2t**.

As in section I (**1s**−**t**), macrocycles can also be attached to 4′-aryl-substituted 2,2′:6′,2′′-terpyridines. Ward et al. have described the preparation of 4′-phenyl-substituted terpyridines with aza-18-crown-6 groups **2u**.[44] Martinez-Manez et al. have reported similar systems functionalized with 1,4,8,11-tetraazacyclotetradecane (**2v**).[45]

Table 2. 4′-Aryl-substituted terpyridines



	R
2a[84]	 R′ = CH_3, H, C(O)Ph, C(O)Et, CH_2Ph
2b[88]	*p*-C_6H_4-NH_2
2c[88]	*p*-C_6H_4-NCS
2d[89]	
2e[90]	
2f[90]	
2g[90]	$B(OH)_2$
2h[91]	*p*-F
2i[92,93]	*p*-*t*Bu
2j[95]	*p*-$PO(OEt)_2$
2k[95]	*p*-PO_3H
2l[95]	

	R
2m[96]	
2n[97]	*p*-$CH_2OC(O)CH_3$
2o[97]	*p*-CH_2OH
2p[78]	 X = CH_2OH, H, TMS
2q[86, 98]	*p*-OH
2r[98]	*p*-$O(CH_2)_nCOOR'$ *n* = 3,5,7,10; R′ = Et, H
2s[98]	*m*/*o*-$O(CH_2)_5COOR'$ R′ = Et, H
2t[99-101]	
2u[44]	
2v[45]	
2w[102]	
2x[14]	
2y[14]	

The azamacrocyclic ligand 4′-[*p*-(1,4,7-triazacyclonon-1-ylmethyl)phenyl]-2,2′:6′,2′′-terpyidine (**2w**) has been prepared by Moore et al. by conversion of 4′-[4-(bromomethyl)phenyl]-2,2′:6′,2′′-terpyridine with "capped" 1,4,7-triazacyclononane in THF in 83% yield.[102]

Jones et al. have prepared dibromothiophene-functionalized terpyridine luminescent receptor sites.[14] 4′-{[4-(2,5-Dibromothiophen-3-yl)methoxymethyl]phenyl}-2,2′:6′,2′′-terpyridine (**2x**) was synthesized from NaH, (2,5-dibromothiophen-3-yl)methanol and 4′-[4-(bromomethyl)-phenyl]-2,2′:6′,2′′-terpyridine in 60% yield. 4′-{4-[2-(2,5-Dibromothiophen-3-yl)vinyl]phenyl}-2,2′:6′,2′′-terpyridine (**2y**) was also prepared from the bromomethyl derivative with triethyl phosphite and 2,5-dibromothiophene-3-carbaldehyde (80% yield).

(III) Other 4′-Functionalized Terpyridines

Phosphane-functionalized terpyridine entities are known to complex many different transition metal ions and to bind strongly to certain semiconductors.[103] 4′-(Diphenylphosphanyl)-2,2′:6′,2′′-terpyridine (**3a**) has been obtained by the treatment of 4′-chloro-2,2′:6′,2′′-terpyridine with Li(PPh_2) in THF (Table 3).[104] Diethyl (2,2′:6′,2′′)-terpyridine-4′-phosphonate (**3b**) (see also ref.[105]) could be prepared from 4′-bromo-2,2′:6′,2′′-terpyridine by replacing the bromo group with phosphonate groups utilizing HPO_3Et_2 in the presence of $Pd(PPh_3)_4$.[106,107]

The 4′-$CH_2P(O)Ph_2$-functionalized terpyridine **3c** has been synthesized starting from 4′-methyl-2,2′:6′,2′′-terpyridine, which was treated with LDA and PPh_2Cl, followed by oxidation with $NaIO_4$. A double Wittig−Horner coupling then led to carotene-substituted terpyridine ligands.[107] 4′-[Bis(diphenylphosphanyl)methyl]-2,2′:6′,2′′-terpyridine (**3e**) has been obtained by treatment of the mono(diphenylphosphanyl) compound **3d** with LDA and Ph_2PCl (**3d** was prepared by the same method from 4′-methyl-2,2′:6′,2′′-terpyridine).[108]

4′-(Phthalimidopropylsulfanyl)-2,2′:6′,2′′-terpyridine (**3f**) and the 4′-[2-(1,3-dioxolan-2-yl)ethylsulfonyl] compound **3g** have been synthesized from acetylpyridine, CS_2 and the corresponding alkyl halides by Sampath et al.[74] Subsequently, the cyclic protective groups were converted into several 4′-alkylsulfanyl derivatives with amino (**3h**), hydroxy (**3i**), halo (**3j**) and aldehyde (**3k**) groups. 4′-Alkyl-based functional groups (**3l**−**p**) were introduced by deprotonation of 4′-methyl-2,2′:6′,2′′-terpyridine and subsequent reaction with the corresponding alkyl halide. Maskus et al. have reported the synthesis of 5-[(2,2′:6′,2′′)-terpyridin-4′-yl]pentane-1-thiol (**3r**) by consecutive treatment of the corresponding 5-chloropentyl compound **3q** with NaOH and dilute sulfuric acid;[32] **3q** was obtained from 4′-methyl-2,2′:6′,2′′-terpyridine after deprotonation and reaction with 1-bromo-4-chlorobutane.

Padilla-Tosta et al. have reported the preparation of 4′-[2-ferrocenyl-2-hydroxyethyl]-2,2′:6′,2′′-terpyridine (**3s**), which was obtained by addition of ferrocenecarbaldehyde to 4′-methylterpyridine in the presence of LDA in 80% yield.[109] Dehydration of the product yielded 25% of the corresponding 4′-(ferrocenylvinyl)-2,2′:6′,2′′-terpyridine (**3t**) (see also refs.[110,111]).

Ziessel et al. have reported the synthesis of 2,2′:6′,2′′-terpyridine frameworks substituted with L-tyrosine fragments **3u**.[112] Thus, optically active L-tyrosyl moieties bearing an iodo functionality were cross-coupled with 4′-ethynyl-2,2′:6′,2′′-terpyridine[113] in the presence of $[PdCl_2(PPh_3)_2]$ (R = H: 42%; R = COPh: 49%).

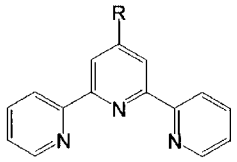
Williams et al. have synthesized 4′-boronate ester substituted 2,2′:6′,2′′-terpyridine ligands utilizing the palladium-catalyzed Miyaura[62] cross-coupling reaction.[90] Ligand **3v** was prepared from 4′-bromo-2,2′:6′,2′′-terpyridine bis(neopentylglycolato)diboron, KOAc and [1,1′-bis(diphenylphosphanyl)ferrocene]palladium dichloride $[PdCl_2(dppf)_2]$ in 69% yield. Butyl 2,2′;6′,2′′-terpyridine-4′-carboxylate (**3w**) was obtained in 76% yield by refluxing 4′-{[(trifluoromethyl)sulfonyl]oxy}-2,2′:6′,2′′-terpyridine,[114] *n*BuOH and Bu_3N.[115,116] Fallahpour et al. have utilized the Stille reaction to introduce nitro and amino groups into the 4′-position of the terpyridine ligands.[87] For this purpose, 2,6-dibromo-4-nitropyridine, which was obtained from 2,6-dibromopyridine *N*-oxide, was coupled with 2-(tributylstannyl)pyridine to yield 4′-nitro-2,2′:6′,2′′-terpyridine (**3x**) (68%). Reduction of **3x** with hydrazine hydrate in the presence of palladium on charcoal resulted in the formation of 4′-amino-2,2′:6′,2′′-terpyridine (**3y**) (76%). 4′-Azido-2,2′:6′,2′′-terpyridine (**3z**) was obtained by conversion of the 4′-nitroterpyridine (**3x**) with sodium azide in DMF (70%).[117]

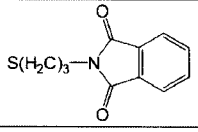
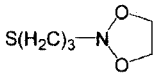
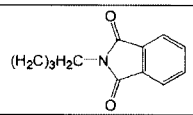
4′-(Hydroxymethyl)-2,2′:6′,2′′-terpyridine (**3aa**) has been synthesized by Martinez-Manez et al. by the reduction of 2,2′:6′,2′′-terpyridine-4′-carboxaldehyde [52] with $NaBH_4$ in THF in 85% yield.[45,109] The reaction of **3aa** with carbon tetrabromide and triphenylphosphane in CH_2Cl_2 yielded 40% of 4′-(bromomethyl)-2,2′:6′,2′′-terpyridine (**3bb**).

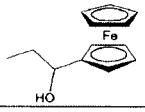
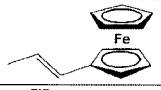
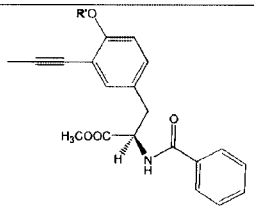
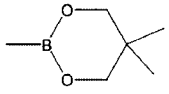
2-Furyl (**3cc**), 3-furyl (**3dd**), 2-thienyl (**3ee**) and 3-thienyl (**3ff**) moieties have been attached to the 4′-position of 2,2′:6′,2′′- and other terpyridine structures.[118] For the preparation, 2-furaldehyde, 3-furaldehyde, 2-thiophenecarboxaldehyde or 3-thiophenecarboxaldehyde was treated with 2-acetylpyridine in the presence of KOH in a methanol/water mixture. The obtained intermediates were converted into the corresponding terpyridines in a 57−78% yield utilizing a modified Kröhnke synthesis. 4′-(2-Thienyl)-2,2′:6′,2′′-terpyridine (**3ee**) has also been prepared by Constable et al. by a one-pot ring-closure reaction of 2 equiv. of 2-acetylpyridine and 2-thiophenecarbaldehyde, via an intermediate diketone, in 40% yield.[119]

Thermally induced [4+2] cycloaddition reactions between 3,5-bis(2-pyridyl)-1,2,4-triazine and tributyl(ethynyl)-tin have allowed the regioselective introduction of a tributylstannyl group, yielding 73% of 4′-tributylstannyl-2,2′:6′,2′′-terpyridine (**3gg**).[120] As described in chapters IV and V, this method also enables the tributylstannyl functionalization of the terminal rings.

Table 3. Other 4′-functionalized 2,2′:6′,2′′-terpyridines



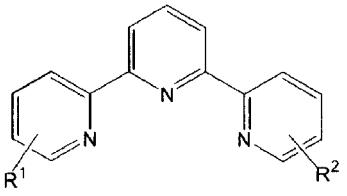
	R
3a[104]	PPh_2
3b[106]	PO_3Et_2
3c[107]	$CH_2P(O)Ph_2$
3d[107]	CH_2PPh_2
3e[107]	$CH(PPh_2)_2$
3f[74]	
3g[74]	
3h[74]	$S(CH_2)_3NH_2$
3i[74]	$S(CH_2)_3OH$
3j[74]	$S(CH_2)_2Cl$
3k[74]	$S(CH_2)_2CHO$
3l[74]	$(CH_2)_3CHO$
3m[74]	$(CH_2)_3CH_2OH$
3n[74]	$(CH_2)_3CH_2Br$
3o[74]	
3p[74]	$(CH_2)_3CH_2NH_2$

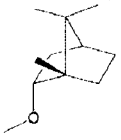
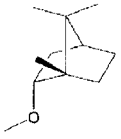
	R
3q[32]	$(CH_2)_5Cl$
3r[32]	$(CH_2)_5SH$
3s[109]	
3t[109]	
3u[112]	 L-tyrosine fragments, R′ = H, COPh
3v[90]	
3w[115,116]	$CO_2C_4H_9$
3x[87]	NO_2
3y[87]	NH_2
3z[117]	N_3
3aa[45,109]	CH_2OH
3bb[109]	CH_2Br
3cc[118]	
3dd[118]	
3ee[118,119]	
3ff[118]	
3gg[120]	$SnBu_3$

(IV) Unsymmetrically Terminal Substituted Terpyridines

A pair of enantiomeric 6-bornyloxy-6′′-methyl-functionalized terpyridine ligands **4b** has been prepared by Constable et al. from the reaction of 6-bromo-6′′-methyl-2,2′:6′,2′′-terpyridine (**4a**) (which was synthesized by the Kröhnke methodology according to ref.[121]) with the sodium salts of (1*S*)-(−)- or (1*R*)-(+)-borneol in 58% yield (Table 4).[122] A similar method was used for the preparation of the chiral monosubstituted 6-bornyloxy-2,2′:6′,2′′-terpyridines **4c** from 6-bromo-2,2′:6′,2′′-terpyridine.[121,123] The same authors have also reported the preparation of 6-phenyl- and 4,6-diphenyl-substituted 2,2′:6′,2′′-terpyridines (**4d**) (66%), (**4e**) (71%) utilizing the Kröhnke methodology.[124]

Table 4. Terminal substituted terpyridines (unsymmetric)



	R^1	R^2
4a[122]	6-Br	6"-CH_3
4b[122]	 *R* + *S*	6"-CH_3
4c[123]	 *R* + *S*	6"-H
4d[124]	6-Ph	6"-H
4e[124]	6-Ph + 4-Ph	6"-H
4f[120]	4-$SnBu_3$	4"-H
4g[120]	4-Br or 4-I	4"-H

By the use of the appropriate tailor-made 1,2,4-triazines, Sauer et al. have synthesized 4-tributylstannyl-2,2′:6′,2′′-terpyridine (**4f**) in a [4+2] cycloaddition with tributyl(ethynyl)tin in 54% yield.[120] Subsequently, the tributylstannyl group was converted into a bromo or iodo group with Br_2 or I_2 at −60 °C, yielding 69% and 61% of the corresponding terpyridines **4g**, respectively.

(V) Symmetrical Terminally Substituted Terpyridines

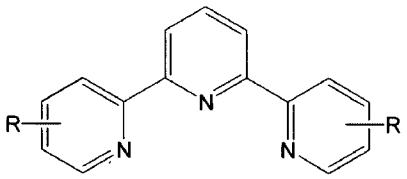
The synthesis of 6,6′′-dimethyl-2,2′:6′,2′′-terpyridine[54] (**5a**) was improved by a Stille-type cross-coupling of 2,6-dibromopyridine and 2-(tributylstannyl)-6-methylpyridine, which yielded 43% of **5a** (Table 5).[68] Constable et al. have used a Kröhnke ring-closure reaction of different Mannich salts to yield 63% of **5a**.[124] The authors have also utilized the same method for the preparation of 6,6′′-diphenyl-2,2′:6′,2′′-terpyridine (**5b**) with a Mannich salt and *N*-phenacylpyridinium bromide (56% yield). Ring closure of the bis(chalcone) of 2,6-diacetylpyridine and *N*-phenacyl- or *N*-methylpyridinium bromide resulted in the analogous 4,4′′-substituted compounds **5c** (71%) and **5d** (61%). Elghayoury and Ziessel have described the preparation of 6,6′′-di-*n*-butoxydicarbonyl-2,2′;6′,2′′-terpyridine (**5e**) from 6,6′′-dibromo-2,2′:6′,2′′-terpyridine, CO and [$PdCl_2(PPh_3)_2$] in *n*BuOH and nBu_3N (50% yield).[115][116] Reduction of **5e** with $NaBH_4$ resulted in an 88% yield of 6,6′′-bis(hydroxymethyl)-2,2′:6′,2′′-terpyridine (**5f**). Subsequent oxidation of **5f** with oxalyl chloride and DMSO in dichloromethane yielded 86% of 6,6′′-diformyl-2,2′:6′,2′′-terpyridine (**5g**). Benniston et al. have published the preparation of 6,6′′-bis[4-(hydroxymethyl)phenyl]-2,2′:6′,2′′-terpyridine (**5h**) by a ring-forming reaction.[125]

A Stille cross-coupling has also been used to improve the synthesis of 5,5′′-dimethyl-2,2′:6′,2′′-terpyridine[126] (**5i**). Savage et al. coupled 2-trimethylstannyl-5-methylpyridine and 2-bromo-5-methylpyridine to yield 67% of **5i**.[72] Schubert et al. have instead utilized 2-tributylstannyl-5-methylpyridine and 2-bromo-5-methylpyridine to yield 90% of the 5,5′′-dimethyl-2,2′:6′,2′′-terpyridine.[127] Subsequent bromination with NBS and AIBN in CCl_4 gave 30% of 5,5′′-bis(bromomethyl)-2,2′:6′,2′′-terpyridine (**5j**). These same authors have also described the synthesis of 4,4′′-dimethyl-2,2′:6′,2′′-terpyridine (**5k**) by a Stille-type cross-coupling (52%).[68]

The highly unusual 3,3′′-positions have been functionalized by Benniston et al. in order to introduce functionality from the "back side" of the chelator.[125][128] 3,3′′-Di-*p*-tolyl-2,2′:6′,2′′-terpyridine (**5l**) was obtained from a six-step synthesis including coupling and ring-closure reactions.

Potvin et al. have described the synthesis of different 4,4′′,6,6′′-tetra-substituted terpyridines **5m**.[129] 6,6′′-Bis[4-(ethoxycarbonyl)phenyl]-4,4′′-diphenyl-2,2′:6′,2′′-terpyridine was obtained from a double Kröhnke reaction in 80% yield. 4,6,4′′,6′′-Tetraphenyl-2,2′:6′,2′′-terpyridine (98%) and 6,6′′-bis(4-methoxyphenyl)-4,4′′-diphenyl-2,2′:6′,2′′-terpyridine (90%) were prepared in the same manner. Starting from 5,5′′-dimethyl-2,2′:6′,2′′-terpyridine, Sasaki et al. have described the synthesis of 5,5"-bis[(dimethylamino)methylidene]-2,2′:6′,2"-terpyridine (**5n**) and 5,5"-diformyl-2,2′:6′,2"-terpyridine (**5o**).[58] The authors utilized *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent) to form compound **5n** in 47% yield by heating 5,5′′-dimethyl-2,2′:6′,2′′-terpyridine in DMF for several days. The formyl derivative **5o** was then obtained in 51% by oxidation of **5n** with $NaIO_4$. By the use of 4,4′′,5,5′′-tetramethylterpyridine, which was obtained — as was 5,5′′-dimethyl-4,4′′-diphenyl-2,2′:6′,2′′-terpyridine — by the Kröhnke procedure, the same authors synthesized the fol-

Table 5. Terminal substituted terpyridines (symmetric)



	R
5a[68,124]	6,6"-CH_3
5b[124]	6,6"-Ph
5c[124]	4,4"-Ph / 6,6"-Ph
5d[124]	4,4"-CH_3 / 6,6"-Ph
5e[115,116]	6,6"-$CO_2C_4H_9$
5f[115,116]	6,6"-CH_2OH
5g[115,116]	6,6"-CHO
5h[125]	6,6"-*p*-C_6H_4-CH_2OH
5i[72,127]	5,5"-Me

	R
5j[127]	5,5"-CH_2Br
5k[68]	4,4"-CH_3
5l[125,128]	3,3"-*p*-C_6H_4-CH_3
5m[129]	4,4"-Ph / 6,6"-*p*-Ph-R' R' = COOH, COOEt, H, OMe
5n[58]	5,5"-CH=CHN$(CH_3)_2$
5o[58]	5,5"-CHO
5p[58]	4,4"-R' / 5,5"-CH_3 R' = Ph, CHO, CH=CHN$(CH_3)_2$, CH_2OH, CO_2CH_3, CH_3, H
5q[120]	4,4"-$SnBu_3$
5r[120]	4,4"-Br, 4,4"-I

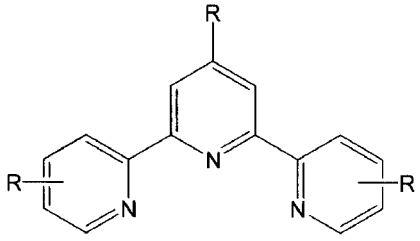
lowing terpyridines, summarized as **5p**: 4,4"-diformyl-5,5"-dimethyl-2,2′:6′,2"-terpyridine by oxidation with H_2SeO_3 (42%) and 4,4"-bis[(dimethylamino)methylidene]-5,5"-dimethyl-2,2′:6′,2′′-terpyridine by conversion with Bredereck's reagent in 67% yield. This compound was reduced with $NaBH_4$ in order to obtain the corresponding hydroxymethyl compound (77% yield).

As described in chapter IV, Sauer et al. have prepared 4,4′′-bis(tributylstannyl)-2,2′:6′,2′′-terpyridine (**5q**) from 2,6-bis(1,2,4-triazin-3-yl)pyridine and tributyl(ethynyl)tin in 47% yield. Upon subsequent treatment with Br_2 or I_2, they obtained the corresponding bromo and iodo compounds **5r** in 79% and 53% yield, respectively.[120]

(VI) Uniform All-Ring Substituted Terpyridines

A symmetrically functionalized 2,2′:6′,2′′-terpyridine with one chloro atom at each pyridine ring (**6b**) has been prepared by Cummings et al.[130] (Table 6). Starting from 4,4′,4′′-trinitro-2,2′:6′,2′′-terpyridine *N*-oxide (**6a**) and an excess of acetyl chloride in glacial acetic acid, compound **6b** could be obtained in 70% yield (according to a method described by Case et al.[131]); 4,4′,4′′-, 4′,5,5′′- and 4′,6,6′′-trimethyl-substituted terpyridines (**6c**−**e**) (for **6c** see also ref.[132]) have been synthesized in 50−60% yield using a Stille-type cross-coupling between the corresponding 4-, 5- or 6-methyl-2-(tributylstannyl)pyridines and 2,6-dibromo-

Table 6. Uniform all-ring substituted terpyridines



	R
6a[130]	4,4',4"-NO_2 *N*-oxide
6b[130]	4,4',4"-Cl
6c[66, 132]	4,4',4"-CH_3
6d[66]	4',5,5"-CH_3
6e[66]	4',6,6"-CH_3
6f[134]	4,4',4"-(5-nonyl)
6g[125]	4,4',4"-Ph

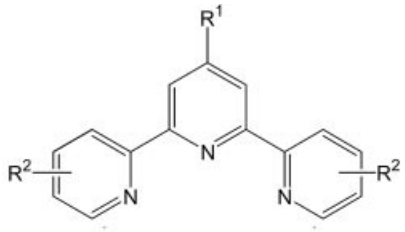
4-methylpyridine.[66] 4,4′,4′′-Tris(5-nonyl)-2,2′:6′,2′′-terpyridine (**6f**) has been obtained by a palladium-catalyzed coupling of 4-(5-nonyl)pyridine.[133,134] A Kröhnke con-

densation has been used to synthesize 4,4′,4′′-triphenyl-derivatized 2,2′:6′,2′′-terpyridine (**6g**).[125]

(VII) Multifunctional Terpyridines with Variable Substituents

2,2′:6′,2′′-Terpyridines bearing different functional groups at the 4′-position and at the outer pyridine rings have recently become an expanding field of terpyridine derivative preparation (Table 7). Fallahpour et al. have reported the treatment of 2,6-diacetyl-4-ethoxypyridine with paraformaldehyde and dimethylamine in DMF to yield a Mannich salt as pink crystals in 71% yield.[59,135] Its reaction with *N*-(methylacetyl)pyridinium chloride in ethanol readily resulted in the formation of 4′-ethoxy-6,6′′-dimethyl-2,2′:6′,2′′-terpyridine (**7a**) in 56% yield. Similar Kröhnke preparations gave compounds **7b**−**7d**. The ether protecting group of **7b** was cleaved in pyridine and HCl to give 4′-hydroxy-5,5′′-dimethyl-2,2′:6′,2′′-terpyridine (**7e**) in 50% yield.

Table 7. Multifunctional terpyridines with variable substituents



	R^1	R^2
7a[59,135]	OCH_2CH_3	6,6"-CH_3
7b[59,135]	OCH_2CH_3	5,5"-CH_3
7c[59,135]	OCH_2CH_3	4,4"-CH_3
7d[59,135]	OCH_2CH_3	6,6"-CH_3, 4,4"-*p*-toluene
7e[59,135]	OH	5,5"-CH_3
7f[67]	$COOCH_2CH_3$	6,6"-CH_3
7g[67]	$COOCH_2CH_3$	6,6"-CH_2Br
7h[136] [68] [67]	COOH or $COOCH_3$ or $COOCH_2CH_3$	5,5"-CH_3
7i[68,137]	$COOCH_3$ or $COOCH_2CH_3$	5,5"-CH_2Br
7j[68,137]	$COOCH_2CH_3$	5,5"-CH_2OAc
7k[68,137]	CH_2OH	5,5"-CH_3
7l[68,137]	$CH_2OTBDMS$	5,5"-CH_3
7m[70]	$CH_2OC_6H_{13}$	5,5"-Cl
7n[70]	$CH_2OC_6H_{13}$	5,5"-Br
7o[70]	CH_2O-MEM	5,5"-Br
7p[87]	NO_2	5,5"-CH_3
7q[87]	NH_2	5,5"-CH_3
7r[117]	N_3	5,5"-CH_3
7s[87]	NO_2	5-CH_3
7t[87]	NH_2	5-CH_3
7u[117]	N_3	5-CH_3
7v[115]	*p*-tolyl	6,6"-$COOC_4H_9$

The Stille cross-coupling of ethyl 2,6-dibromopyridine-4-carboxylate and 6-methyl-2-(tributylstannyl)pyridine has been used to synthesize ethyl 6,6′′-dimethyl-2,2′:6′,2′′-terpyridine-4′-carboxylate (**7f**) in 44% yield.[67] Subsequently, the methyl groups were converted into bromomethyl groups (compound **7g**) by NBS bromination in benzene (27% yield). In the same manner the 5,5′′-dimethyl-2,2′:6′,2′′-terpyridine-4′-ethyl and methyl esters,[68,136] as well as 5,5′′-dimethyl-2,2′:6′,2′′-terpyridine-4′-carboxylic acid[136] (summarized as **7h**), have been prepared in about 60% yield. Bromination of the methyl groups resulted in the formation of the corresponding 5,5′′-bis(bromomethyl)-2,2′:6′,2′′-terpyridine-4′-methyl and ethyl esters **7i** in 10 and 70% yield, respectively. Substitution of the bromo groups by acetate groups with NaOAc in acetic acid gave 70% of ethyl 5,5′′-bis(acetoxymethyl)-2,2′:6′,2′′-terpyridine-4′-carboxylate (**7j**).[68,137] Reduction of the 4′-ester group of **7h** with $NaBH_4$ in methanol yielded 85% of the 4′-(hydroxymethyl)-5,5′′-dimethyl-2,2′:6′,2′′-terpyridine (**7k**).[68,137] The hydroxy function of **7k** could be protected with a *tert*-butyldimethylsilane (TBDMS) group by treatment with TBDMSCl in pyridine to give compound **7l** (85% yield). A variety of 4′-functionalized terpyridines with bromo or chloro groups at the terminal 5,5′′-positions has been prepared by Schlüter et al.[70] Utilizing the Stille cross-coupling of 5-chloro- or 5-bromo-2-(trimethylstannyl)pyridine and 2,6-dibromopyridines functionalized in the 4-position with $CH_2OC_6H_{13}$ or CH_2OMEM (MEM = methoxyethoxymethoxy), the authors synthesized the terpyridine compounds **7m**−**7o** (**7m**: 65%; **7n**: 14%; **7o**: 26%). 5,5′′-Dimethyl-4′-nitro-2,2′:6′,2′′-terpyridine (**7p**) has been synthesized by Fallahpour and co-workers utilizing the Stille reaction of 2,6-dibromo-4-nitropyridine and 5-methyl-2-(tributylstannyl)pyridine in 64% yield. The nitro group was reduced to an amino function in the presence of palladium on charcoal and hydrazine hydrate to yield 69% of compound **7q**.[87] The reaction of the nitro derivative **7p** with sodium azide in DMF resulted in a 72% yield of 4′-azido-5,5′′-dimethyl-2,2′:6′,2′′-terpyridine (**7r**).[117] The corresponding monomethyl-substituted compounds have also been prepared by Fallahpour and co-workers. 5-Methyl-4′-nitro-2,2′:6′,2′′-terpyridine (**7s**) was obtained by the Stille coupling of 2,6-dibromo-4-nitropyridine and 5-methyl-2-tributylstannylpyridine.[87] The nitro group could be converted into an amino function by reduction in the presence of Pd/C (**7t**) or to an azido group by the reaction of the nitro derivative with sodium azide in DMF (**7u**).[117] Ziessel et al. have reported the preparation of 6,6′′-bis(*n*-butoxycarbonyl)-4′-(4-methylphenyl)-2,2′:6′,2′′-terpyridine (**7v**).[115] This compound was prepared from the corresponding 6,6′′-dibromo derivative[53] in the presence of $[PdCl_2(PPh_2)]$, CO and Bu_3N in 1-butanol (52% yield).

Summary and Outlook

The many interesting applications of functional metal-coordinating 2,2′:6′,2′′-terpyridine compounds in the fields of supramolecular and macromolecular chemistry as well as electrochemistry has resulted in an impressive growth in the number of novel synthetic procedures. Modern ring assembly and cross-coupling procedures enable the well-directed introduction of different functionalities into almost every position of the terpyridine ring system. Nevertheless, the number of terpyridine derivatives is still relatively easy to survey. The methods for terpyridine construction are only compatible with a few less-reactive functional groups. Therefore, subsequent functional group conversions have to be carried out to multiply the "pool" of terpyridine ligands. In particular, in the field of multifunctional terpyridines further progress is required to introduce different highly reactive groups into one molecule. This could allow the incorporation of these chelating ligands into more complex architectures and would open avenues to novel materials in the fields of supramolecular, polymer or surface chemistry.

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