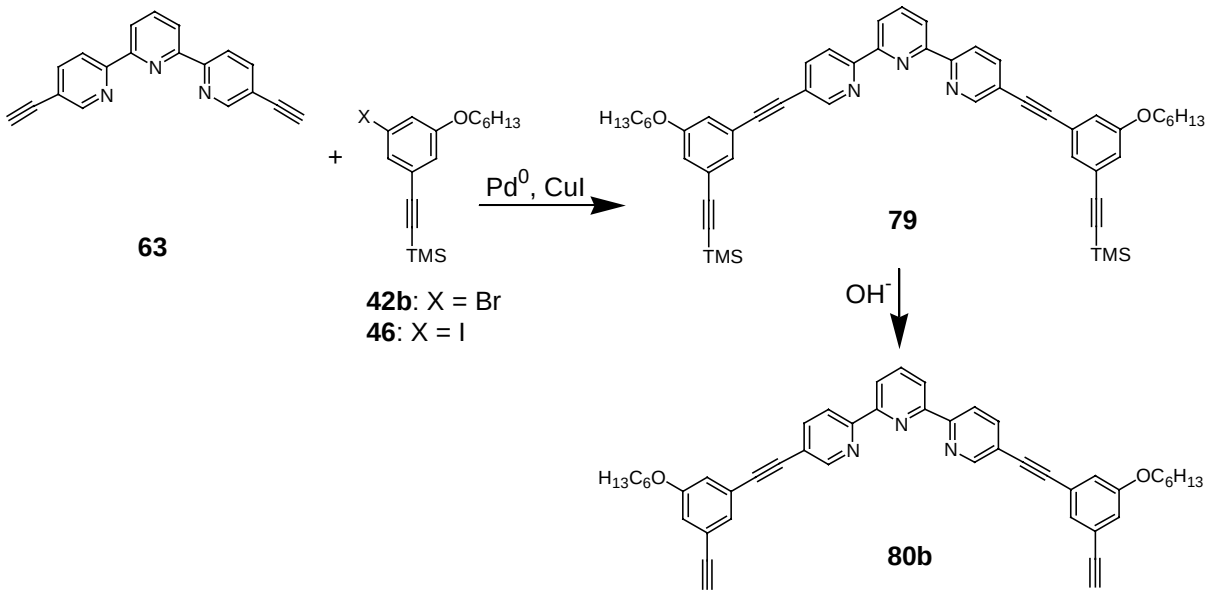
4.3 Synthesis of the 46-membered cycles

4.3.1 Attempt to close a cycle from a dibromo functionalized precursor

The most straightforward way to the envisaged structure **A** (Figure 3, p. 15) is by cyclization of two half rings of about the same size (ref. Scheme 15, p. 19). A bisethynyl and a dihalo functionalized precursor can be cyclized under Sonogashira conditions. Different strategies to build up these precursors were examined (i.e., Route 1 and 2, Scheme 16, p. 20).

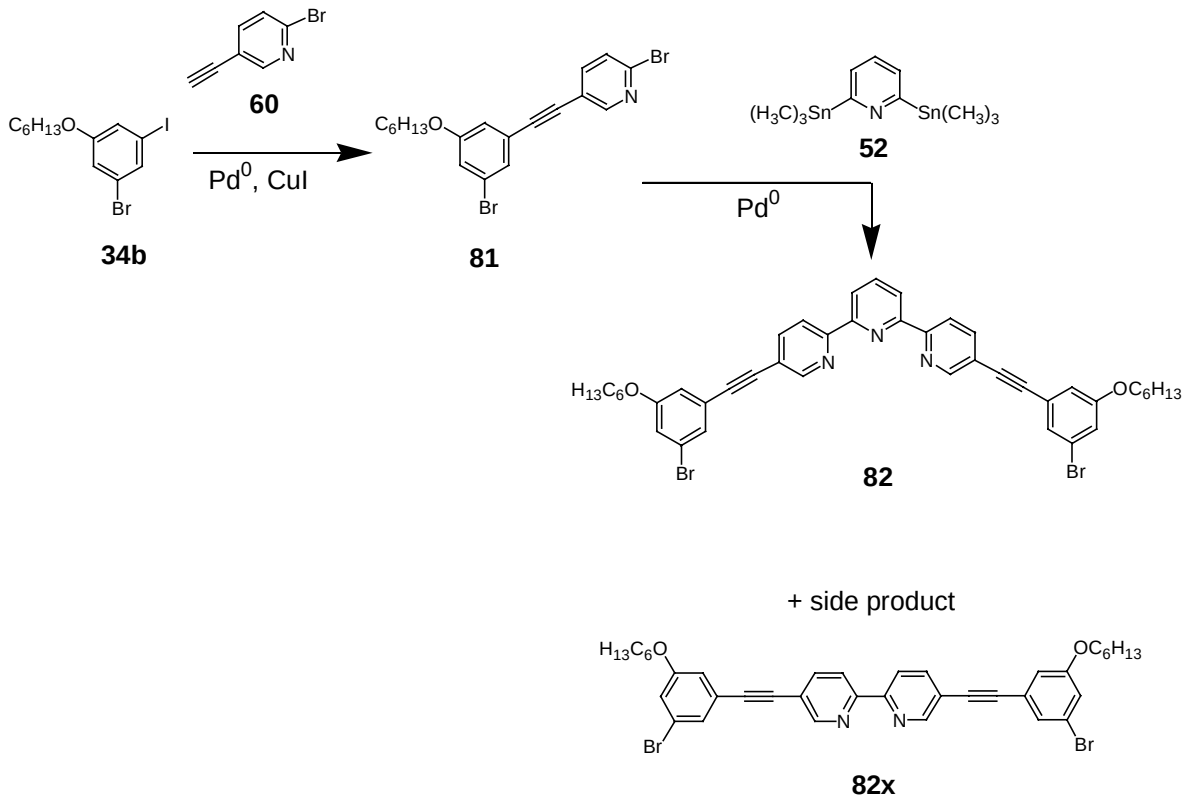
Synthesis of the ring precursors



*Scheme 31. Synthesis of half ring **80b** via route 1.*

According to Route 1, the half ring is synthesized from an already existing terpyridine (Scheme 31). The bisethynyl functionalized terpyridine **63** was Sonogashira coupled with two equivalents of bromo functionalized **42b** to give the silyl protected half ring **79**. The isolated yield of the coupling reaction after chromatography over silica gel, however, was only 27-32 %. For different runs, amounts of 28-56 % of starting material **42b** could be regained; no traces of unreacted **63** were found by TLC. The side products, which were more polar and remained on the starting line for TLC with hexane/ethyl acetate mixtures, were not analyzed. From other couplings between bromoaryls and acetylene, however, it is known that dimerization products of acetylenes can form.[139a] It is not clear if this kind of oxidative side

reaction happens during the synthesis – which was performed under nitrogen – or during work-up.[139b] When the above reaction is performed with the iodo functionalized precursor **46**, the yield rises up to 84 % of pure **79**. This was quantitatively deprotected to ethynyl functionalized half ring **80b**.



*Scheme 32. Synthesis of half ring **82** via route 2.*

In another approach according to Route 2 (Scheme 16, p. 20), the pyridines were coupled in the final step to give the dibromo functionalized half ring **82** (Scheme 32). First, difunctional pyridine **60** was reacted with difunctional aromatic **34b**; the Sonogashira coupling was selective regarding both the ethynyl and the iodo functionality, leaving the bromo substituents unaffected. The coupling product **81** was purified by column chromatography (74-82 %). Stille coupling of two equivalents of **81** with bisstannylated central pyridine **52** yielded dibromo half ring **82** in isolated yields of 50-60 % after purification by column chromatography.

Bipyridine side product **82x**, which results from the homocoupling of two molecules of **81**, was separated from one batch (7 %, ref. to **81**). All terpyridine couplings afforded a bipyridine side product, easily identified by its characteristic spot on the TLC, which is more strongly fluorescent, sharper, and at higher R_f-values than the largely smeared terpyridine

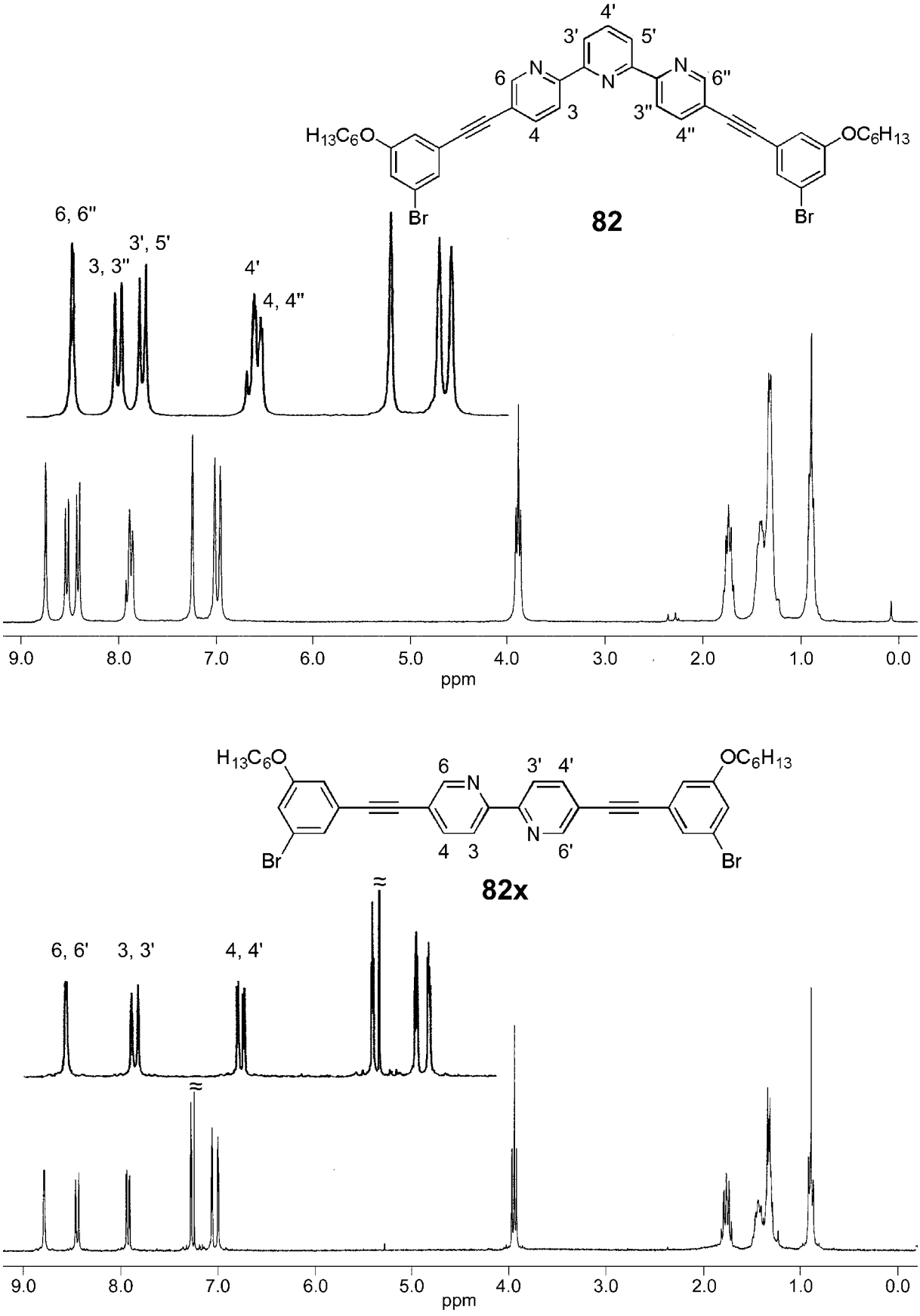
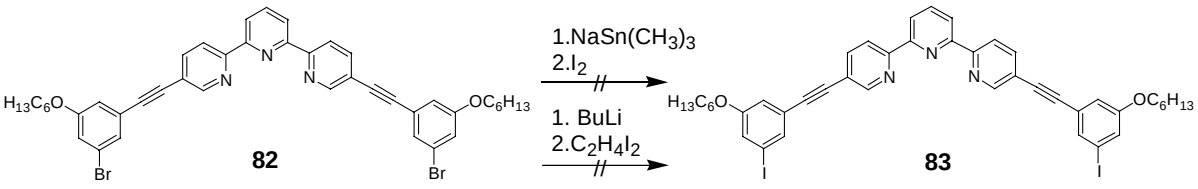


*Fig. 8. ^{1}H-NMR spectrum of compounds **82** and **82x** (270 MHz, ≈ = $CDCl_3$ (signal cut)).*

spot. In some cases, the bipyridines were separated and characterized; yields of these side-products were generally around 10-20 %.

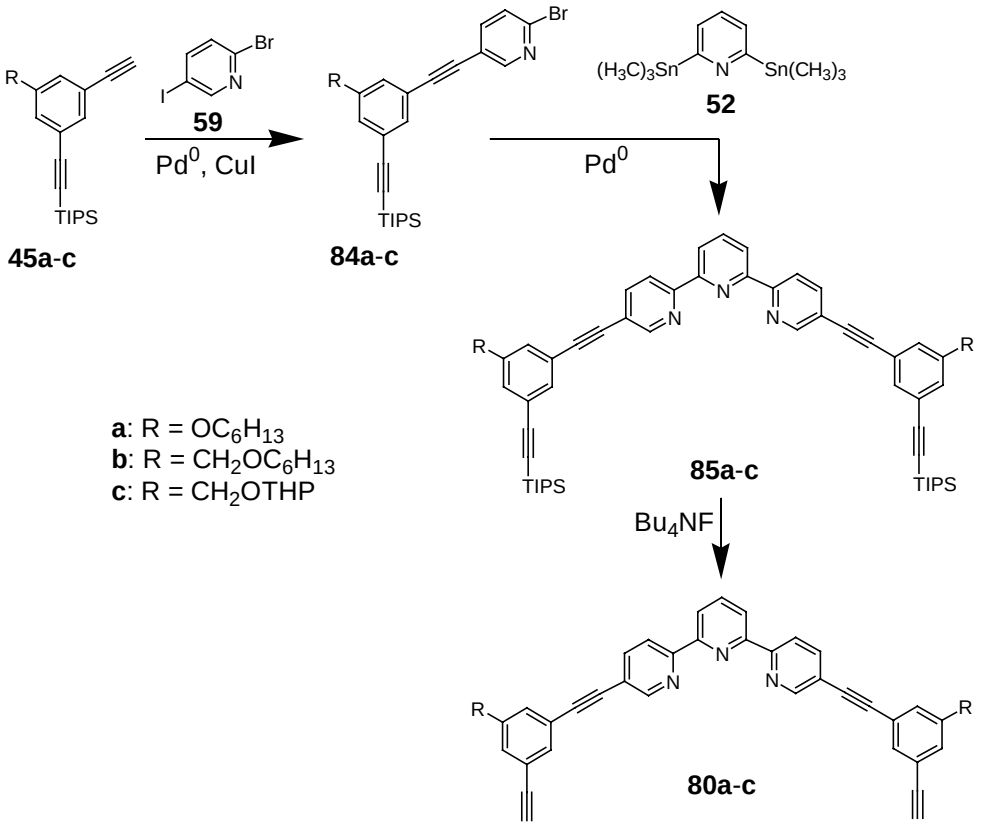
The characteristic features of the ^{1}H-NMR spectra of bi- and terpyridins are shortly described on the example of the compounds **82** and **82x**; only the pyridine signals are considered here (Fig. 8). Terpyridine **82** shows an A_2B spin system (for H-3‘,4‘,5‘) and an ABC spin system (for H-3,4,6,3‘‘,4‘‘,6‘‘). As expected from the resonance structure of pyridine, the doublet of H-6,6‘‘ has the highest chemical shift with δ = 8.75 ppm. The doublet of H-3,3‘‘ is shifted to δ = 8.53 ppm, and the doublet of H-3‘,5‘ to δ = 8.41 ppm. These two signals show the strongest downfield change in shift compared to unsubstituted pyridine. This can be explained by a favorite *trans,trans*-conformation of the terpyridine. The protons H-3,3‘‘ and H-3‘,5‘ are then especially influenced by the deshielding effect of the free pairs of electron on the nitrogen atoms.[140] The doublet assigned to H-4,4‘‘ and the triplet of the single H-4‘ overlay at δ = 7.87 ppm. Bipyridine **82x** shows an ABC spin system. Also here, the highest shifted signal with δ = 8.78 ppm can be assigned to H-6,6‘, which is neighbored to the nitrogen atom. A doublet for H-3,3‘ appears at δ = 8.45 ppm, and a doublet of doublet for H-4,4‘ at δ = 7.92 ppm. Also here, the large change of shift for H-3,3‘compared to pyridine can be attributed to a favored *trans*-conformation of the bipyridine.



*Scheme 33. Attempts to transform bromo functionalized terpyridine compound **82** into iodo functionalized **83**.*

Attempts to transform the bromo functionalities of **82** into iodo failed (Scheme 33). Lithiation of **82** with BuLi led to a dark solution; the supposed anion then was scavenged with diiodoethane. After work-up, only 50 % of starting material was regained. Similar problems with extended terpyridine compounds and BuLi have been described by Lehmann.[27] A strategy, which is only second choice due to its laborious chemistry and the highly toxic intermediates, but was successfully applied by Lehmann and Manickam for similar transformations on extended bi- or terpyridines, has also been tried here. The nucleophilic substitution of the halo functionalities in **82** with in situ generated sodium stannane, however, led to an inseparable mixture of products.

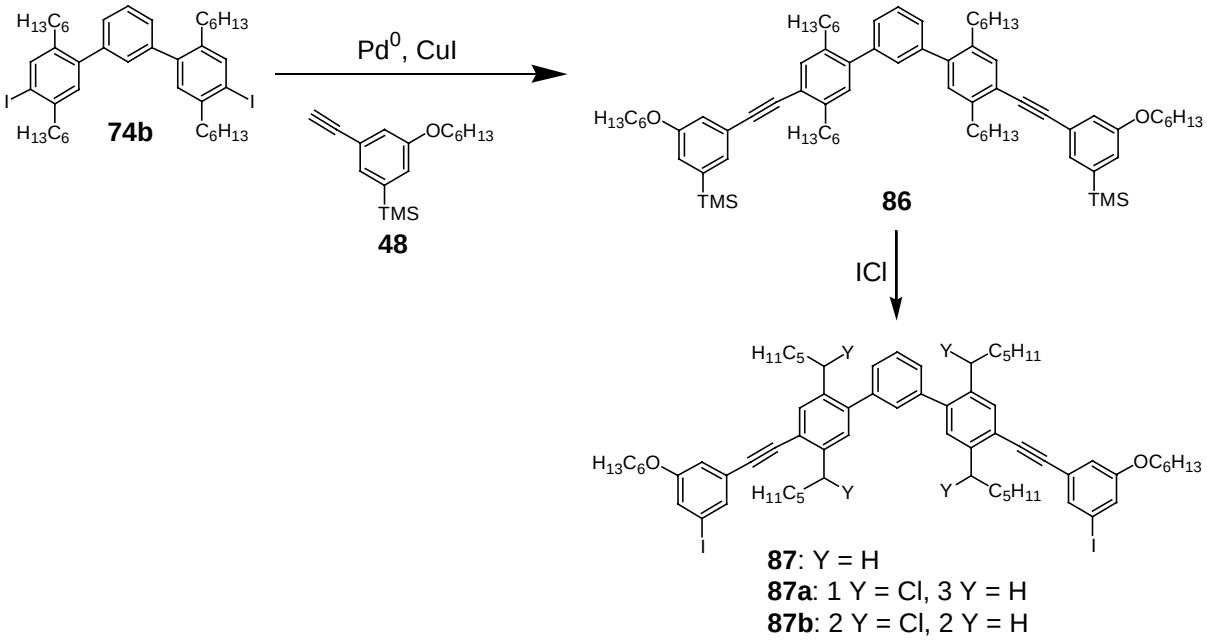
By Route 2 (Scheme 16, p. 20), also ethynyl functionalized half rings with different side chains were prepared (Scheme 34). Sonogashira coupling of **59** with ethynyl functionalized aromatics **45a-c** gave 72-87 % of pure **84a-c** after purification by column chromatography. Stille cross coupling of two equivalents of the substituted pyridine sides **84a-c** with stannylated central pyridine **52** yielded the TIPS protected terpyridines **85a-c** in yields varying from 45 % for **85c** to 61 % for **85b**. The terpyridines were purified by column chromatography from side products. In all cases, bipyridine side products could be observed (not shown in Scheme 34). For **85a** and **85b**, the bipyridines **85x** (15 %) and **85y** (22 %) were isolated and characterized. Cleavage of the TIPS protecting group to yield ethynyl half ring **80a-c** was less efficient compared with TMS deprotection (Scheme 31); yields are around 80 %, and the purification of the half ring from TIPS-F by column chromatography is tedious.



*Scheme 34. Synthesis of half rings **80b-80c** via Route 2.*

Additionally to the extended terpyridines, also a purely hydrocarbon half ring basing on the terphenyl unit was prepared (Scheme 35). Iodo functionalized terphenyl **74b** was coupled with an excess of ethynyl functionalized ring corner unit **48** to yield the silyl protected half ring **86**. Iodo-de-silylation with an excess of ICl in $CHCl_3$ at –30°C afforded only 43 % isolated yield of **87** after column chromatography. The remaining material

consisted mainly of unreacted **86** and TMS,I-functionalized intermediate product as revealed by MS. The reaction was obviously not complete; even though, product **87** was slightly contaminated with a small percentage of side products, as seen from the ^{1}H-NMR. The MS revealed two side products at $[M+Cl]^{+}$ and $[M+2Cl-2H]^{+}$, which probably arise from chlorination of the α-methylene groups. The characteristic peak at $\delta \approx 60$ ppm for the CHCl-carbon in the ^{13}C-NMR spectrum, however, could not be detected, as the amount of side product was too small. This side reaction has been described by Lützow;[69] by using the very same reaction conditions as were applied here, however, she had been able to oppress the chlorination. For the similar transformation of **73b** into **74b**, this side reaction was fortunately not observed (Scheme 30, p. 33).



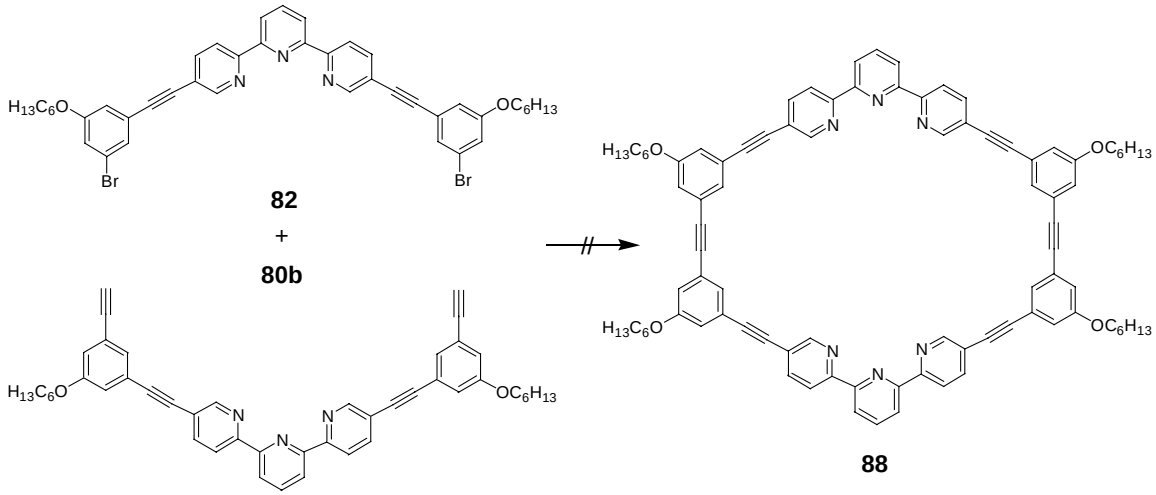
*Scheme 35. Synthesis of hydrocarbon half rings **86** and **87**.*

Cyclization

With **82** and **80b**, a dibromo and a bisethynyl half ring precursor were available. The ring closure reaction to attempt macrocycle **88** was performed under Sonogashira conditions in an oxygen free TEA/toluene mixture with $Pd[PPh_3]_4$(="Pd^0")/CuI as catalytic system (Scheme 36).

For his phenylene ethynylene macrocycles, Moore reacted the precursors under "pseudo high dilution" conditions by inserting them with a syringe pump to a solution of the catalyst system over a long period of time.[44] The injection speed is chosen in a way that the concentration of the precursors in the reaction mixture remains low and constant during the

reaction. For his bipyridine containing phenylene ethynylene macrocycles, Henze adopted Moore's procedure but could not achieve satisfying results.[31] Only when he omitted the syringe pump, i.e., brought the precursors to reaction directly together with the catalyst, he succeeded. In test runs, he compared the yields of cycle for different conditions and came to the following standard protocol: concentration of precursor: 0.0014 mol/l; catalyst concentration: 4 mol% Pd^0/CuI; solvent: TEA/toluene 1:1; temperature: 60°C; reaction time: 4 days.



*Scheme 36. Attempted ring closure between **82** and **80b**.*

Under adapted conditions, **82** and **80b** were brought to reaction [for a test run, a high concentration of precursor (0.025 mol/l) was chosen to enforce reaction]. Work-up followed a standard protocol by Henze. The reaction mixture was extracted with an aqueous NaCN solution to bind the copper, which might complex the terpyridines. The phases were separated and the aqueous one extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$, the solvent evaporated and the residue freeze-dried from benzene.

The raw GPC elution curve showed that practically all dibromo precursor **82** had remained unreacted, while the bisethynyl precursor **80b** has reacted to oligo- or polymeric material (Fig. 9). These homocoupling reactions may be catalyzed by traces of Pd^{2+} which forms during work-up.[139] The only peak, which could be assigned to the expected macrocycle **88**, appeared at a retention time of 14.4 min, M_p = 2249. It is obviously not monodisperse, as can be seen from the dominant shoulder in the GPC curve (ref. Chapter 4.3.2 for a discussion of GPC, and Chapter 4.3.4 for a GPC of the successful approach towards **88**). For a different catalyst/solvent system – Pd^0 without cocatalyst in a 1:1 pyrrolidine/toluene mixture[91] – this peak was likewise small.

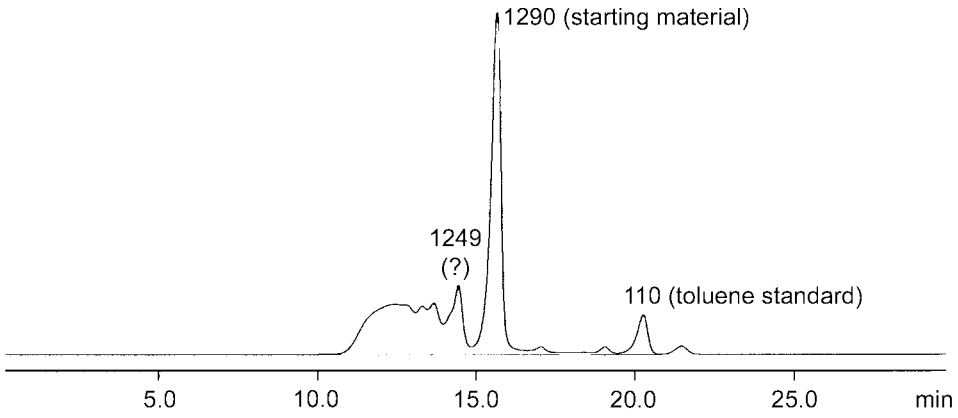
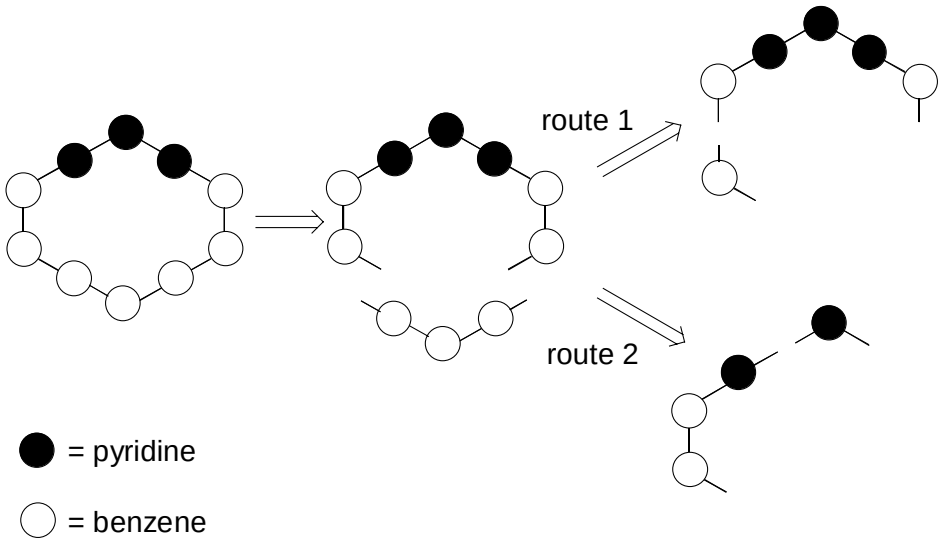


*Fig. 9: GPC trace of the soluble part of the raw product of the reaction of **82** and **80b** (Scheme 35).*

The macrocyclization by Suzuki-coupling was shown by Hensel to proceed with dramatically higher yields when reacting an iodo instead of a bromo functionalized halide precursor.[68] Even with an improved catalytic system, he was not able to improve the yields for the bromo-macrocyclization. Among the large number of shape-persistent macrocycles which can be found in the literature over the past four years, to my knowledge only one example is cyclized from a bromoaryl precursor under Sonogashira conditions.[18] Parallel to the work presented here, Henze failed in synthesize his bipyridine macrocycles (Scheme 12, p. 14) from a bromo precursor under Sonogashira couplings, while he succeeded with analog iodo precursors. For all this, it seemed not promising to further try to close the cycles from bromo functionalized precursors. Even if a range of new and more potential Pd^0 catalysts awaits to be tested for the macrocyclization of the above precursors, alternative strategies via an iodo functionalized half ring seemed more promising. First attempts aiming at those structures have been shown in this chapter; two successful alternative strategies towards a final cyclization step from an iodo and an ethynyl precursor will be described in the next chapter.

4.3.2 Cycles containing one terpyridine unit

The synthetic principle here bases upon ring closure from one “large” and one “small” precursor (Scheme 37). The “small” one can be an easily accessible diiodo terphenyl. The other, “large” one, is an extended terpyridine. Also here, two retrosynthetic routes can be distinguished, where the half ring is either built up on the existing terpyridine (Route 1), or, the terpyridine unit is generated last in the synthesis (Route 2; ref. Scheme 16, p. 20).



Scheme 37. Retrosynthetic pathways to cycle B (ethylene units, functionalities and side groups not shown).

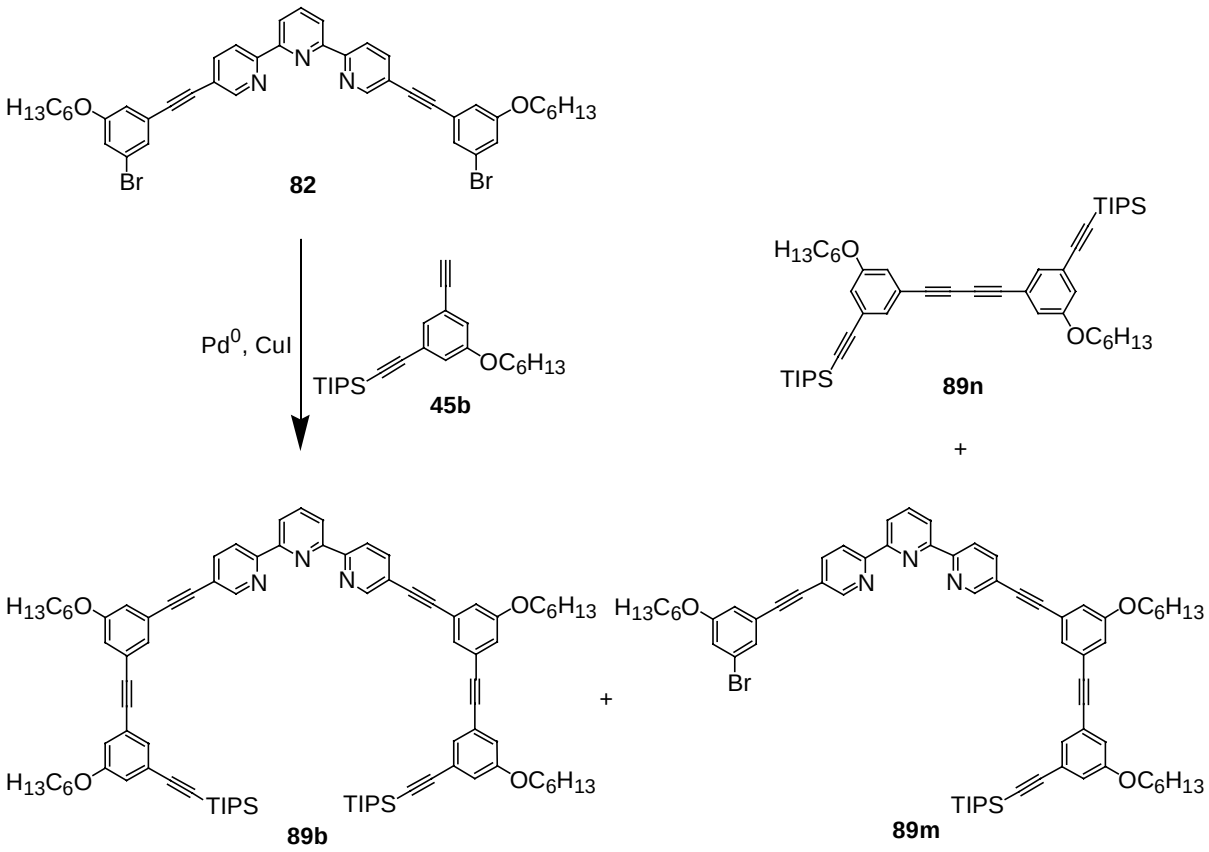
Synthesis of the ring precursors

Coupling of dibromoterpyridine **82** with an excess of ethynyl functionalized corner **45b** according to Route 1 yielded product mixtures of one- and twofold coupling product **89b** and **89m** besides homocoupling butadiyne product **89n** and unreacted starting material **82** (Scheme 38). The separation of these products by repeated column chromatography proved to be extremely tedious.

*Table 1. Yields of product **89b** and side product **89m** for different reaction conditions (to Scheme 38).*

solvent	catalyst	**89b**	**89m**	**82**
NEt_3/toluene	[Pd] / CuI	49–55 %	42–46 %	3–5 %
DIPA/toluene	[Pd]	45 %	49 %	6 %
propylamine	[Pd]	63 %	8 %	29 %

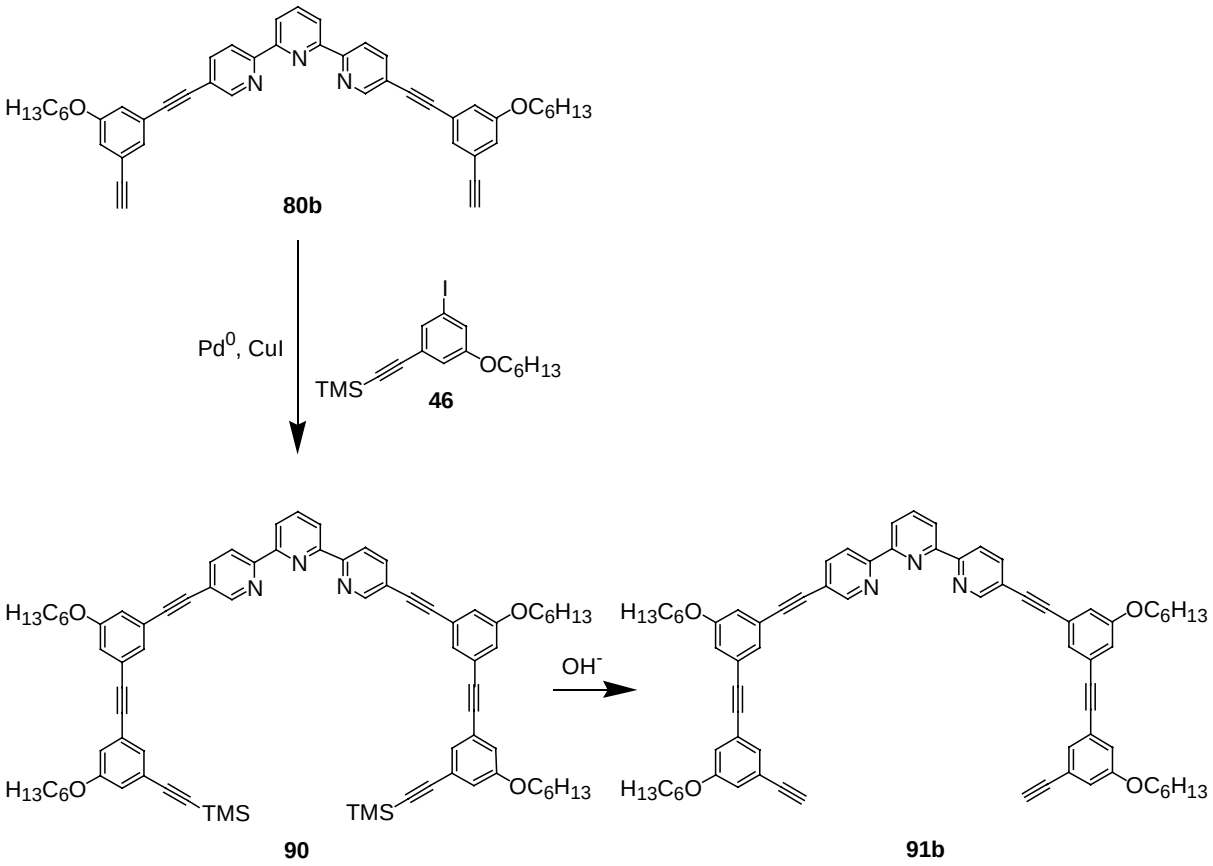
Therefore, the composition of the raw product for different reaction conditions was examined by analytic GPC (Table 1). In each case, the solvent of the reaction mixture was removed, the residue dissolved in dichloromethane, washed with water, and dried. Obviously, the samples still contained varying amounts of solvents; the GPC values could therefore not be correlated to the raw yields in mass. Instead, the numbers quoted in Tab. 1 were calculated under the assumption, that all starting material **82**, which has been consumed during the



*Scheme 38. Synthesis of half ring **89b** via Route 1.*

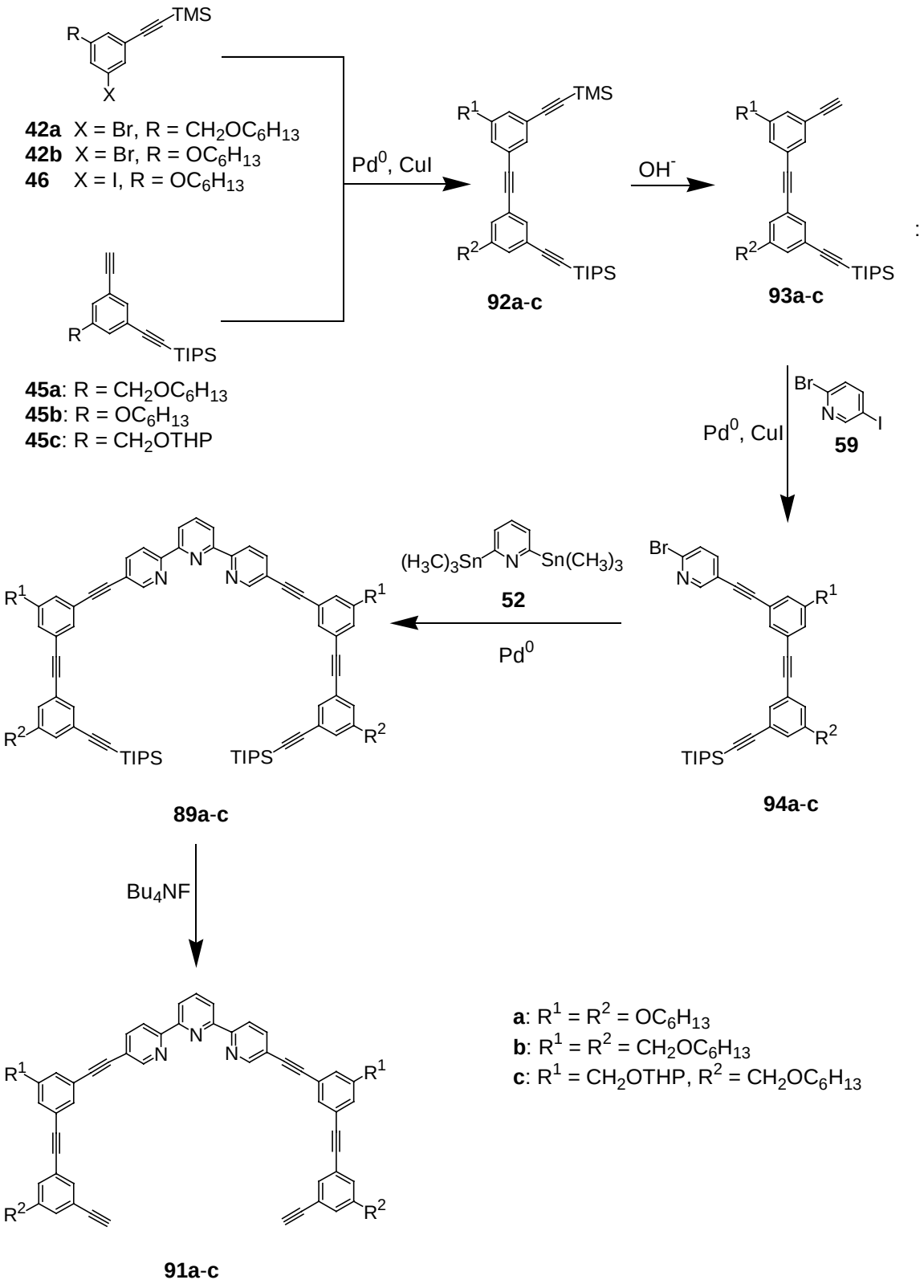
reaction, has been reacted to **89b** or **89m**, i.e., no other (terpyridine-) side products were formed. While for the standard conditions using triethylamine/toluene mixtures, nearly equal amounts of mono- and biscoupled product were formed, these values were only slightly less favorable for a solvent mixture of DIPA/toluene[18]. For propylamine as solvent, biscoupled product **89b** prevailed over **89m**, while 29 % of the starting material **82** remained totally unreacted. This astonishing result, for which I have no explanation, suggests that the two bromo functionalities of **82** in this case do not react independently from each other, i.e., statistically like for the other conditions. It is not clear, whether detailed investigation into this reaction could bring up conditions, under which the yield of **89b** can be driven to completion. The synthetic approach via Route 2 (Scheme 40), but also via an alternative Route 1 (Scheme 39), proved to be more effective here.

In this alternative Route 1, the functionalities were switched, i.e., a bisethynylterpyridine and a halobenzene unit were coupled. Sonogashira reaction of bisethynylterpyridine **80b** with iodo functionalized corner **46** gave TMS protected half ring **90** in 60 % yield (Scheme 39). Deprotection under basic conditions led to ethynyl functionalized terpyridine telechel **91b**.



*Scheme 39. Synthesis of half ring **91b** via Route 1.*

In the strategy according to Route 2, first one halo- and one ethynyl functionalized corner, **42**/**46** and **45**, are Sonogashira coupled to give compound **92**, which can be deprotected by selective cleavage of TMS under basic conditions to **93** (Scheme 40). While this deprotection is quantitative – **93** usually was simply purified by extraction with ether – yields for the coupling range from 63 % (for **92c**, which was, however, only prepared once) to 88 % (for **92b**). Purification was by column chromatography, with hexane for phenyl ether derivative **92b**, and hexane/toluene mixtures for benzyl ether derivatives **92a** and **c**. A further Sonogashira coupling of **93** with difunctionalized pyridine **59** was selective at iodo and yielded **94** in yields from 80 % (for **94a**) to 93 % (for **94c**). Stille coupling of 2 equivalents of **94** with bisstannylated pyridine **52** gave the TIPS protected half ring **89**. The yields varied between different batches; generally, numbers of around 40 % were achieved. In all cases, bipyridine side products were observed. From the purification of **89a** and **89b**, bipyridines **89x** and **89y** were isolated and characterized. Cleavage of the TIPS groups from **89** gave half rings **91**. The efficiency of the deprotection is demonstrated by the complete disappearance of the signal for the 42 (!) protons of the silyl protection groups of precursor **89a** at δ = 1.12 ppm. (Fig. 10).



*Scheme 40. Synthesis of half ring **91b** via Route 2.*

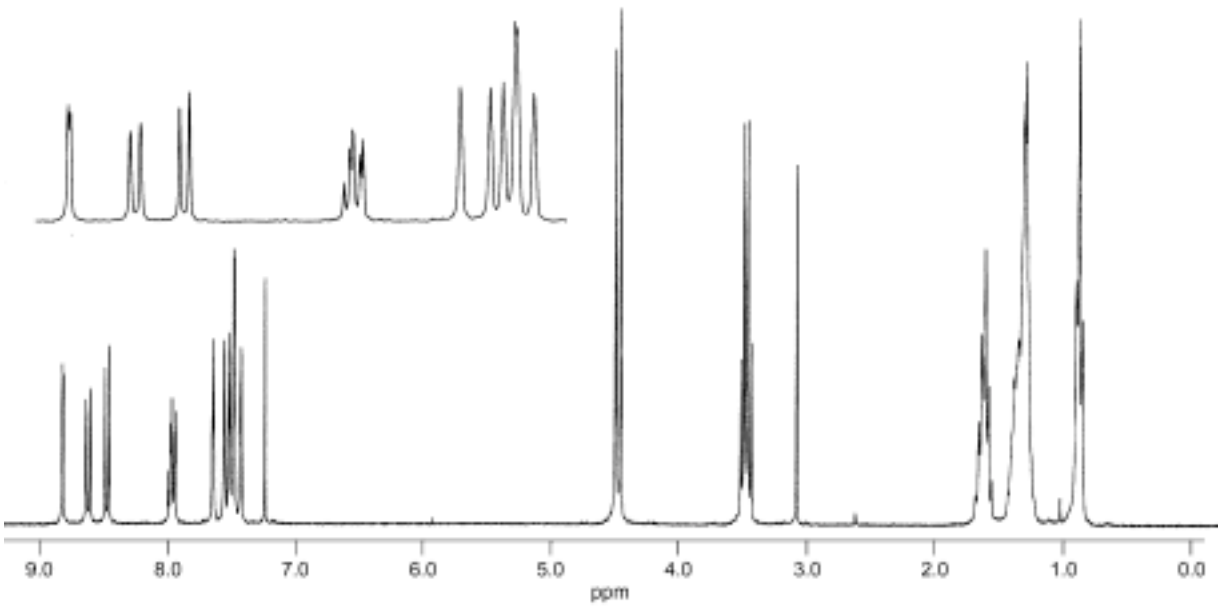


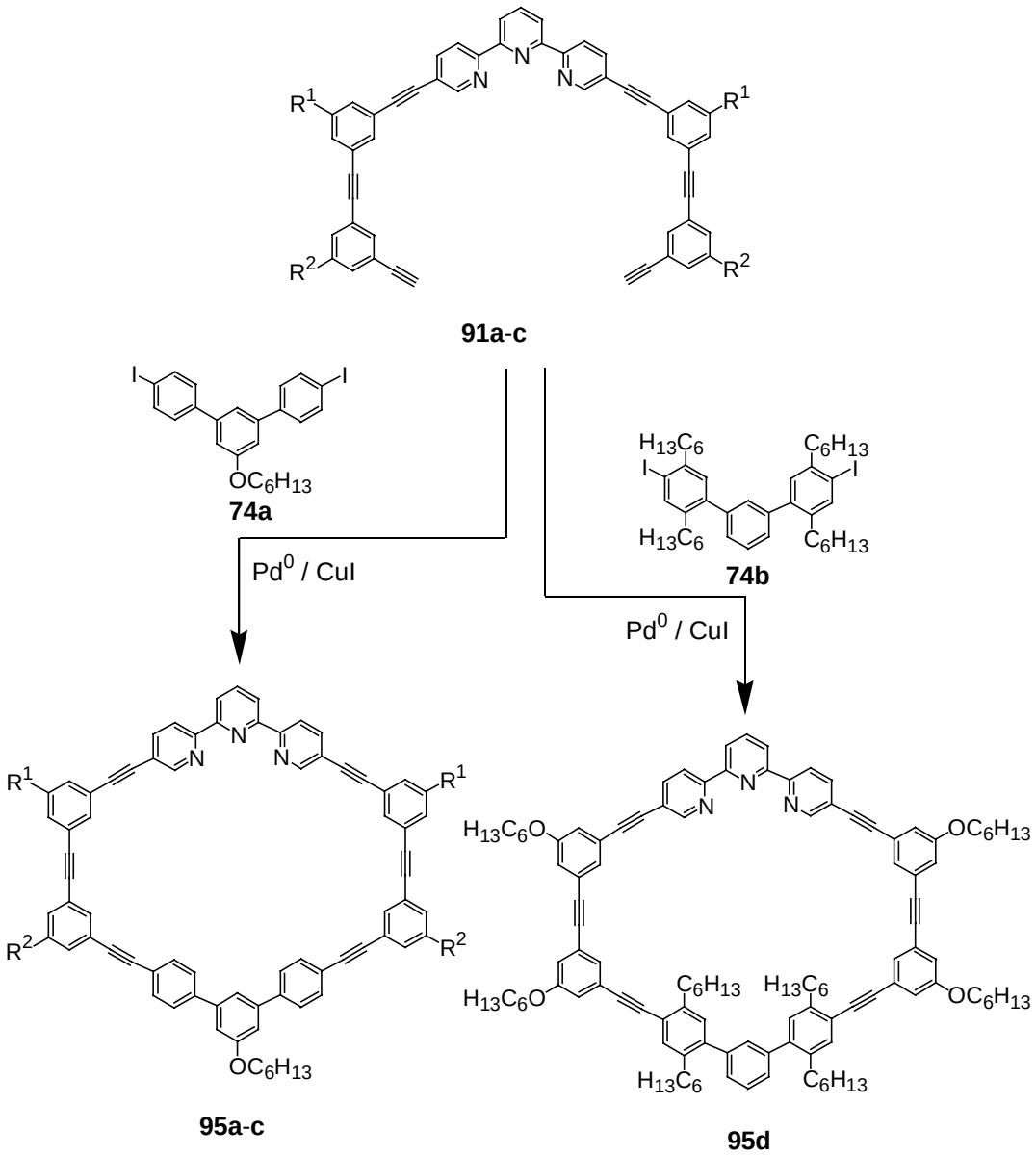
*Fig. 10. ^{1}H-NMR spectrum of compound **91a** (270 MHz, * = $CDCl_3$).*

Cyclization

The ring precursors were brought to reaction according to the protocol described in Chapter 4.3.1 (Scheme 41). After work up – in all cases, the residue was completely soluble in dichloromethane -, the crude product was examined by analytic GPC. The result for the very first cyclization of this series, which was done with the precursors **74a** and **91b** (Fig. 11), shows two distinct signals at retention times of ca. 13.5 and 14.5 minutes, and higher molecular species between 10-13 min. The peak at ca. 20.5 min. belongs to the toluene standard. The fractions represented by the two sharp signals were isolated by preparative GPC. By NMR and mass spectrometry, they were interpreted as the desired cycle **95b** and a cyclic side product **[95b]$_2$** with double mass. Their real molar masses, 1409 and 2818 Dalton, are significantly lower than those assigned to the according peaks in the GPC, 2620 and 4434 Dalton, resp. This discrepancy can be explained by the rigidity of the cycles. Different from polystyrene, which is used as calibration standard for the GPC, the phenylene ethynylenes cannot adopt randomly coiled conformations; their hydrodynamic volume is larger and therefore pretends a higher molar mass.[70]

Likewise, cycle **95a** from **74a** and **91a**, **95c** from **74a** and **91c**, and **95d** from **74b** and **91a** were prepared. Yields, which were calculated from GPC under consideration of the amount of raw product, are compared with isolated yields (Table 2). In the cases here, the

GPC values are generally considerably higher than the yields of the isolated products. This, however, does not inevitably hint at losses during separation by preparative GPC. It has to be noted that the GPC yields are calculated from the peak integrals, which are detected by UV light with a wavelength of 280 nm. Different extinction coefficients of compounds therefore make it impossible to compare these values otherwise than relatively.



a: $R^1 = R^2 = OC_6H_{13}$
b: $R^1 = R^2 = CH_2OC_6H_{13}$
b: $R^1 = CH_2OTHP$, $R^2 = CH_2OC_6H_{13}$

*Scheme 41. Synthesis of 46-membered cycles **95a-d** with one terpyridine unit.*

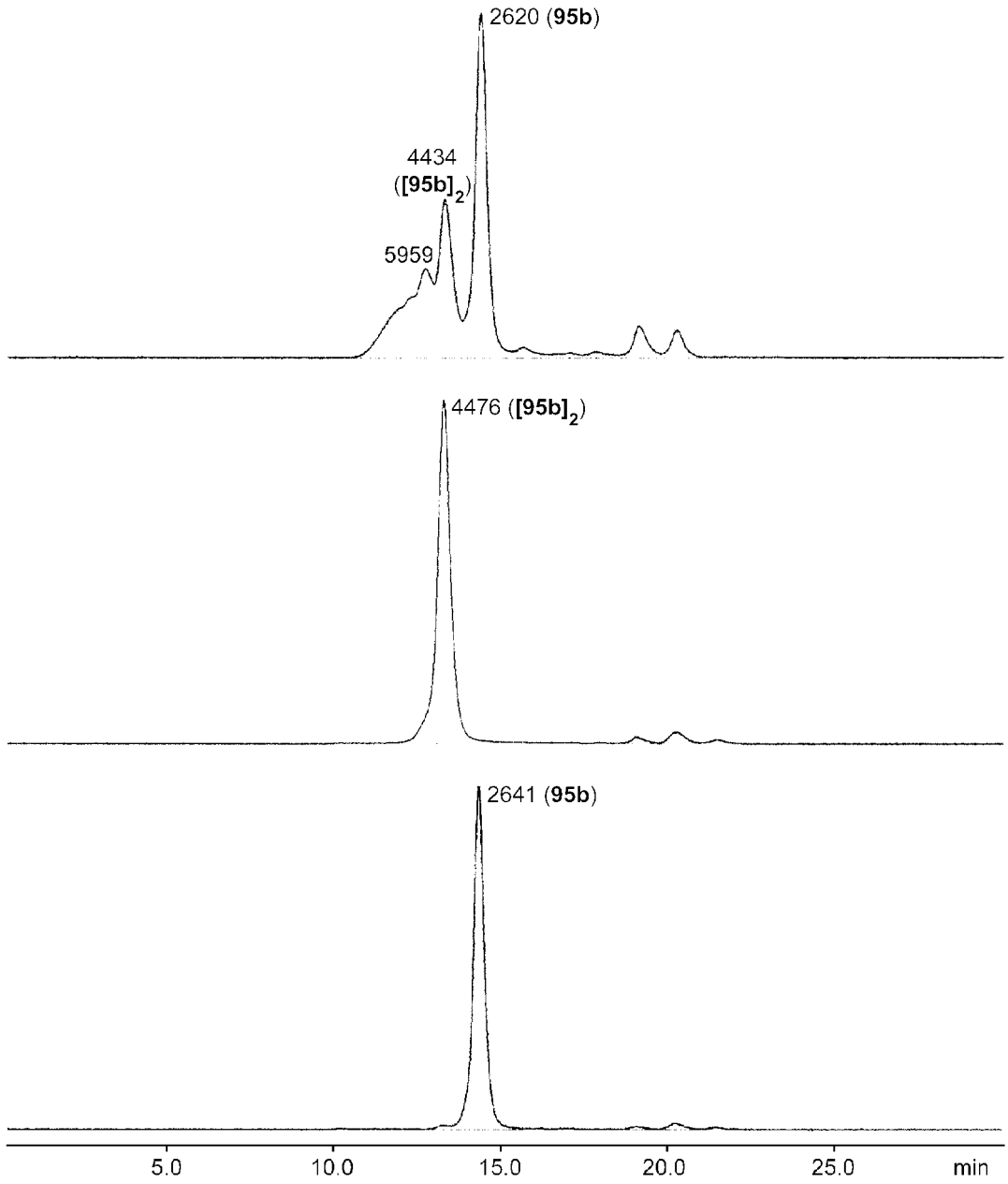


*Fig. 11. GPC traces of the raw product of the cyclization to **95b** (top), of isolated **[95b]$_2$** (middle) and **95b** (bottom; ref. Scheme 41).*

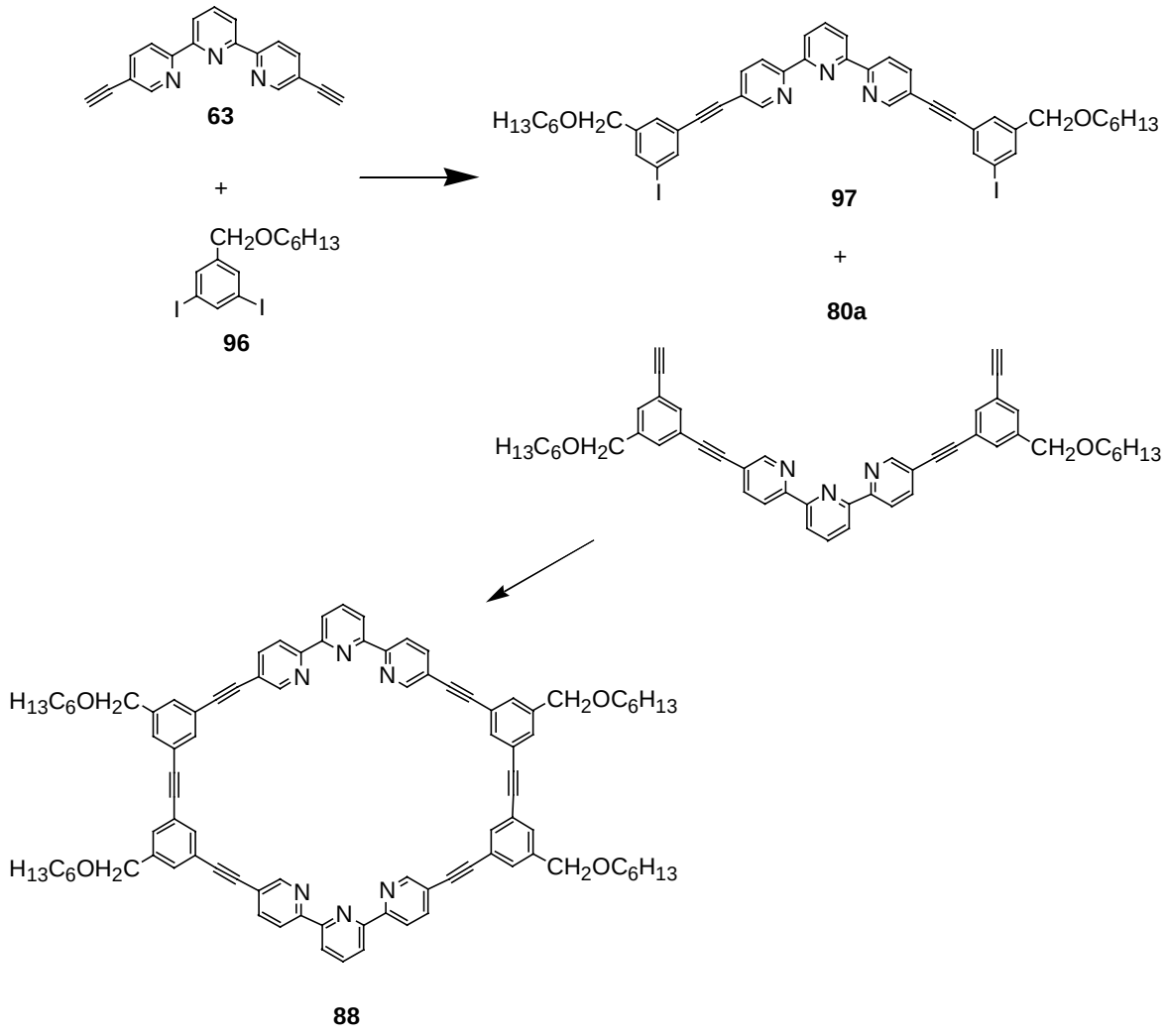
Table 2. GPC and isolated yields of cyclization (to Scheme 41).

cycle	GPC yield	Isolated yield
95a	42 %	21 %
95b	35 %	21 %
95c	29 %	18 %
95d	25 %	14 %

cycle	GPC yield	Isolated yield
[95a]$_2$	17 %	9 %
[95b]$_2$	22 %	12 %
[95c]$_2$	18 %	5 %

The yields are lowest for **95d**. Diiodo precursor **74b** carries voluminous hexyl side chains neighbored to its coupling functionalities. The lower cyclization yields for **95d** may be due to this steric hinderance, in that the geometry of the functionalities in the last of the two coupling steps, which is yet restricted by the connectivity of the two functionalities, becomes even more hindered, and intermolecular couplings to oligomers gain importance.

4.3.3 A cycle with two terpyridine units



*Scheme 42. Synthesis of 46-membered cycle **88** with two terpyridine units.*

Schmittels strategy to prepare his diiodo functionalized half ring **10** based upon the statistic coupling reaction between the diethynyl precursor **11** and a large excess of diiodo functionalized aromatic (Scheme 5, p. 8).[58] By this, he could circumvent the standard methods to transform a placeholder group into an iodo functionality, which have proved problematic in the case of extended bi- or terpyridine ring precursors (see, e.g., Scheme 33, p. 38, and

lit.[28,31]). The synthetic pathway towards macrocycle **88** rests on a similar strategy to gain diiodo half ring **97** from the coupling reaction of ethynyl functionalized **63** and an excess of diiodo functionalized ring corner module **96** (Scheme 42). Compound **96** was prepared according to Lehmann by twofold lithiation of **34a** in ether/THF, scavenging of the anion with trimethylsilyl chloride, and subsequent treatment with iodine chloride.[28] From the coupling with **63**, the raw product was easily purified by column chromatography over aluminium oxide to afford 60 % of product **97**; 78 % of unreacted **96** could be regained.

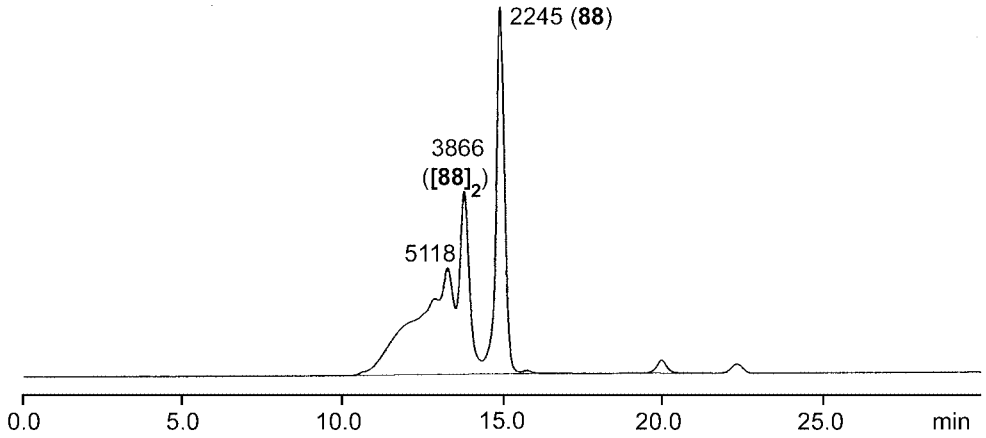


*Fig. 12. GPC trace of the raw product of the cyclization to **88** (Scheme 42). The compounds **88** and **[88]$_2$** could be separated by preparative GPC and gave clean traces (not shown).*

Cyclization of **97** and **80a** under standard conditions afforded a raw product which showed a GPC trace (Fig. 12) similar to those observed for the cycles with one terpyridine unit (Fig. 11). By preparative GPC, two macrocyclic compounds, the expected macrocycle **88** and the higher mass cyclic oligomer **[88]$_2$** were separated [**88**: 25 % (GPC), 27 % (isolated); **[88]$_2$**: 16 % (GPC), 6 % (isolated)]. While **88** precipitated microcrystallinic after separation and was difficult to characterize, **[88]$_2$** was well soluble.