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Fifty Shades of Phenanthroline: Synthesis Strategies to Functionalize 1,10-Phenanthroline in All Positions

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Fifty shades of Phenanthroline: synthesis strategies to functionalize 1,10-phenanthroline in all positions

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Abstract

1,10-phenanthroline (phen) is one of the most popular ligands ever used in coordination chemistry due to its strong affinity for a wide range of metals with various oxidation states. Its polyaromatic structure provides robustness and rigidity, leading to intriguing features in numerous fields (luminescent coordination scaffolds, catalysis, supramolecular chemistry, sensors, theranostics...). Importantly, phen offers eight distinct positions for functional groups to be attached, showcasing remarkable versatility for such a simple ligand. As a result, phen has become a landmark molecule for coordination chemists, serving as a must-use ligand and a versatile platform for designing polyfunctional arrays.

The extensive use of substituted phenanthroline ligands with different metal ions has resulted in a diverse array of complexes tailored for numerous applications. For instance, these complexes have been utilized as sensitizers in dye-sensitized solar cells, luminescent probes modified with antibodies for biomaterials, and in the creation of elegant supramolecular architectures like rotaxanes and catenanes, exemplified by Sauvage's Nobel Prize-winning work in 2016. In summary, phen has found applications in almost every facet of chemistry.

An intriguing aspect of phen is the specific reactivity of each pair of carbon atoms ([2,9], [3,8], [4,7], and [5,6]), enabling the functionalization of each pair with different groups and leading to polyfunctional arrays. Furthermore, it is possible to differentiate each position in these pairs, resulting in non-symmetrical systems with tremendous versatility.

In this review, the authors aim to compile and categorize existing synthetic strategies for the stepwise polyfunctionalization of phen in various positions. This comprehensive toolbox will aid coordination chemists in designing virtually any polyfunctional ligand. The survey will encompass seminal work from the 1950s to the present day. The scope of the review will be limited to 1,10-phenanthroline, excluding ligands with more intracyclic heteroatoms or fused aromatic cycles.

Overall, the primary goal of this review is to highlight both old and recent synthetic strategies that find applicability in the mentioned applications. By doing so, the authors hope to establish a first reference for phenanthroline synthesis, covering all possible positions on the backbone, and hope to inspire all concerned chemists to design new, still unraveled strategies.

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1. Introduction

Generalities on 1,10-phenanthroline (phen)

Some molecules are emblematic in the realm of chemistry, because they alone convey an extraordinary quantity of ideas and discoveries and are an inexhaustible source of inspiration.

1,10-phenanthroline, aka orthophenanthroline or just “phen” is definitely one of them. With

more than 70000 articles dealing with phen and its derivatives, this simple aromatic ligand is associated with many revolutions, from their discovery in the 1930's to the latest breakthroughs in coordination chemistry.

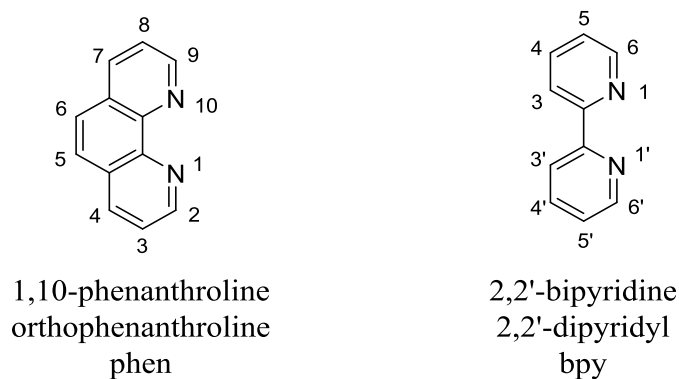


Figure 1. Structures of 1,10-phenanthroline and 2,2'-bipyridine

Summarily, phen is a rigid α,α' -diimine polyaromatic ligand featuring a structured strong absorption in the UV at ca. 260-280 nm ($\pi-\pi^*$ transition)^{1,2} and a weaker one (often seen as a shoulder at lower energy and assigned to an $n-\pi^*$ transition). It is a conjugated electro-deficient molecule, with a substantially negative reduction potential (-2.66 V vs. Fc^+/Fc in THF).³ The oxidation potential of phen is not reported. Upon excitation in the $\pi-\pi^*$, a weak, short lived (< 1 ns) fluorescence signal at ca. 360-380 nm ($\phi_{\text{em}} < 0.1\%$ in apolar solvents)^{1,2,4,5} can be observed. The low emission quantum yield of excited phen could be due to the population of non-radiative $^1n-\pi^*$ states lying too close in energy to the emissive $^1\pi-\pi^*$ state.² Interestingly, the emission wavelength is significantly red-shifted and the fluorescence intensity is enhanced when phen gets protonated.² This is due to a stabilization of the emissive $^1\pi-\pi^*$ state.

Of course, phen is first and foremost an excellent bidentate chelating ligand. Almost all possible elements can be coordinated by phen, as demonstrated in Figure 2.

Phen and bpy: two “sister ligands”

Phen is often compared to bpy, another famous chelating bis-diimine ligand, owing to their obvious structural similarities (Figure 1). Basically, phen is a rigidified version of bpy where positions 3 and 3' are bridged with an ethylene spacer. This has a number of consequences which contribute to increase the cleavage between phen and bpy.

First of all, and as mentioned above, the nitrogen atoms of phen are necessarily always in the cis-configuration, whereas the most stable geometry of bpy in absence of ions is the trans geometry because of favorable dipolar interactions. The pre-organization of phen favors its chelating ability over bpy for entropic reasons. As a result, phen is a more powerful base than bpy ($\text{pKa}(\text{bpy}/\text{bpyH}^+) = 4.30$ and $\text{pKa}(\text{phen}/\text{phenH}^+) = 4.96$)⁸ and the binding constants of phen with metal ions is usually significantly higher than the binding constant of bpy with the same ions, for complexes with the same stoichiometry (Table 1).^{9,10}

Table 1. Comparison of the association constants for a series of metal complexes $[\text{ML}_3]^{2+}$ where L is either phen or bpy. Values measured in 0.1 M KCl.⁹

L	$[\text{MnL}_3]^{2+}$	$[\text{CdL}_3]^{2+}$	$[\text{ZnL}_3]^{2+}$	$[\text{CoL}_3]^{2+}$	$[\text{CuL}_3]^{2+}$	$[\text{FeL}_3]^{2+}$	$[\text{NiL}_3]^{2+}$
bpy	5.6	10.2	13.0	16.1	17.0	17.5	20.1
phen	12.7	14.3	17.1	20.1	20.4	21.1	23.9

The superior coordinating ability of phen over bpy remains true when considering substituted analogues. In what follows, we will designate all phen ligands which are functionalized by diverse substituents in various positions by the term “phen_{sub}”. For example, Harwood and co-workers have demonstrated that the extraction of radioactive Am³⁺ ions from nitric acid

solutions is much faster when using phen_{sub} ligand BTPPhen than bpy-like ligand BTBP.^{11,12}

The pre-organization of the N[∧]N pincer in BTPPhen would be responsible for this result.

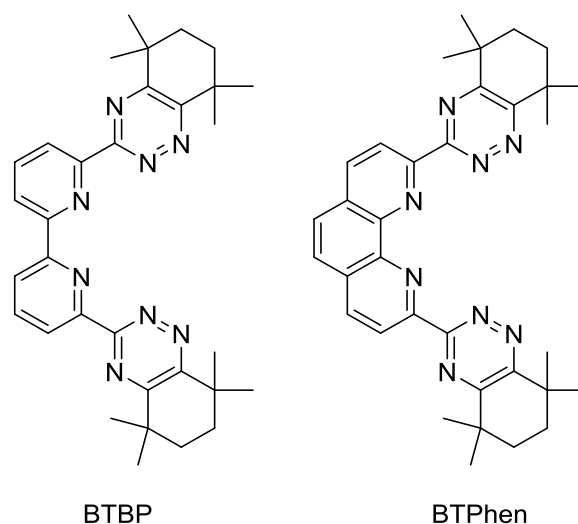


Figure 3. Ligands BTBP and BTPPhen for actinide extractions

The increased rigidity of phen *vs.* bpy has other important effects. For example, phen is more capable of making hydrates than bpy because the coplanarity of the nitrogen atoms facilitates H bonding with H₂O molecules.¹³ In addition, the increased rigidity can improve the photoluminescence parameters of photoluminescent M^{x+}-phen *vs.* M^{x+}-bpy complexes (e.g. [Ru(phen)₃]²⁺ being 1.4 times more luminescent than [Ru(bpy)₃]²⁺).¹⁴

As regards molecular catalysis, there are a few accounts where M^{x+}-phen catalysts surpass M^{x+}-bpy ones thanks to the expanded aromaticity and rigidity of phen.¹⁵⁻¹⁷ A case-by-case study to rationalize this feature with a consistent set of examples is out of the scope of this review.

Using phen in chemistry

The uses of phen, phen_{sub} and their complexes have been reviewed in previous publications^{4,18-21} and will therefore only be briefly reported here.

As a bulk material, they are a good electron conductors and conversely poor hole conductors.²² For example, layers of 4,7-diphenyl-1,10-phen, best known as bathophenanthroline, have been cast on the active surfaces of OLEDs,^{23,24} acting as hole blocking layers and thus limiting electron-hole pairs recombination. Despite their rather low emission quantum yield, they have been used as fluorescent sensors too, their emission being efficiently quenched in presence of a number of metal ions.²⁵ Because phen is planar, rigid and hydrophobic, it can intercalate within DNA base pairs.^{26,27} In addition, phen and appropriately substituted derivatives phen_{sub} have been successfully used to stabilize a specific guanine tetrameric structure, the so-called “G-quadruplex”, with potential applications as anti-cancer drugs.²⁸ Finally, phen belongs to the vast family of molecules featuring anti-mycoplasmal and anti-malarial activity.^{13,29–31}

Phen has been naturally very abundantly used for its chelating properties. For example, phen and its derivatives phen_{sub} have been used as chemosensors, because the coordination/interaction of molecular species (ions or anions, or H bonding interactions) by phen or phen_{sub} can entail a measurable change of the properties which can be exploited for sensing.²¹ Further, phen can be employed to treat polluted samples by making stable complexes with polluting cations.³² The strong complexing ability of the N[∧]N cavity makes phen a potent herbicide too.^{33–35} M^{x+}-phen complexes (M = Pd, Pt, Rh, Re, Ru, Ir, Os, Cu, Ni, lanthanides...) have been developed and used as drugs,^{36–40} homogeneous catalysts^{16,17,41–49} and photosensitizers with applications in photochemistry^{50–57} or luminescent probes and materials.^{58–64} In other well-known examples, M^{x+}-phen complexes have been used to design supramolecular architectures through the template effect.^{65–70} Furthermore, the rigidity and hydrophobicity of phen have conferred to the corresponding M^{x+}-phen complexes (with M^{x+} = Cu²⁺ and Ru²⁺ mostly)^{28,71–74} strong affinity for DNA and RNA strands, either by interactions with the minor or major groove or by intercalation between base pairs.

Functionalizing phen

In all the above-mentioned fields, the functionalization of phen in one or several positions has allowed to remarkably improve the targeted properties, or even lead to a complete change of paradigm, as will be exemplified below. The interests of functionalizing phen are numerous, but the aim is basically to improve the properties of phen, by exacerbating its electronic and/or geometric properties:

- The substitution of the phen ligand(s) can have blatant impacts on the optical and electrochemical properties of phen_{sub} and of the corresponding M^{x+}-phen_{sub} complexes^{20,75-82};
- it can tune the coordination sphere to strengthen or weaken the M^{x+}-phen bond, with important fallouts in the fields of catalysis⁸³ in terms of reactivity and selectivity.⁸⁴⁻⁸⁶
- it can modify the hydrophobicity or hydrophilicity to favour or disfavour solubilization (of phen_{sub} or M^{x+}-phen_{sub}) in organic or aqueous medium, thus increasing the activity of the corresponding molecule;⁸⁷⁻⁹⁰ similarly, it can promote/tune the affinity of phen and its complexes towards a target (phen functionalized with fatty chains, oligonucleotide^{91,92} or even DNA strand, or to a biomolecule; phen functionalized with amides for urea detection).⁹³

Incidentally, the relevance of functionalizing phen is well exemplified by the number of different phen_{sub} readily available from commercial sources (Figure 4), which can be used as received or serve as building blocks for further decoration. For accuracy, we will designate by the term phen_{(x,y,z,...)sub} a phen_{sub} ligand substituted in positions x, y, z etc... It is interesting to notice that some families of phen_{sub} are better represented than others. Indeed, there are many more commercially available compounds from families phen_{(2)sub}, phen_{(2,9)sub}, phen_{(4)sub}, and phen_{(4,7)sub}, followed by phen_{(5)sub} and phen_{(5,6)sub}, phen itself being available from more than

200 suppliers. The choice of compounds where phen has been functionalized in positions 3 and 8 is more restricted. Nevertheless, some molecules with well extended structures can be purchased, and a few multiply substituted phen derivatives are available too.

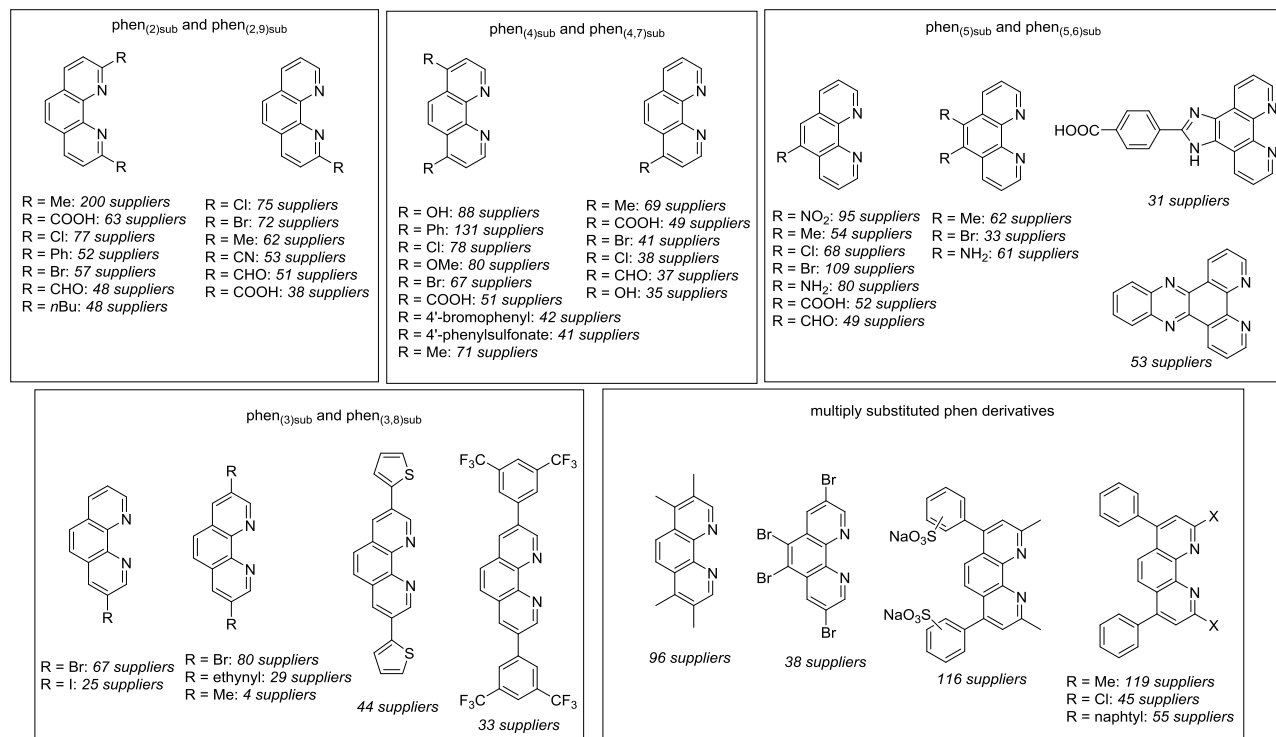


Figure 4. Non-exhaustive list of commercially available phen derivatives bearing substituents in various positions. The numbers below the structures indicate the number of suppliers (source: scifinder). The search has been limited to at least 20 suppliers.

Generalities on the synthesis of functionalized phen

From the point of view of synthetic strategies, phen exhibits remarkable features. Indeed, there are eight different positions which can bear substituents (Figure 1) and, as will be demonstrated in this review, the methods to prepare the diversely functionalized phen_{sub} molecules are highly dependent on the positions (nitrogen atoms N₁ and N₁₀ can be functionalized too but this is out of the scope of the review, unless the corresponding molecules are worthy intermediates towards the functionalization of phen). This appears as an

advantage when considering multiple functionalization in different positions. However, all functionalization methods are not compatible with each other, and shrewd multi-step methodologies have to be developed in order to achieve poly-functionalization of phen in different positions. We will strive to report these methodologies in this review. For obvious symmetry reasons, positions 2 and 9, positions 3 and 8, positions 4 and 7 and positions 5 and 6 can be considered as equivalent from the point of view of the methodology. However, this does not mean that the same conditions can be blindly applied to functionalize phen in symmetrical positions: the functionalization of one position can indeed strongly affect the reactivity of the symmetric position.

Comparison of the influence of substitution on standard properties of phen and related M^{x+} -phen complexes

Comparing the effects of substituents grafted on phen, position by position, on the properties of the ligand is a challenging task because all relevant data are not necessarily available for all the different substitution patterns, in the same conditions. We will thus concentrate on a few selected examples where comparisons are feasible.

Owing to the coordinating nitrogen atoms, phen and phen_{sub} are moderately basic. Various methyl-substituted phen_{sub} compounds are given in Figure 5 and the pKa of the couples (phen_{sub}/phen_{sub}-H⁺) are reported in Table 2. At first glance, the pKa are all significantly larger for methyl-substituted phen_{sub} than phen. This can be easily rationalized by considering the electron donating effect of the methyl groups which strengthens the σ -donating ability of the nitrogen atoms and stabilizes the N⁺-H bond of phen_{sub}-H⁺. The ordering of the pKa vs. the position of the methyl groups follows the trend: phen < **2** \approx **4** < **3** < **1**. Clearly, the electronic effects of the methyl groups depend on the positions onto which they are tethered. Methyl groups attached in positions (2,9) and (4,7) more substantially impact the σ -donating

character of the nitrogen atoms than methyl groups linked to positions (3,8) or (5,6) (Figure 5). This is more blatant when considering the tetramethylated compound **6**, where the couple (**6/6-H⁺**) features only a marginally larger pKa than (**2/2-H⁺**) or (**4/4-H⁺**). On the other hand, cumulating the electronic effects of methyl groups in positions (2,9), and (4,7) allows to reach a higher pKa value for (**7/7-H⁺**). The highest pKa of the series is obtained for **8/8-H⁺**, where the cumulation of methyl groups in positions 2, 3, 4, 7, 8 and 9 allows to doubly protonate the phen cavity⁹⁴ in aqueous medium (pKa **8-H⁺/8-H₂²⁺** = 1.36).

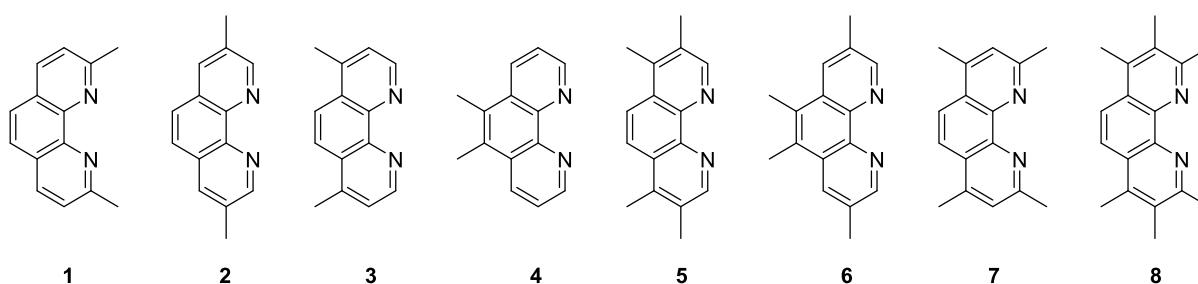


Figure 5. Structures of phen_{sub} molecules functionalized by methyl groups in various positions.

Table 2. pKa of (phen_{sub}/phen_{sub}-H⁺) couples in aqueous solutions

	phen	1	2	3	4	5	6	7	8
pKa	4.86 ^a	6.17 ^a	5.23 ^a	5.95 ^b	5.20- 5.47 ^c	6.31 ^a	5.54 ^a	6.50 ^a	7.37 ^b

^{a,b} Ref⁹⁴, ^cRef^{8,95}

Concluding that functionalizing phen in positions (3,8) or (5,6) will affect to a lesser extent the overall electronic properties of the N[∧]N chelating moiety compared to positions (2,9) and (4,7) would be too hasty. For example, the association constants of phen and phen_{sub} with metal ions M^{x+} can be correlated to pKa (M^{x+} = H⁺).⁹⁶ But protonation of phen and phen_{sub} is probably the sole chemical process where the steric hindrance of the substituents is unlikely to

interfere with their electronic properties. When considering a metal ion, which is necessarily much larger than a proton, and possible coordination of the latter by more than one phen or phen_{sub} ligands, both the steric and electronic factors have to be considered,⁹⁷ leading to other trends which are difficult to predict.

There are several studies comparing the stability constants of M^{x+}-phen_{sub} complexes^{76-78,96,98-100} but it is difficult to find a consistent set of quantitative data. Considering the case of an Fe(II) ion coordinated to three phen ligands substituted by methyl groups in various positions (ligands phen, **2**, **3** and **4**)²⁰ it was observed that substitution in positions 5 and 6, and especially in positions 4 and 7 lead to an increase in the stability of [Fe(**3**)₃]²⁺ and [Fe(**4**)₃]²⁺ compared to [Fe(phen)₃]²⁺, due to the improvement on the donating capacity of the N[∧]N cavity. Tethering methyl groups in positions 3 and 8 seems to decrease the stability of the complex [Fe(**2**)₃]²⁺, probably for steric reasons. This is exacerbated when methyl groups are attached in positions 2 and 9, since neocuproine **1** is unable to form the iron complex in the same conditions.⁷⁹

This trend is rather similar to what is observed for the pK_as, save for positions 2, 3, 8 and 9, probably because the steric strain imposed by methyl groups increases when they are closer to the nitrogen coordinating atoms. However, the geometry of the complexes has to be considered too. For example, [Cu^IL₂]⁺ and [Cu^{II}L₂]²⁺ complexes respectively feature tetrahedral and square planar geometries. Therefore, the steric clash between the two ligands L is larger in the case of copper (II) complexes, explaining the large difference between the stability constants for [Cu(dmp)₂]²⁺ and [Cu(dmp)₂]⁺ ($\Delta\log K_{\text{assoc}} = 7.4$).^{77,101}

The general impact of the position of a substituent on the optical and electrochemical properties of phen is not easy to rationalize because steric and electronic properties are again both involved.

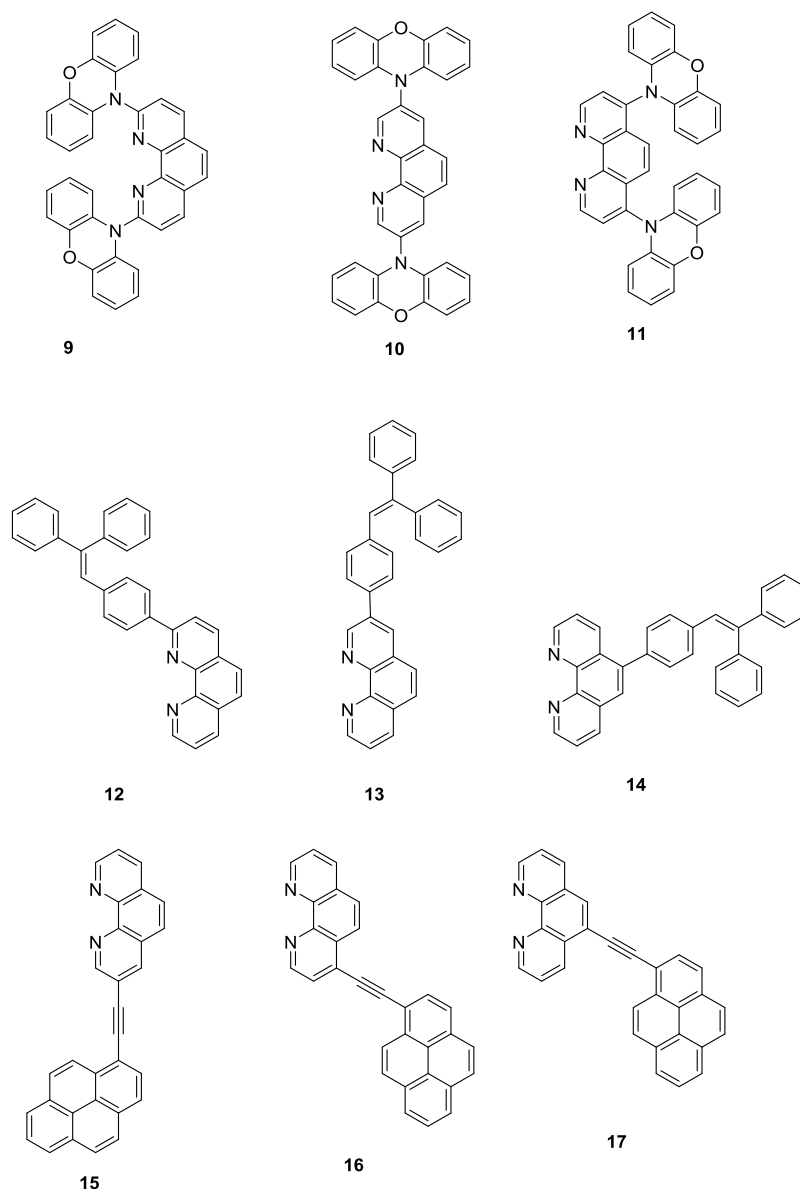


Figure 6. Structures of phen_{sub} ligands where the impact of the position of the substituents on the electronic properties of phen_{sub} has been reported

For example, Gong, Lu, Yang and co-workers have designed phen derivatives **9**, **10** and **11** where phenoxazine groups have been grafted either on positions (2,9), (3,8) or (4,7) respectively,⁷⁵ to prepare charge-transfer dyes acting as energy donors for organic light emitting devices (Figure 6). All phen_{sub} molecules feature significantly shifted absorption maxima compared to plain phen showing that the functionalization of the latter is impactful on the electronic properties (Table 3). There are nevertheless differences between spectra,

depending on the position of the phenoxazine on the phen skeleton. The structures of **9-11** show that the phenoxazine fragments are almost perpendicular to the phen plane in the cases of **10** and **11**, whereas significantly flatter dihedral angles are measured in the case of **9**. This is due to the fact that the sp_2 N_{phen} atoms are less sterically hindered than sp_2 $[C_{\text{phen-H}}]$ fragment. The calculated electron density for **9** consequently spreads over phen and phenoxazine while there is less electronic communication between the latter in the case of **10** and **11**. As a result, the absorption spectrum of **9** is significantly different from those of **10** and **11**. Given the geometrical arrangement of the phenoxazine and phen are similar for **10** and **11**, it is possible to focus on the impact of electronic effects on the properties of those two molecules. Interestingly, the transitions centered on phen are more shifted in the case of **10** than **11**. In addition, charge transfer transitions between electron rich phenoxazine moieties and electron accepting phen are more prominent for **10** than **11**. This tends to prove that tethering an electro-active group in positions (3,8) can have more impact on the overall properties of phen than in positions (4,7) and contrasts with the observations made by reading Table 2.

Table 3. Optical properties of a few selected phen_{sub} molecules

	9 ^b	10 ^b	11 ^b	12 ^{a,c}	13 ^{a,c}	14 ^{a,c}	15 ^{a,d}	16 ^{a,d}	17 ^{a,d}	phen
λ_{abs} (nm)	303	318, 417	307, 405	340	335	320	233	235	231	229 ^{d, 102}

^aGraphical reading from ref ¹⁰³; ^bdata in toluene; ^cdata in hexane; ^ddata in cyclohexane.

A similar study has been reported by Wang and co-workers, where (2,2-diphenyl-vinyl)-phenyl moieties were grafted on positions 2, 3 or 5 of phen (Figure 6, molecules **12**, **13** and **14**).¹⁰³ The twist angles of those substituents with respect to the plane of phen increase from

12 (22.9°) to **14** (51.9°). Charge transfer transitions between the substituents and phen modify again the electronic spectrum of phen, but **14** is the least impacted, which could be due to a weaker interaction between the (2,2-diphenyl-vinyl)-phenyl group positioned in C₅ and the phen moiety. Finally, Thummel and Mc Farland have reported the very mild effect of a pyrene-ethynyl substituent appended on positions 3, 4 and 5 of phen¹⁰⁴ (Figure 6, molecules **15**, **16** and **17** respectively). Here, the spectral features of phen and pyrene are basically preserved within the dyads, and no particular impact from the position of the substituents on phen has been observed on the free ligand.

Delineating a reliable trend of the impact of the position of a substituent on phen on its properties is thus very difficult when considering the available set of data in the literature, which sometimes contradict each other. A case by case study would be necessary but it is not the goal of this review which focuses on the synthetic strategies to obtain phen_{sub}, not their properties. However, we notice that, all things being equal, the electronic effect of substituents tethered to phen would follow the trend (5,6) < (4,7) ≤ (3,8) where < means “less prominent”. Positions (2,9) are not ranked in this trend because of the difficulty to predict the combined impact of the electronic properties and the steric hindrance of the grafted substituents.¹⁰⁵ Incidentally, substituting phen in positions 2 and 9 by large substituents implies that the bulky group in position 2 will experience the steric strain of the phen plane itself and of the bulky group appended in position 9, with difficultly predictable consequences (as we will see in the next sections, this can lower the yields of the reactions phen_{(2)sub} → phen_{(2,9)sub}).

Appending substituents on different positions of phen can have consequences on the electronic properties of phen_{sub} as exposed above, and all the more on the properties of the corresponding coordination complexes M^{x+}-phen_{sub}. Again, the steric hindrance and the electronic properties are strongly interfering, because the ligands are closely packed together

within the coordination sphere. Nevertheless, it could be anticipated that the impact of the steric hindrance decreases in the order (2,9) > (3,8) > (4,7) > (5,6).

A consistent study by Day and Saunders report on the absorption spectra of a series of Fe(II) complexes $[\text{Fe}(\text{phen}_{\text{sub}})_3]^{2+}$ depicted in Figure 7.⁷⁹ The substituents in this case are electron-donating methyl groups. Despite their reasonably small size, their presence in positions 2 and 9 prevent the formation of the corresponding complex $[\text{Fe}(\mathbf{1})_3]^{2+}$. For all other substitution patterns, the complexes were isolated and studied. At first glance, the absorption bands of $[\text{Fe}(\mathbf{2})_3]^{2+}$ and $[\text{Fe}(\mathbf{4})_3]^{2+}$ are the most shifted compared to $[\text{Fe}(\mathbf{3})_3]^{2+}$ and model $[\text{Fe}(\text{phen})_3]^{2+}$, meaning that functionalizing phen in positions 5 and 6 or 3 and 8 seems more impactful than in positions 4 and 7. Conversely, the Fe(III)/Fe(II) redox potential is more affected in the case of $[\text{Fe}(\mathbf{3})_3]^{2+}$ (0.88 V) than $[\text{Fe}(\mathbf{2})_3]^{2+}$ (1.03 V) or $[\text{Fe}(\mathbf{4})_3]^{2+}$ (1.0 V) ($E(\text{Fe(III)/Fe(II)}) = 1.10$ V for $[\text{Fe}(\text{phen})_3]^{2+}$). The fact that the optical and redox properties are not similarly affected is not surprising and depends on the orbitals involved in the electronic transitions which are not necessarily the HOMO and LUMO probed by electrochemistry.

The experimental trend observed by Day and Saunders is unfortunately not general. The metal ion and the geometry of the $\text{M}^{\text{x}+}$ -phen complex play major roles in the overall properties of the complex which must all be considered in order to understand the evolution of the various physical parameters as a function of the substitution. For example, neocuproine **1** is too sterically hindered to allow the formation of octahedral $[\text{Fe}(\mathbf{1})_3]^{2+}$ and destabilizes the square planar $[\text{Cu}(\mathbf{1})_2]^{2+}$ vs. the tetrahedral $[\text{Cu}(\mathbf{1})_2]^+$,⁷⁷ because there is no steric clash of the methyl groups in the latter case. Establishing “the one trend” between the substitution pattern and the electronic properties of a $\text{M}^{\text{x}+}$ -phen complex is thus probably impossible because each case is requiring its own in-depth analysis, carefully analyzing both the steric and electronic effects. However, there is an “array of presumptions” when considering a few, well-defined cases,

which are given in Figure 7, which makes it tempting to establish a crude trend, to be taken with great caution.

Table 4 gathers the emission energies (taken at the wavelength of maximum emission intensity) and the reduction/oxidation potentials $E_{\text{red}} / E_{\text{ox}}$ of a series of M^{x+} -phen_{sub} complexes, to characterize the influence of the substituent pattern on the energy of the excited state and on the LUMO (phen_{sub} centered) and HOMO (metal centered) of those complexes. Karnahl and Tschierlei have reported the properties of a series of heteroleptic copper(I) complexes $[\text{Cu}(\text{XantPhos})(\text{phen}_{\text{sub}})]^+$ where the metal ion is coordinated by XanthPhos and different phen_{sub} ligands **18-25** bearing various phenyl groups attached in positions (4,7)⁸⁰ or (5,6).⁸¹ Remarkably, the emission properties of the complexes built with phen_{(4,7)sub} (**22-25**) are more impacted than with phen_{(5,6)sub} (**18-21**). The reduction potentials are less affected, but follow the same trend. A similar conclusion can be drawn from the study of a collection of iridium complexes $[\text{Ir}(\text{ppy})_2(\text{phen}_{\text{sub}})]^+$ (ppy = 2-phenylpyridine) where methyl groups have been grafted to phen in different positions (ligands **1, 3** and **4**, Figure 7, Table 4).¹⁰⁶ The reduction potentials of $[\text{Ir}(\text{ppy})_2(\mathbf{3})]^+$ and $[\text{Ir}(\text{ppy})_2(\mathbf{4})]^+$ are more negative than the reduction potential of the reference $[\text{Ir}(\text{ppy})_2(\text{phen})]^+$ by 120 mV and 40 mV only, respectively. The functionalization of phen in positions 2, 3 and 5 by (2,2-diphenyl-vinyl)-phenyl afforded ligands **12, 13** and **14** respectively (Figure 7) and the emission properties of the corresponding $[\text{Ru}(\text{bpy})_2(\mathbf{12-14})]^{2+}$ complexes were studied.¹⁰⁷ It appears that the emission wavelength is more red-shifted in the case of $[\text{Ru}(\text{bpy})_2(\mathbf{13})]^{2+}$ than in the case of $[\text{Ru}(\text{bpy})_2(\mathbf{14})]^{2+}$ underlining that a substituent tethered to position 3 would impact more efficiently the electronic properties of the complex than in position 5.

To finish, the study of dendritic rhenium complexes $[\text{ReCl}(\text{CO})_3(\mathbf{26-28})]^+$ (Figure 7) lead to the same conclusions, namely that functionalizing phen in positions (3,8) and (4,7) will have a stronger influence on the electronic properties of the corresponding metal complexes.¹⁰⁸

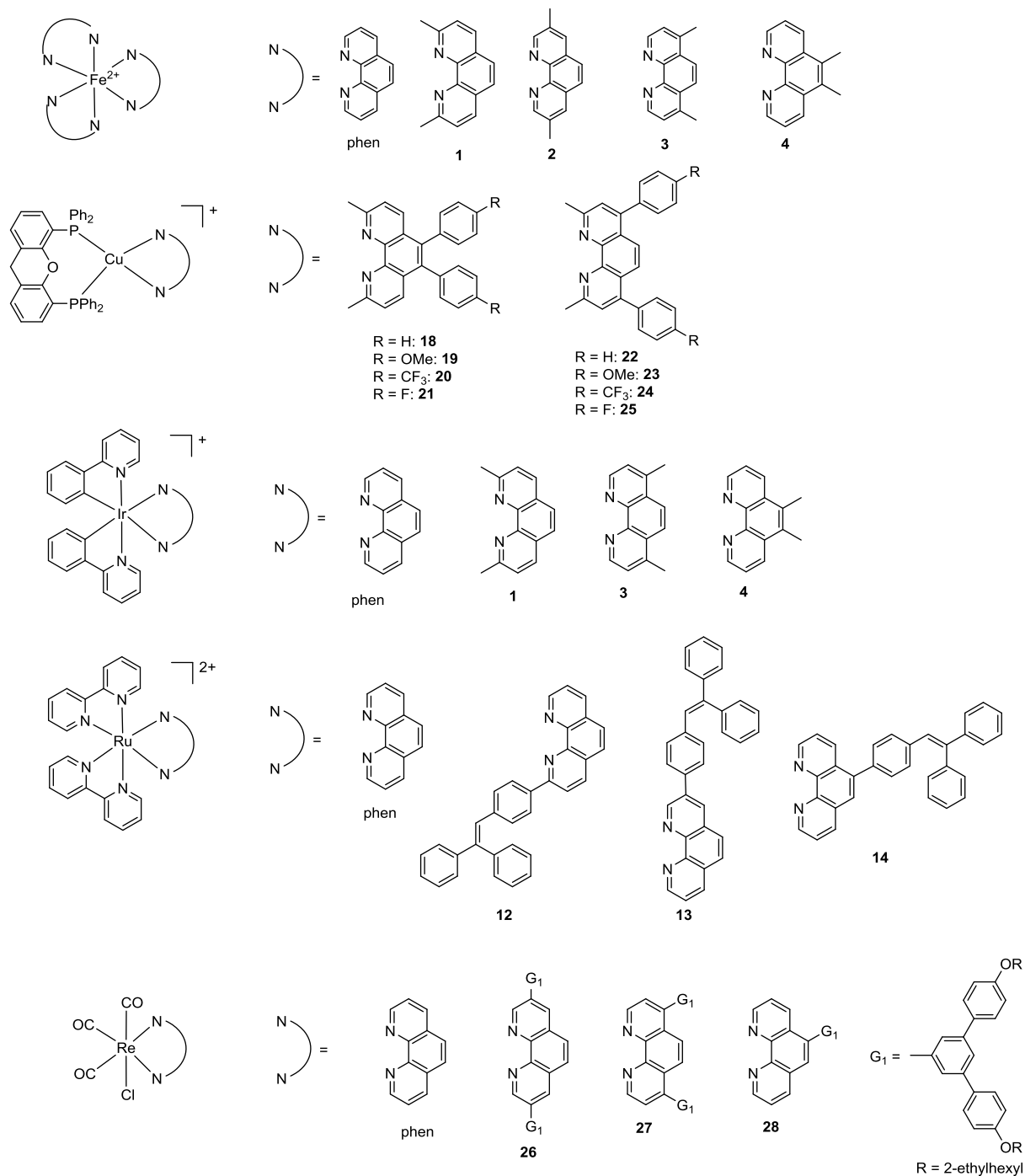


Figure 7. Structures of phen_{sub} ligands where the impact of the position of the various substituents on the electronic properties of phen has been consistently studied.

Table 4. emission wavelength and reduction potentials E_{red} of a series of M^{x+} -phen_{sub} complexes.

	$[\text{Cu}(\text{Xantphos})(\text{L})]^+$								
L	1	18⁸¹	19⁸¹	20⁸¹	21⁸¹	22⁸⁰	23⁸⁰	24⁸⁰	25⁸⁰
λ_{em} (eV)	2.20	2.30	2.38	2.23	2.23	2.15	2.16	2.07	2.13
E_{red} (V)	-2.10	-2.09	-2.11	-2.04	-2.08	-2.04	-2.08	-1.93	-2.02
E_{ox} (V)	0.82	0.89	0.89	0.92	0.93				
	$[\text{Ir}(\text{ppy})_2(\text{L})]^+,^{106}$				$[\text{Ru}(\text{bpy})_2(\text{L})]^{2+},^{107}$				
L	phen	1	3	4	12	13	14		
λ_{em} (eV)	2.22	2.32	2.25	2.18	1.95	1.94	1.99		
E_{red} (V)	-1.28	-1.37	-1.40	-1.32	n.r.	n.r.	n.r.		
E_{ox} (V)	1.36	1.43	1.35	1.35	n.r.	n.r.	n.r.		
	$[\text{Re}(\text{Cl}(\text{CO})_3(\text{L}))]^+,^{108}$								
L	phen	26	27	28					
λ_{em} (eV)	1.97	1.94	1.95	1.96					
E_{red} (V)	-1.74	-1.63	-1.67	-1.70					
E_{ox} (V)	0.93	1.15	0.92	0.94					

Therefore, one is tempted to conclude that the properties of M^{x+} -phen_{(5,6)sub} complexes are less affected than the properties of M^{x+} -phen_{(3,8)sub} or M^{x+} -phen_{(4,7)sub}, when compared to M^{x+} -phen

(incidentally, positions (5,6) are the less impacted by the steric factor too). This is highly empirical and based on a reduced population of complexes and should therefore be considered with caution.

Clearly, substituents grafted to phen in positions 2 and 9 always have a strong effect on the properties of the complex, but the combination of strong steric hindrance and electronic effects make it impossible to compare M^{x+} -phen_{(2,9)sub} with the other complexes.

Impact of phen functionalization on catalysis

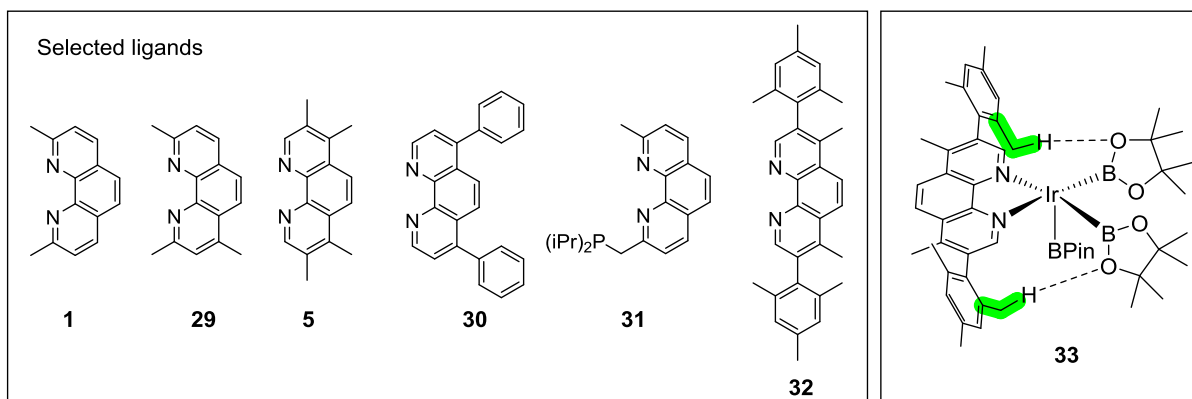
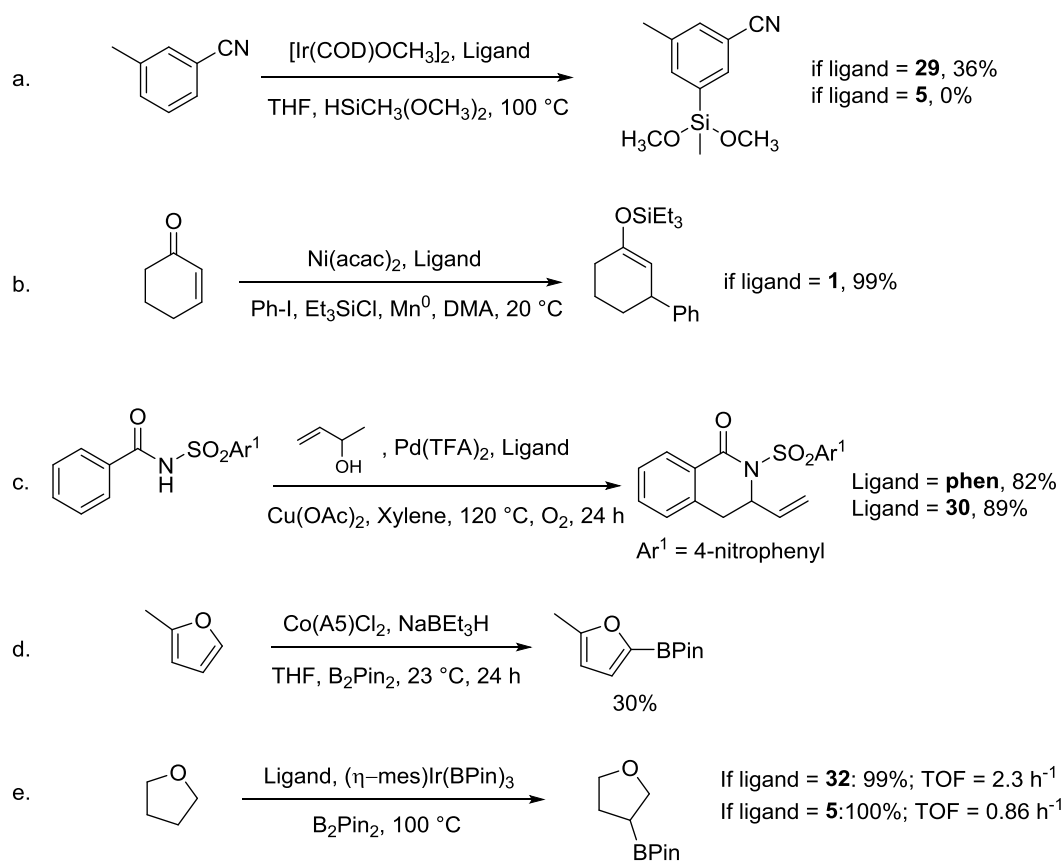
One of the fields in which phenanthroline has been most utilized is catalysis. This is likely due to its ability to coordinate many different metals, in all types of oxidation states, making it possible to envisage a wide range of photo-, electro- and molecular catalytic processes.

In addition, phen functionalization is very versatile. Such versatility allows to tune the steric and electronic properties of phen to a great extent and with great accuracy. This has allowed to design a plethora of molecular catalysts with various substitution patterns, various metal ions and diverse applications (C-H activation, C-C and C-Heteroatom cross-couplings, challenging oxidation and reduction processes etc...).

To see just how crucial phenanthroline is today in catalysis, we need look no further than recent articles where phen and phen_{sub} are used to design new molecular catalysts e.g. with copper (oxidation catalysts),^{109,110} iron (CO₂ reduction, C-H bond activation),^{111,112} nickel (reductive couplings,¹¹³ C-S cross coupling),¹¹⁴ Pd (C-H bond activation,¹¹⁵ borylation,¹¹⁶ defluorinative coupling¹¹⁷) and many more whose listing is out of the scope of this review.

Several examples of those catalysts will be presented all along this review and we wish to give here a few selected ones where the substitution of phen is particularly relevant for the outcome of the catalytic reaction, and has been properly rationalized.

Functionalizing phen is particularly relevant to catalysis in that it can tune the coordination capacity of the ligand, through steric or electronic effects, towards a given metal, either strengthening or weakening the M-phen_{sub} scaffolds. The iridium-catalyzed silylation of arenes^{118,119} (C-H activation) is a relevant example where increasing the steric hindrance nearby the metal centre favors the outcome of the reaction (Scheme 1A). Indeed, the highest conversion and yields for the silylation of 3-methyl benzonitrile were obtained when **29** was added as co-ligand to the iridium precursor dimer [Ir(COD)OCH₃]₂, outperforming **5** (where COD is 1,5-cyclooctadiene). The rationale is that methyl groups in positions 2 and 9 in **29** generate a significant steric hindrance around the iridium ion. This prevents the saturation of the coordination sphere by silyl fragments, which otherwise lead to the deactivation of the Ir-phen_{sub} catalyst.



Scheme 1. Examples of catalytic reactions where substituted phen co-ligands are used to generate *in situ* efficient molecular catalysts.

Similar observations have been made on cobalt-catalyzed cross-dimerization of alkynes,¹²⁰ or the nickel-catalyzed reductive addition of aryl halides on α -enones (Scheme 1B). Using **1** as co-ligand in presence of Ni(acac)₂ precursor leads to a molecular complex where the steric

strain around nickel is significant and disfavours the counter-productive homo-coupling of enones, thus improving the yield and selectivity of the catalytic process.¹²¹

However, it should be borne in mind that (excessive) steric hindrance around the metal center can be detrimental to catalysis. Determining the right balance is largely empirical. For example, neocuproine **1** is more efficient as co-ligand than phen in presence of palladium to catalyse the aerobic aqueous oxidation of alcohols into ketones. This is due to the steric bulk of the methyl groups in positions 2 and 9 which discourage the formation of a catalytically inactive Pd dimer;¹²² however, increasing the steric strain around Pd with larger substituents in positions 2 and 9 leads to a decrease of the turnover frequency.

The electronic effects of substituents tethered to phen can contribute to promoting a catalytic process too. For example, using bathophenanthroline **30** as co-ligand instead of phen allowed to increase the yield of the Pd-catalysed C-H annulation described in Scheme 1C from 82 to 89%, because phenyl groups in positions 4 and 7 increase the Lewis acidity of the Pd which is favourable in the course of the catalytic cycle.¹²³

Finally, appending a coordinating fragment onto phen can lead to drastic changes of its coordinating ability, which can have important fallouts with regards to catalysis. For instance, “pincer” ligands like **31** have been prepared to turn the N \wedge N coordinating cavity of phen into a N \wedge N \wedge P coordinating cavity, more appropriate for the Co-catalysed C-H borylation of arenes (Scheme 1D).¹²⁴ Subtler modifications can lead to drastic effects too, as exemplified by Hartwig and co-workers.¹²⁵ Indeed, the Ir-catalysed C-H borylation of THF is promoted when ligand **32**, bearing mesityl groups in positions 3 and 8 and methyl groups in positions 4 and 7, is used as co-ligand (Scheme 1E). The electron-donating character of the latter favours a faster borylation step. On the other hand, the effect of the mesityl groups is not electronic nor steric: C-H...O interactions (between the C-H bonds of methyls on mesityl groups, highlighted in green in Scheme 1, and the oxygen atoms on BPin moieties linked to the

iridium ion) develop within intermediate **33**. This leads to the stabilization of **33** and of the relevant transition state formed in presence of THF (here the substrate), resulting in an overall faster borylation step of the latter. We notice that substituting phen in positions 5 and 6 is little explored in the field of molecular catalysis (with the notable exception of dyad design for solar fuels, *vide infra*).

Why substituting phen: considering each set of positions separately

The substitution pattern of phen can have a drastic influence on the overall properties of the associated complexes. This will be briefly overviewed in the following section, and illustrated with a few selected cases. Many more examples will be given throughout the manuscript.

- Substituting phen in positions 2 and 9

Those positions are the easiest to functionalize, and many different strategies exist to synthesize phen_{(2,9)sub} or phen_{(2)sub}.

Ligands. As previously mentioned, phen and its derivatives are good candidates to stabilize the G-quadruplex structure of DNA, making those molecules powerful telomerase inhibitors and therefore potent anti-proliferative drugs for the therapy against cancer. This is due to their rigid planar, π -delocalized structure, allowing phen to stack on the face of guanidine quartets.^{30,126,127} Crescent-shaped phen_{(2,9)sub} **34**, bearing positively charged pendant chains in positions 2 and 9, further stabilize the G-quadruplex structure (Figure 8).¹²⁸ Incidentally, the bpy version of **34** is far less efficient as G-quadruplex binder, probably because of the easy rotation around the C₃-C_{3'} bond denaturing the useful crescent shape. The most frequent phen-based G-quadruplex stabilizers are phen_{(2,9)sub} (but there are many examples with all other substitution patterns).^{60,129,130}

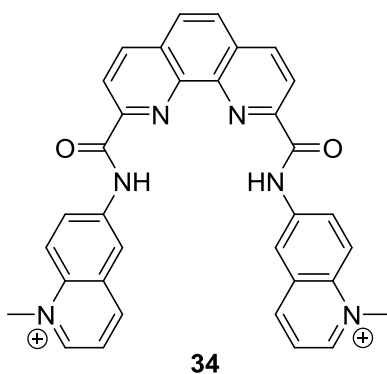


Figure 8. Example of phen_{(2,9)sub} as G-quadruplex stabilizer

Complexes. When considering the case of M^{X+} -phen_{(2,9)sub} complexes, groups R tethered to phen in positions 2 and 9 are the most impactful on its coordinating ability because R is the closest to the chelate N \hat{N} ring. As stated above, both the electronic and steric effects of R strongly influence the M-N bonds in terms of geometry and stability.

From the sheer steric point of view, bulky R groups can of course fragilize the M-N bonds. For example, phen can significantly bind to gold surfaces, while neocuproine cannot.¹³¹ Sterically challenging the N \hat{N} chelate has been shrewdly applied in different fields. For example, using phen_{(2,9)sub} ligands has allowed to open the field of copper(I) photochemistry.^{132,133} The presence of bulky R groups in positions 2 and 9 of phen prevents, to a certain extent, the occurrence of deleterious phenomena leading to the premature extinction of the excited state.⁵³ Table 5 reports the Cu-N bond length of several homoleptic copper(I) complexes [Cu(phen_{(2,9)sub})₂]⁺ (Figure 9) where the copper(I) ion is coordinated by bulkier and bulkier phen_{(2,9)sub} ligands. It could be anticipated that the average Cu-N bond would increase with the size of the R group. This is partially true, since the Cu-N distance for complex [Cu(**35**)₂]⁺ is the largest among the series. However, there is virtually no difference between the average Cu-N distances of [Cu(**1**)₂]⁺ and [Cu(**36**)₂]⁺ despite the large difference in the sizes of methyl and isopropyl groups respectively. Because isopropyl groups strengthen more efficiently the σ -donating character of phen than methyl groups, the steric and electronic

effects here are opposing, thus resulting in the similar measured Cu-N distances for both complexes. In the case of $[\text{Cu}(\mathbf{37})_2]^+$, the steric factor is prominent. On the other hand, the electronic factor is prominent in the case of $[\text{Cu}(\mathbf{38})_2]^+$, the phenyl groups are indeed electron-withdrawing and weaken the σ -donating character of $\mathbf{38}$ compared to $\mathbf{36}$ or $\mathbf{1}$ (however, stabilizing intramolecular π interactions make $[\text{Cu}(\mathbf{38})_2]^+$ one of the most stable copper(I) complexes).¹³⁴ Interestingly, $[\text{Cu}(\text{phen})_2]^+$ features a longer Cu-N distance than $[\text{Cu}(\mathbf{1})_2]^+$, again due to the lesser σ -donating ability of phen vs. $\mathbf{1}$. This example nicely shows that steric considerations alone can be misleading and that the geometry of the complex has to be considered too. Here indeed, the complexes are all more or less tetrahedral, and all substituents in positions 2 and 9 are actually in a void, free space above the copper(I) ion, explaining that longer chains for $[\text{Cu}(\mathbf{35})_2]^+$ do not impact the average Cu-N distance.

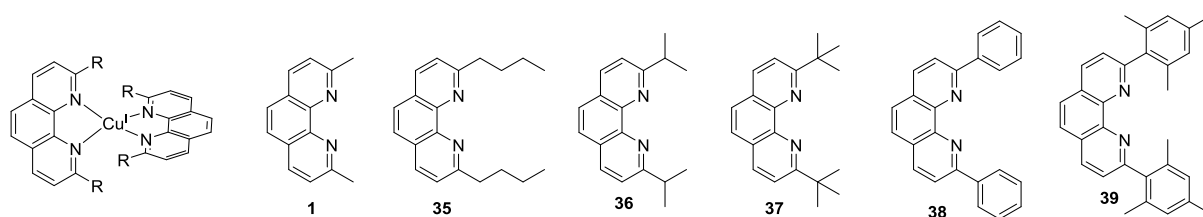


Figure 9. Structures of ligands used to generate photosensitive copper(I) complexes.

Table 5. Average Cu-N distances (average calculated on the four Cu-N distances) in Angström for a selection of homoleptic copper(I) complexes

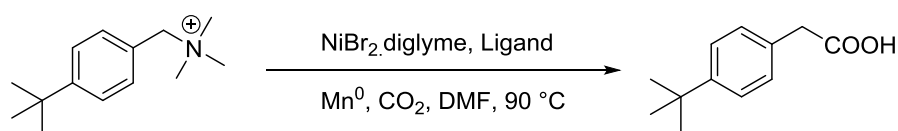
	$[\text{Cu}(\text{phen})_2]^{+135}$	$[\text{Cu}(\mathbf{35})_2]^+$	$[\text{Cu}(\mathbf{1})_2]^{+136}$	$[\text{Cu}(\mathbf{36})_2]^{+137}$	$[\text{Cu}(\mathbf{38})_2]^{+134}$	$[\text{Cu}(\mathbf{37})_2]^{+138}$
Cu-N	2.055	2.033	2.048	2.049	2.062	2.112

In the case of $[\text{Cu}(\mathbf{37})_2]^+$, although the σ -donating effect of *t*Bu is important, the complex is very unstable because of the steric hindrance. Loss of a ligand is very favorable for steric

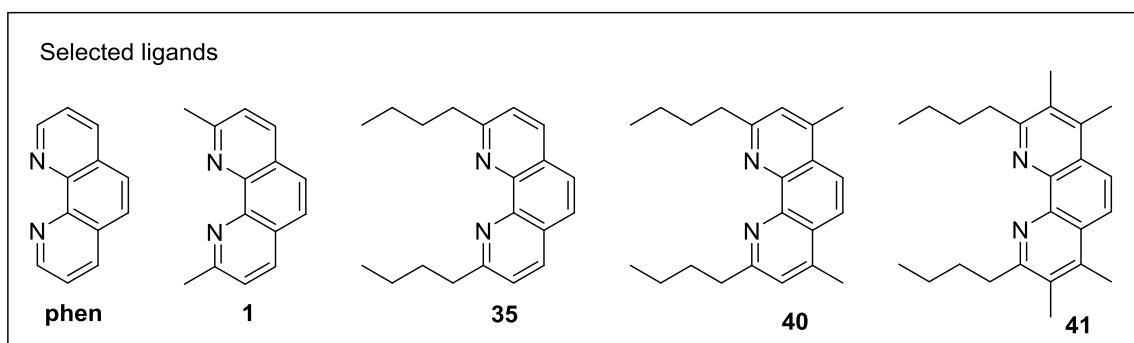
relief.¹³⁹ This drawback has been turned into an advantage by Schmittel and co-workers,¹⁴⁰ who used highly bulky phen_{(2,9)sub} ligand **39** to prepare heteroleptic copper(I) complexes. Indeed, in the case of **39**, the steric hindrance of the mesityl groups is so large that the homoleptic complex will not form while the heteroleptic will, by virtue of the maximum occupancy law, because it is less sterically strained. This strategy has allowed to design many impressive molecular machines, which have been reviewed elsewhere.^{141,142}

The weakening of the coordinating strength of phen upon functionalization in positions 2 and 9 can be a positive boon in the field of homogeneous molecular catalysis, as exposed briefly in a few examples above. Generally speaking, fragilizing a metal-ligand bond in a molecular (pre)catalyst facilitates de-coordination of ligand, an important step in organometallic catalysis,^{6,143} facilitating the ligation and/or the oxidative addition of a substrate on the metal centre.

There are many examples of M^{x+}-phen_{(2,9)sub} complexes acting as better catalysts than simple M^{x+}-phen (Scheme 1).¹¹⁸⁻¹²⁵ One additional example is the nickel-catalyzed carboxylation of C-N bonds with carbon dioxide (Scheme 2).¹⁶ Here the steric strain likely stabilizes the catalytically active Ni⁰(L)₂ tetrahedral complex (like what is observed with copper(I)-phen_{(2,9)sub} complexes). It is interesting to pinpoint again that electronic effects are likely to intervene too (**40** more efficient than **35**) and that increasing too much the steric strain (with **41**) can be counter-productive.



Ligand = **phen**: 0%
 Ligand = **1**: 26%
 Ligand = **35**: 35%
 Ligand = **40**: 81%
 Ligand = **41**: 56%



Scheme 2. Illustration of the impact of sterically challenging the chelating moiety of phen in positions 2 and 9 on the outcome of the Ni-catalyzed carbonylation of benzylic ammoniums.

Additionally, attaching a chiral R group in position 2 or in positions 2 and 9 allows to design chiral catalysts with enantioselective or diastereoselective properties. The proximity of the chiral copula to the metal centre ensures an optimal chirality transfer.^{144–150}

Conversely to what precedes, in a few cases, R groups appended in positions 2 and 9 of phen can strengthen the coordination sphere of the resulting complexes M^{x+} -phen_{(2,9)sub}. For example, taking R as an aromatic group (case of ligand **38**, Figure 9) induces an additional enthalpic effect thanks to π -stacking interactions (face-to-face or lateral face-to-edge) between R and the opposite identical ligand.^{101,151} R can as well exhibit a coordinating ability (R = COOH, R = 2'-pyridine...), thus strengthening the chelating character of phen. For instance, tethering pyridine moieties allows to convert bidentate phen ligand into a more rigid version of terdentate terpyridine **42**¹⁵² or a tetradentate ligand **43** forcing a square planar geometry (Figure 10).¹⁵³ In some cases, functionalizing phen with coordinating fragments can tune its affinity for certain ions. Taking the example of **44** (Figure 10), the presence of carboxylates in

positions 2 and 9 turns soft phen into a harder ligand able to accommodate large and highly charged ions like Gd^{3+} ,¹⁵⁴ Bi^{3+} ,¹⁵⁵ Th^{4+} ,^{156,157} or Pu^{4+} ,¹⁵⁸ and many more, with larger association constants than phen alone. Finally, Harwood and co-workers drastically improved the affinity of phen for actinide ions with the development of ligands BTPhen (Figure 3) or **45**, which can selectively bind americium(III) vs. europium(III),¹⁵⁹ a significant breakthrough in the field of nuclear waste decontamination. A last example explored quite early in the history of phen is the transformation of bidentate phen into a strongly coordinating macrocycle **46**. This is best achieved by closing the open $\text{N}^{\wedge}\text{N}$ chelating bow of phen by a coordinating linker tethered in positions 2 and 9, this linker being sometimes phen itself.^{160–164}

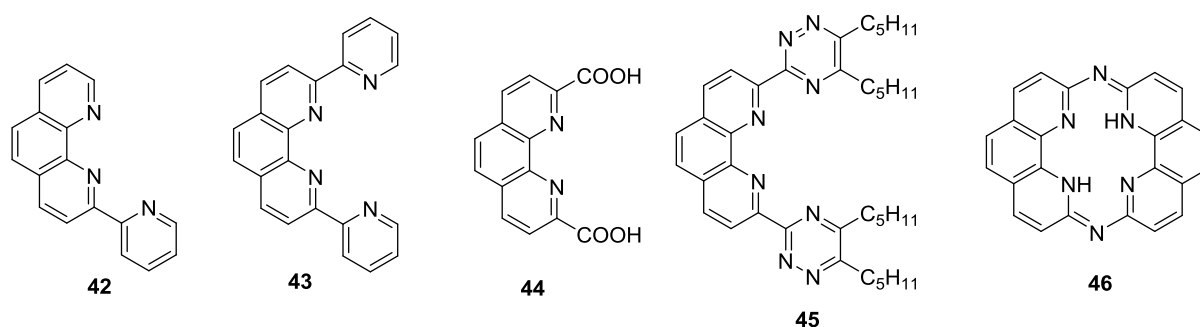


Figure 10. Examples of phen_{(2)sub} and phen_{(2,9)sub} showing improved chelating properties.

Functionalizing phen in positions 2 and 9 can have topological advantages too. For example, phen_{(2,9)sub} can be used as a rigid spacer forcing functional groups grafted in α of the chelating nitrogen atoms to stand in a non-parallel face-to-face geometry (case of the complex **47** in figure 11).¹⁶⁵

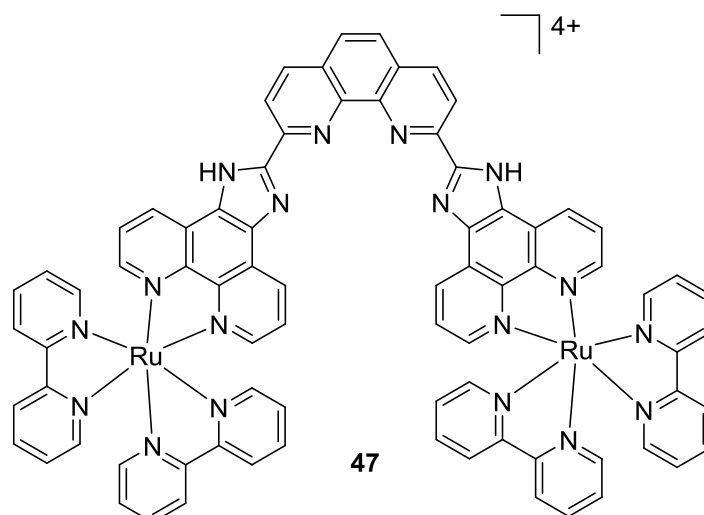


Figure 11. Example of a phen bridged ruthenium dinuclear complex.

The best example of using positions 2 and 9 of phen for their topological advantages is the famous method developed by Sauvage and co-workers to design the first template-base self-assembled catenanes.¹⁶⁶ The strategy relies on appending chains in positions 2 and 9 of phen, bearing reactive ends. In presence of copper(I) ions, a homoleptic tetrahedral complex forms, pre-organizing the chains which can be connected in the adequate conditions. Demetallation leads to two interlocked rings. This proved to be the start of a long and successful story in supramolecular chemistry.¹⁶⁷⁻¹⁶⁹ Many related molecular objects (catenanes, rotaxanes, molecular knots...) were designed using this strategy or similar ones and their synthesis and properties are reviewed somewhere else.¹⁷⁰⁻¹⁷⁴¹⁷⁵⁻¹⁷⁸

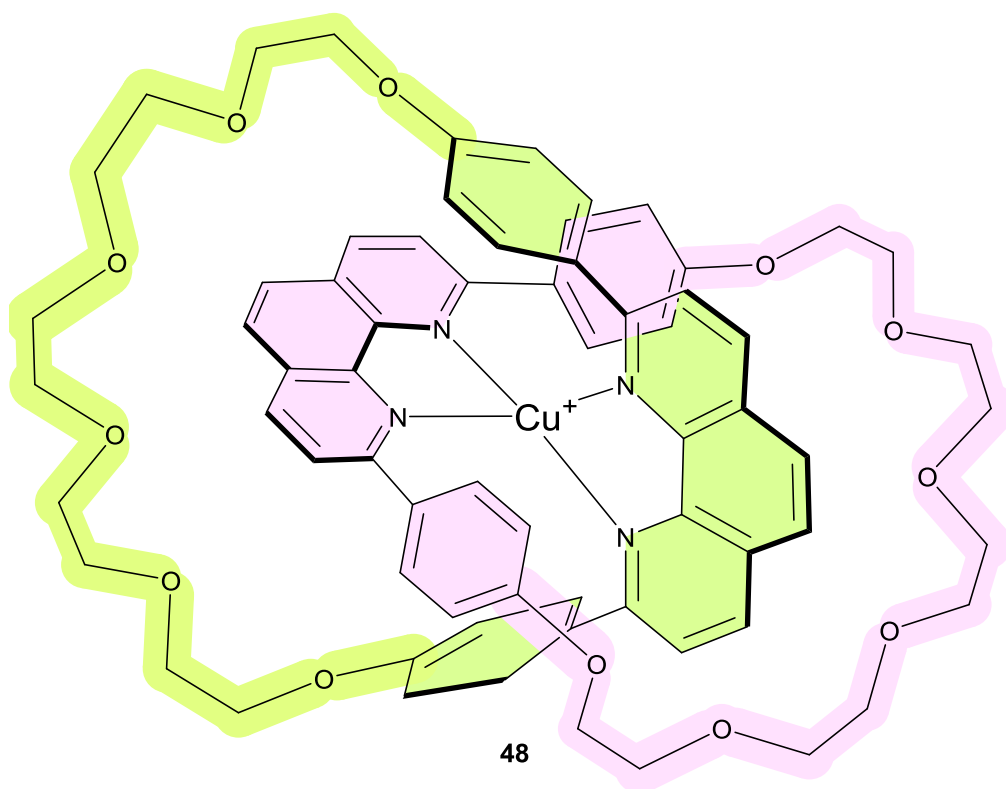


Figure 12. Historical example of the first catenane **48** obtained via the template effect.¹⁶⁶

- Substituting phen in positions 3 and 8

As will be seen, the functionalization of phen in positions 3 and 8 is certainly the less documented among all eight positions. For example, only one phen_{(3)sub} and one phen_{(3,8)sub} are commercially available from a decent number of suppliers (3-bromo-1,10-phenanthroline and 3,8-dibromo-1,10-phenanthroline, 80 suppliers on average, Figure 4).

There are nevertheless different motivations justifying the functionalization of phen in positions 3 and 8, like allowing to design linear “rod-like” arrays bearing fully available coordination sites all along the structure.^{179,180} This was especially exploited in the field of metal organic frameworks,^{181,182} for the design of coordinating molecular axle for rotaxane design (**49**, Figure 13)^{183,184} and for the elaboration of original supramolecular self-assembled nano-objects (boxes, ladders,¹⁸⁵ triangles¹⁸⁶).

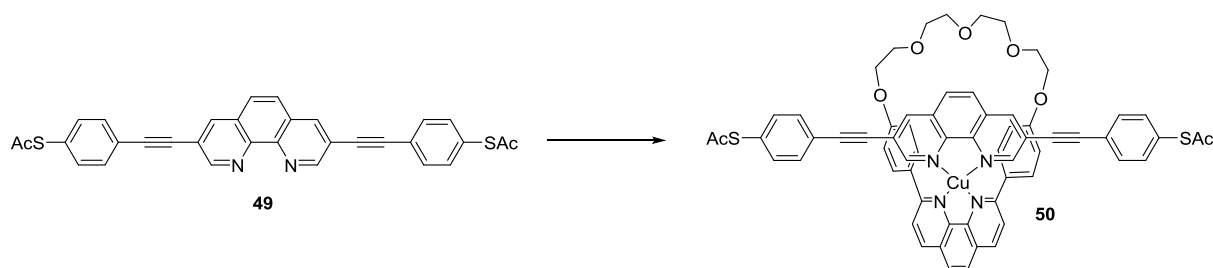


Figure 13. Axle **49** for the design of rotaxane.

Positions 3 and 8 are often chosen to extend the structure of phen without modifying to a large extent its chelating properties. For instance, Meunier and co-workers have designed phen dimers (“clip-phen”) allowing to prepare copper complexes which remained stable in dilute biological medium, and were able to cleave DNA efficiently.^{73,187} Initially, the two phen moieties were linked by a spacer attached in position 2 (**51**, Figure 14) but this negatively affected the DNA cleavage activity of the complexes. Bridging the two phen units by a spacer attached to position 3 in each case (**52**, Figure 14) entailed a more efficient cleavage activity of the corresponding copper complex.¹⁸⁸

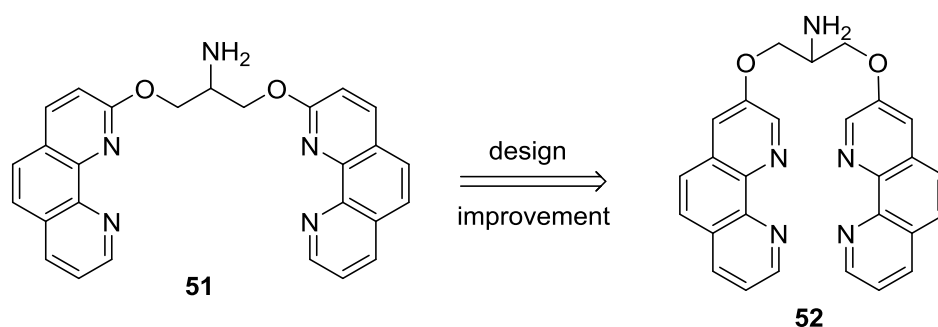


Figure 14. “Clip-phen” ditopic ligands: from mildly efficient phen_{(2)sub} dimer to efficient phen_{(3)sub} dimer.

The presence of sterically challenging groups in positions 3 and 8 can strengthen the steric hindrance in other positions, in particular in positions 2 or 2 and 9. In the example of ligand **53**, phenyl groups in positions 3 and 8 can prevent the free rotation of a binaphthyl substituent

tethered in position 2. This increases the efficiency of the enantioselective epoxidation of α -enones catalyzed by Fe^{2+} -**53** complexes (Figure 15).¹⁸⁹ Similarly, methyl groups in positions 3 and 8 are believed to reinforce the rigidity of the phen_{(2,9)sub} ligands and thus strongly increase the emission quantum yield and lifetime of the corresponding homoleptic copper(I) complexes (Figure 15).^{190,191} As mentioned above, the excited state properties of the latter complexes strongly depend on the rigidity of the coordination cage. Here, the emission quantum yield of $[\text{Cu}(\mathbf{41})_2]^+$ is seven times higher than the one of $[\text{Cu}(\mathbf{35})_2]^+$.¹⁹¹

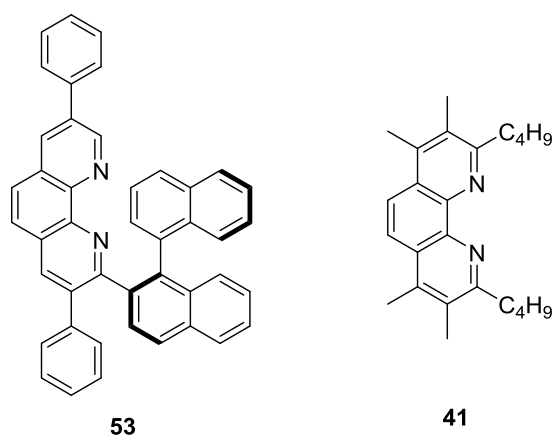
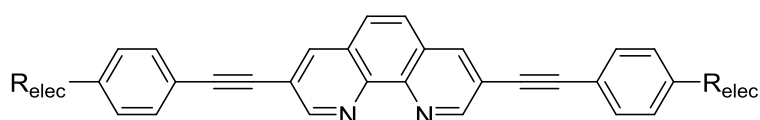


Figure 15. Examples of phen_{sub} ligands **53** and **41** where substituents in positions 3 and 8 strengthen the steric strain in position 2 or positions 2 and 9.

Functionalizing positions 3 and 8 with R groups impacts the electronic properties of phen (Table 3). Tor and co-workers have reported another case study where alkynyl-phenyl moieties, bearing electron withdrawing and donating groups R_{elec} , were grafted onto positions 3 and 8 of phen (Table 6).^{192,193} Importantly, the alkynyl spacer ensures that steric effects can be ignored and that the electronic communication between phen and the phenyl substituents is significant. As can be observed, extending the conjugation in positions 3 and 8 leads to a substantial red-shift of the π - π^* and n - π^* transitions compared to plain phen (Table 6). The remote substituent R_{elec} exerts a sizable influence: electron donating groups tend to exacerbate the observed red-shift of the absorption bands (**55** and **56**, probable stabilization of π^*

orbitals), while electron accepting groups (**57**, destabilization of π^* orbitals) have the opposite effect. This study has permitted to highlight another interesting feature. Although phen is only weakly luminescent, phen_{(3,8)sub} can be impressively fluorescent.^{193–195} In the case described in Table 6, Tor and co-workers have hypothesized that increasing the conjugation of phen on positions 3 and 8 would lead to highly fluorescent phen-based dyes because the most intense electronic transition of phen is polarized along the C₃-C₈ axis.¹⁹⁶ This strategy has proved successful, since ϕ_{em} (**54-57**) are spectacularly larger than $\phi_{em}(\text{phen})$ (Table 6).

Table 6. Impact of the presence of alkynyl moieties in positions 3 and 8 of phen on the optical properties of phen_{(3,8)sub}. Absorption¹⁹² and emission¹⁹³ data recorded in acetonitrile.

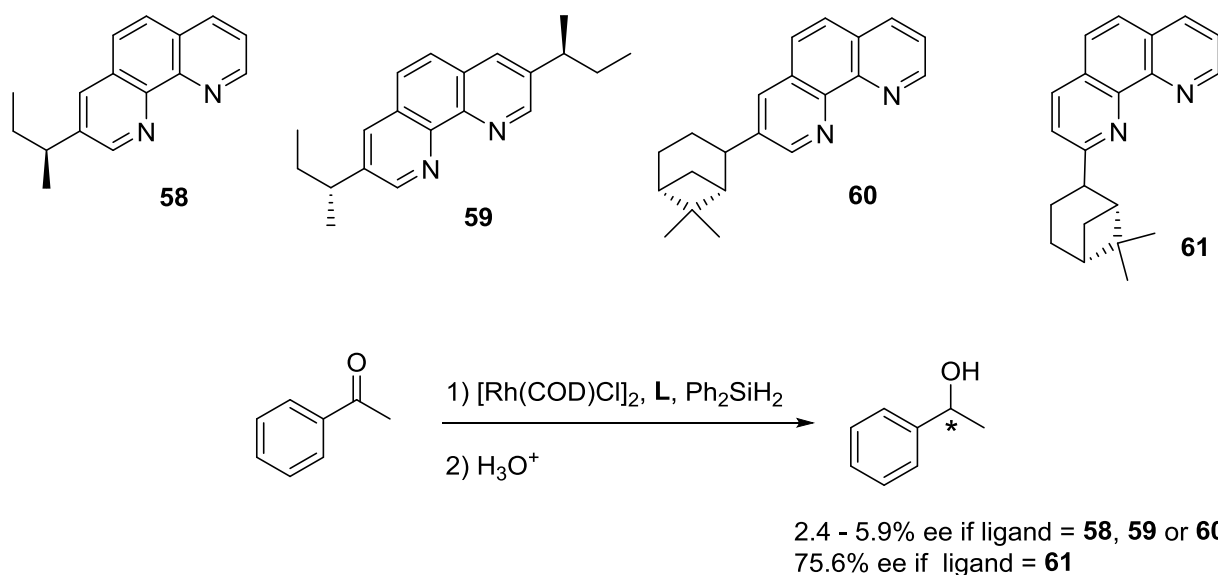


R _{elec}	Identity	λ_{abs}	λ_{em}	ϕ_{em}
-	Phen	230, 264		< 0.1%
H	54	284, 340	375, 392	0.41
CH ₃	55	286, 346	383, 396	1.0
OCH ₃	56	290, 352	441	0.64
CF ₃	57	286, 338	n.r.	n.r.

The reported reduction potentials of phen_{(3,8)sub} ligands are ordinarily affected by the presence of substituents.^{179,183} For example, if R_{elec} = S-acetyl (Table 6), the cyclic voltammogram of the corresponding phen_{(3,8)sub} exhibits a reduction potential at ca. -1.67 V vs. SCE in dichloromethane solutions,¹⁸³ which is considerably less negative than the reduction potential

of phen (more negative than -2 V vs. SCE, value estimated from Al-Anber et al.)³ and due to the increased conjugation over phenyl-ethynyl appendices.

Chiral copula were attached to positions 3 and 8 of phen,¹⁴⁷ leading to chiral catalysts such as **58-60**. Those catalysts were developed for the enantioselective Rh-catalyzed hydrosilylation of ketones (Scheme 3). The catalytic systems are operational but lead to moderate enantiomeric excesses; interestingly, when the same chiral copula is affixed to position 2 (**61**) instead of 3 (**60**), the enantiomeric excess of the catalysed reaction is increased by one order of magnitude. This tends to demonstrate that the chirality transfer is much more prominent when the chirality center is closer to the metal ion.



Scheme 3. Enantioselective hydrosilylation of ketones in presence of chiral phen ligands

- Substituting phen in positions 4 and 7

Positions 4 and 7 are sometimes designated as “para” positions with regards to the nitrogen atoms of phen. Substituents in these positions “diverge away” from the phen fragment. Usually, functionalization in those positions is motivated by the will to modify the properties

of phen without sterically hindering the coordinating cavity. Indeed, positions 4 and 7 are remote from the N[∧]N chelate and therefore functionalization in those positions by large groups is unlikely to affect the coordination capacity of the ligand. For example, large dendrons have been grafted to positions 4 and 7 affording very bulky ligands **62**¹⁹⁷ and **63**¹⁹⁸ (Figure 16). Yet, their copper(II) or ruthenium(II) complexes were easily prepared in standard conditions (N.B. homoleptic Cu(I) complexes bearing phen_{(2,9)sub} ligands decorated in positions 2 and 9 by dendrons have been obtained despite the steric strain,¹⁵¹ thanks to the tetrahedral geometry which limits steric clashes between dendrons).

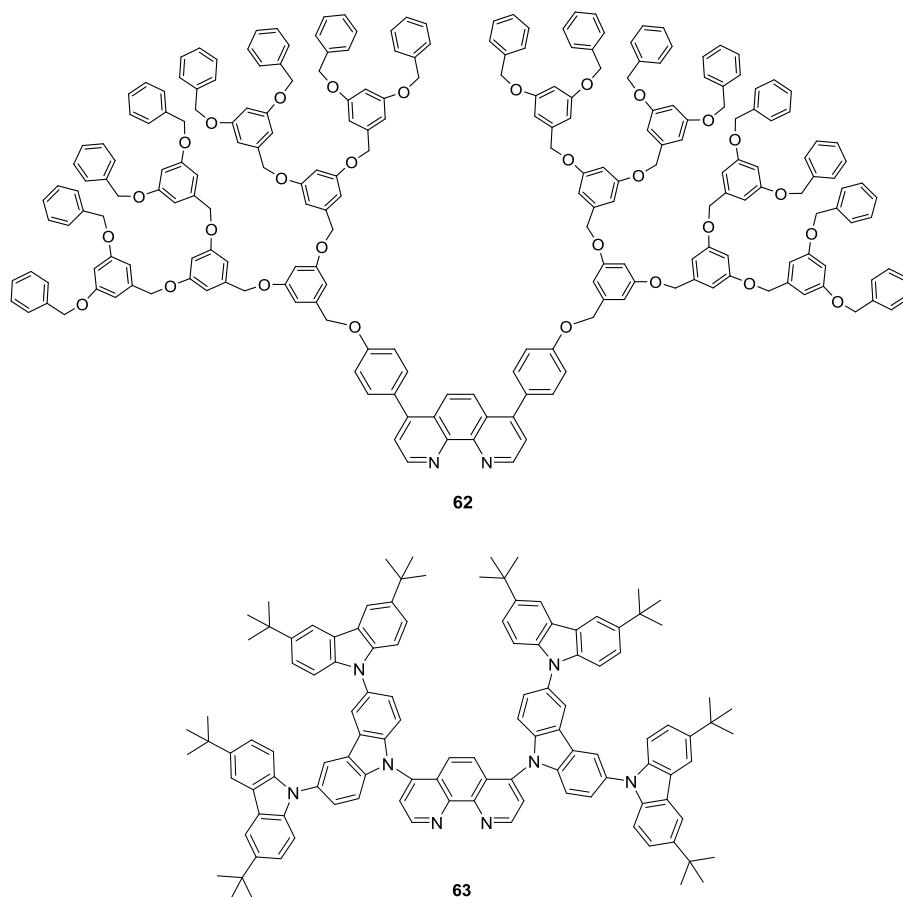


Figure 16. Examples of dendritic phen_{(4,7)sub} ligands

Preserving the chelating properties of phen may be crucial in a few catalytic processes, as demonstrated by Yuan and co-workers who have developed a series of phen ligands substituted in different positions by oligoethyleneglycol chains (Figure 17).^{89,199} The obtained

ligands **64** and **65** are used to design water soluble catalysts and aqueous metallomicelles.²⁰⁰ In the latter case, the metallomicelles are used to catalyze aerobic Glaser coupling reactions in water; in presence of copper(I), ligand **65** has proved to be much more efficient than **64** to catalyze the Glaser homocoupling of ethynylbenzene, probably because the ethyleneglycol chains positioned in α of the chelating nitrogen atoms can interfere with the binding of the metal and the overall catalytic efficiency.

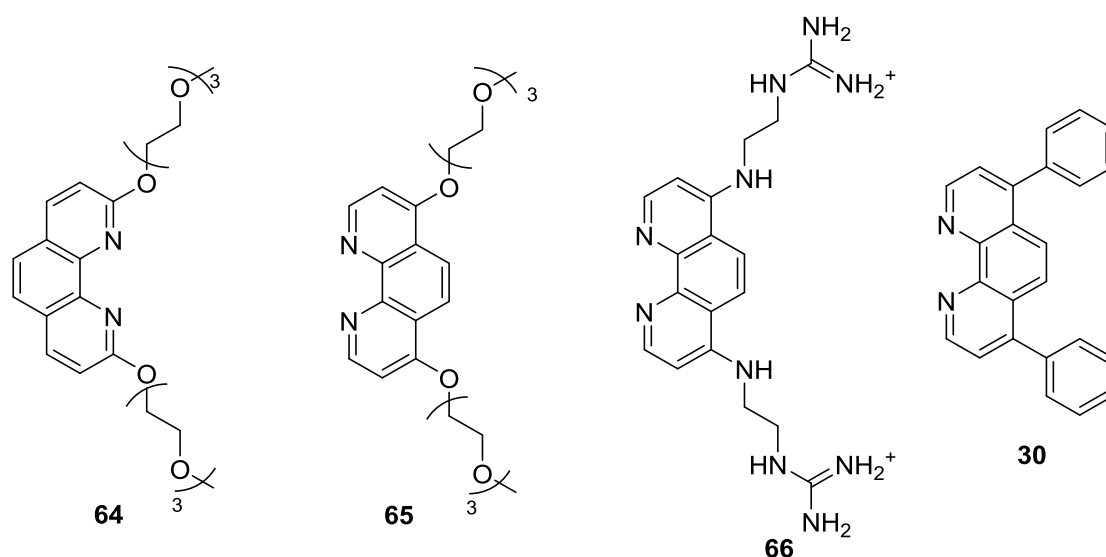


Figure 17. Ligands **64** and **65** developed for the aqueous Glaser homo-coupling of alkynes. Ligand **66** developed as G-quadruplex binder. Structure of bathophenanthroline **30**.

The impact of substituents on the electronic properties of phen and related complexes is usually strong, as presented above (Tables 3 and 4). For example, Ulven and co-workers have reported that tethering amines in positions 4 and 7 enhanced the basicity of the ligand and thus its capacity to protonate or to coordinate small ions (e.g. **66**, Figure 17).²⁰¹ **66** proved to be an efficient G-quadruplex stabilizer.

Appending electron-poor aryl or alkynyl-phenyl substituents leads to a destabilization of the phen-centred LUMO and therefore shifts the reduction potential of the ligand to less negative potential, and the HOMO to more positive potentials. This is the reason why 4,7-diphenyl-

1,10-phenanthroline **30**, best known as bathophenanthroline, is used as hole blocking layer in OLEDs.

Finally, conjugating electron deficient or electron rich moieties to positions 4 and 7 allows to strongly influence the extinction coefficient and the wavelength of the metal-to-ligand charge transfer transitions of associated M^{x+} -phen_{(4,7)sub} complexes. This phenomenon results from the more extended π system of the considered phen_{(4,7)sub} ligands. Considering again the case of bathophenanthroline **30**, the phenyl groups in positions 4 and 7 are barely conjugated to phen because they stand almost perpendicular to the planar polyaromatic system, but in spite of this ruthenium complex $[Ru(\mathbf{30})_3]^{2+}$ is endowed with a significantly larger ϵ than $Ru(phen)_3^{2+}$. This is exacerbated when the phenyl rings are fully conjugated to phen through an ethynyl spacer.²⁰²

- Substituting phen in positions 5 and 6

Similar to positions 4 and 7, positions 5 and 6 are located far away from the coordinating nitrogen atoms. Therefore, tethering sterically challenging substituents in those positions will not affect the coordinating capacity of phen, from the steric point of view. However, since C₅ and C₆ are vicinal, the functionalization of both positions with bulky groups can be difficult and requires optimization of the reaction conditions.⁸¹

Groups attached to positions 5 and 6 are diametrically opposed to the N \widehat{N} chelating ring. Those positions have been chosen in many instances to attach functional molecular arrays through molecular linkers in order to design linear dyads. Those dyads were especially designed for photo-induced electron transfer such as the complex **67** (Figure 18).²⁰³ In the latter case, the Ru-phen moiety acts as a sensitizer, which is linked to the Os³⁺ electron acceptor *via* a spacer. This spacer is bound purposefully in positions 5 and 6 of phen, in order to place the acceptor as far as possible from the sensitizing Ru-phen fragment to try and limit

counter-productive back electron transfer. Similar photo-induced events occur within dyad the complex **68** (Figure 18), where the electron acceptor is a H₂ evolving catalyst.²⁰⁴

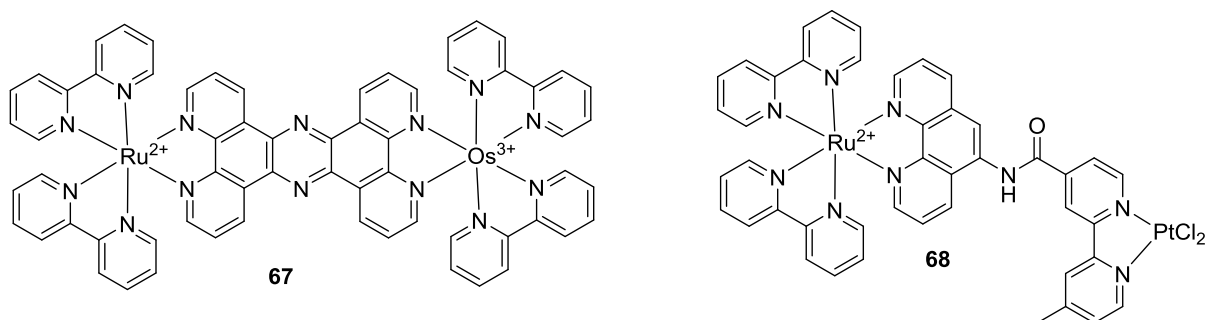


Figure 18. Example of molecular dyad (right) designed for the implementation of long-lived photo-induced charge separation states.

The presence of substituents in positions 5 and 6 impacts the overall electronic properties of phen as presented above (Table 4). The examination of a few selected studies has made us tentatively state that the effect of substituents in those positions is less prominent than it is in other positions of phen.

From the synthesis point of view, positions 5 and 6 of phen show a particularity. Indeed, the C₅-C₆ bond features a significant olefin character.²⁰⁵

One of the most famous phen_{(5,6)sub} derivative is dppz (dipyrido[3,2-a:2',3'-c]phenazine, **69**, Figure 19). This ligand consists in the fusion of a quinoxaline moiety with the phen core. This ligand and associated complexes have been widely studied.²⁰⁶ In particular the fusing of one or several aromatic rings on phen has allowed to increase the rigidity and planarity of phen, therefore promoting its intercalative capacity in DNA.^{207–209} This is again epitomized by DPPZ ligand and its derivatives, which have led to large collection of DNA probes and cytotoxic molecules.^{209–212}

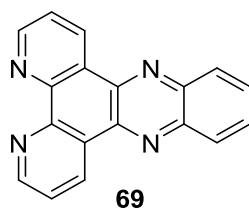


Figure 19. Structure of the dppz ligand

Scope and limitations

Considering all the above examples, the functionalization of phen in one or several positions allows to tune its properties and implement desired functionalities in this “all-terrain” ligand. We plan in this review to gather and sort all the existing synthetic strategies for the stepwise polyfunctionalization of phen in all various positions, in order to provide to all coordination chemists a useful tool box for the design of virtually any polyfunctional ligand. We wish to allow all the researchers to identify quickly the best methods to make surgical alterations of the phen backbone on any position.

We identified two main ways to figure out the synthesis of an extended phen molecule. The first, maybe more obvious one, is to start from plain phen or derivatives which are easily commercially available (Figure 4) and further decorate those phen molecules using different strategies. As such, the extension of the structures from simple phen to more complicated phen-based molecules can be pictured as diverging away from a phen core, and for this reason we will qualify those methods of “divergent synthetic pathways” (Figure 20, right). Another way to envision the preparation of a functionalized phen molecule is to exploit the synthesis of plain phen itself from simpler, smaller reagents (like orthophenylenediamine or 8-aminoquinoline for example). More complex starting materials are first prepared and the polyfunctional phen is obtained in a subsequent condensation step. This strategy opposes to the previous one, since the phen motif is formed after preliminary functionalizations of

relevant reagents, and will therefore be qualified of “convergent synthetic pathway” (Figure 20, left).

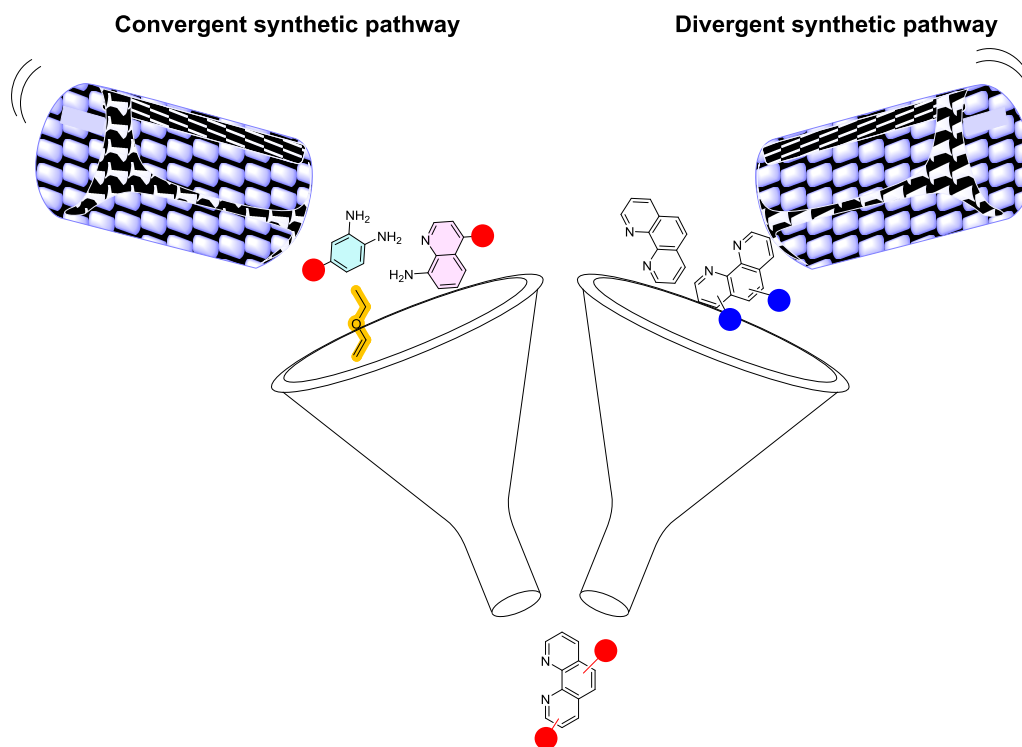


Figure 20. Illustration of the convergent and divergent synthetic pathways

We will thus present both approaches in this review: we will first focus on the convergent syntheses of phen_{sub} because virtually all commercially available phen-based starting materials (which will be used in the divergent syntheses section) are obtained from convergent methods.

The aim of this review is not to give a list of all possible phen ligands but to provide the reader with an exhaustive list of all methods and strategies to functionalize phen in all positions, with a focus on relevant useful versatile phen-based building blocks. Occasionally we will present landmark examples of such complex structures.

The scope of our review will be limited to 1,10-phenanthroline, excluding all related ligands bearing more intracyclic heteroatoms or polyaromatic systems (with a few exceptions) where one or several aromatic cycles have been fused to the phen original molecule.

2. Convergent synthetic pathway

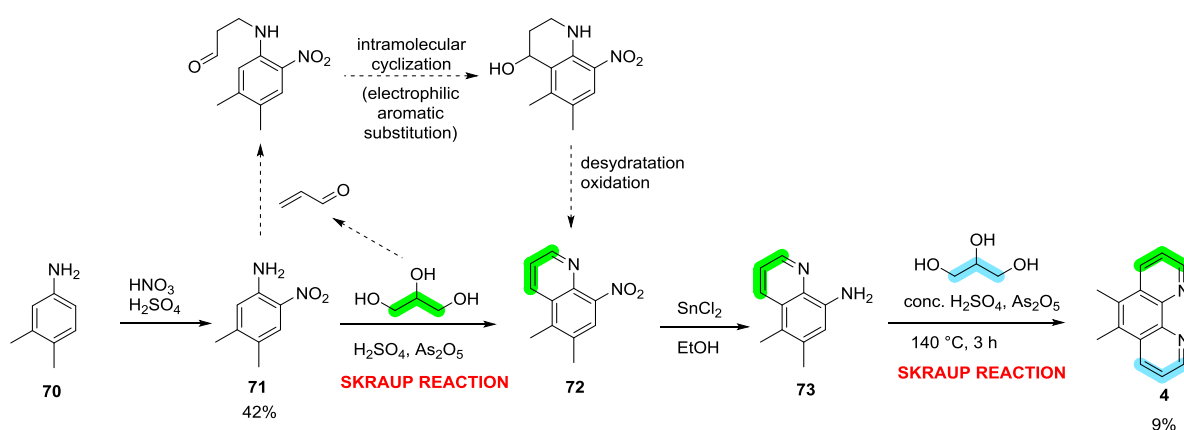
In the so-called “convergent functionalization”, polyfunctional phen_{sub} are obtained in a last condensation step from well-designed precursors like hydroxyquinoline or substituted quinolines or o-phenylenediamine. The seminal work on the convergent synthesis of phen was proposed by Pr. Case using for the condensation reaction the Skraup reaction. Other methods have been developed using the Povarov, the Friedländer or the Doebner Von-Miller reactions and more recently the use of β -ketoester or Meldrum’s acid to obtain polyfunctional phen and they will be discussed in the following part.

2.1. Skraup and Doebner-Von Miller reactions

The Skraup and Doebner-Von Miller reactions consist in the condensation of a Michael acceptor (e.g. an α -enone or a precursor of α -enone like glycerol) followed by a intramolecular cyclization in strongly acidic medium, sometimes at high temperatures, and finally completed by an oxidation step leading to the aromatization. The differences between the two protocols are unclear (in many cases, Skraup reaction is called and Doebner-Von Miller reaction and conversely).²¹³ Usually the Skraup reaction is performed in strongly acidic medium, between 8-aminoquinoline and glycerol (or any α -enone precursor), in presence of As₂O₅ as oxidant. The Doebner-Von Miller reaction is performed in strongly acidic medium too, between 8-aminoquinoline and α -enones. Although the frontier between the two protocols is often crossed, we will attempt to address those two strategies in two sections.

2.1.1. Skraup reaction

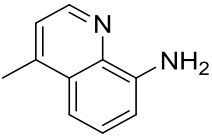
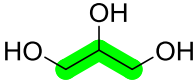
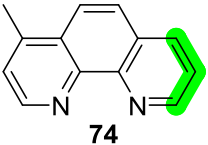
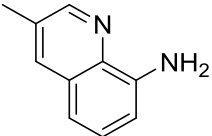
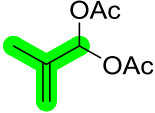
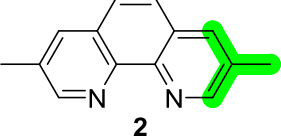
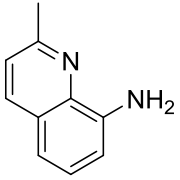
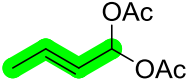
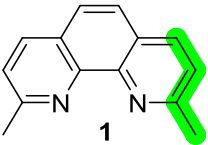
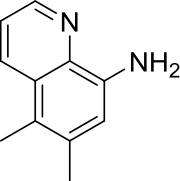
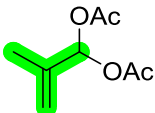
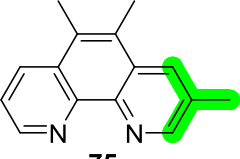
As mentioned above, the seminal work on convergent synthesis of phen_{sub} was developed by Pr. Case using the Skraup reaction. This reaction consists in the synthesis of quinoline derivatives using primary aromatic amines, glycerol, and an oxidizing agent such as arsenic pentoxide in concentrated sulfuric acid. Briefly, glycerol is oxidized in acroleine in acidic medium and condense on the aromatic amine *via* a Michael addition leading to an aminoaldehyde. Intramolecular cyclization followed by deshydration leads to the desired quinoline (Scheme 4). Applying the same protocol, but using 8-aminoquinolines instead of primary aromatic amines as reactants logically leads to the formation of the phen molecular skeleton. In Case's work,²¹⁴⁻²¹⁶ the preparation of functionalized phen_{sub} has been carried out starting with 3,4-dimethylaniline **70** that is nitrated to yield 2-nitro-4,5-dimethylaniline **71**. Then by using a Skraup reaction with glycerol and arsenic pentoxide, the quinoline **72** was formed and after reduction of the nitro group yielding **73**, a second Skraup reaction was performed to obtain **4** (Scheme 4).²¹⁴⁻²¹⁷ We can underline that obtaining **4** from naked phen is a very difficult task, putting premium on the relevance of convergent synthetic procedures.

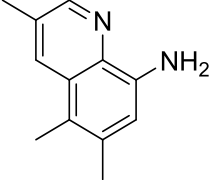
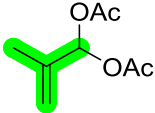
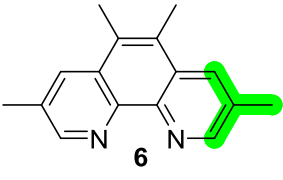
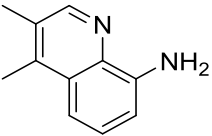
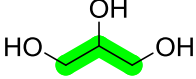
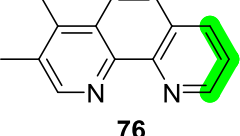
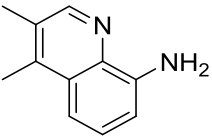
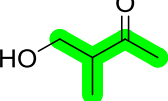
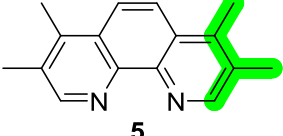
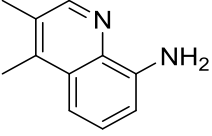
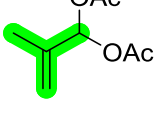
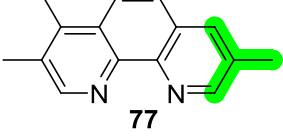
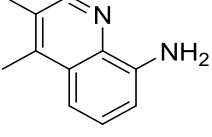
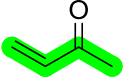
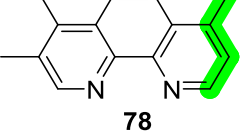
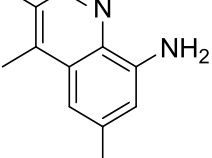
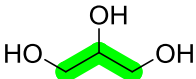
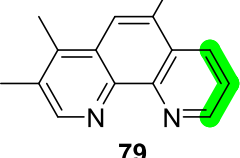
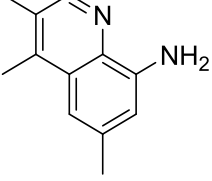
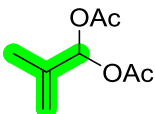
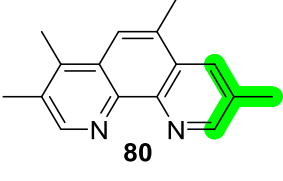


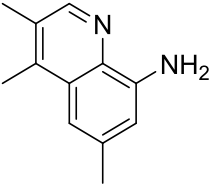
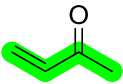
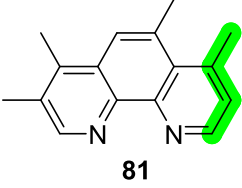
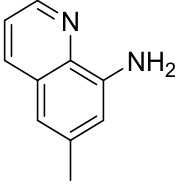
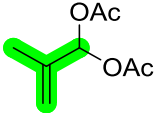
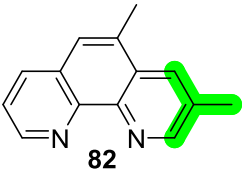
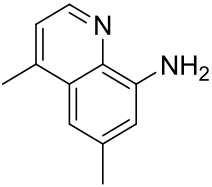
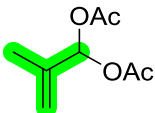
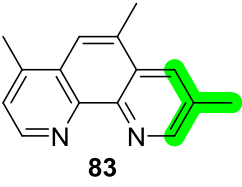
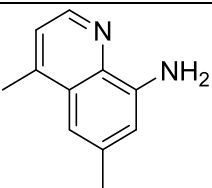
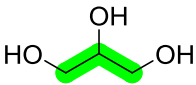
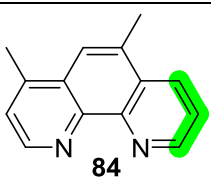
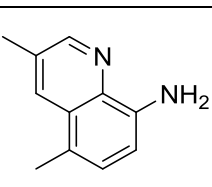
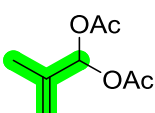
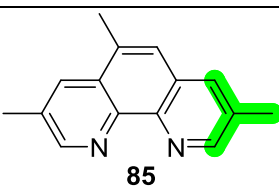
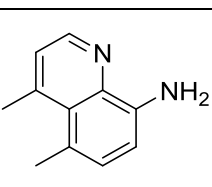
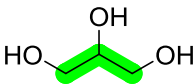
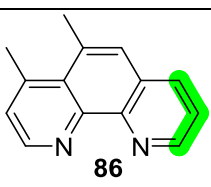
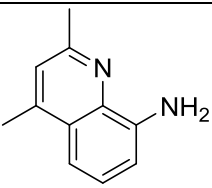
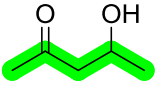
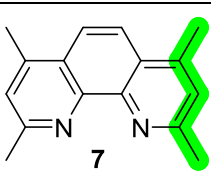
Scheme 4. First convergent synthesis of 5,6-dimethyl-1,10-phenanthroline **4** described by Case.²¹⁴

Then, by varying the different substituents on the intermediate quinoline and changing the glycerol by either 2-methyl-2-propene-1,1-diol diacetate or 2-butene-1,1-diol diacetate or methyl vinyl ketone compounds (namely acroleine precursors with various substituents) and arsenic acid as oxidizing agent, various functionalized phenanthroline were obtained with yields varying from 1 to 31% (Table 7).

Table 7. Reagents used to yield methyl or phenyl polyfunctionalized phen. The fragments of the final phen_{sub} coming from the reagent (glycerol or derivatives) are highlighted in green.

Substituted quinoline	Reagent for the Skraup reaction	Phenanthroline	Yields (%)	Ref
		 74	15	214
		 2	9	214
		 1	7.5	214
		 75	9	214

			22	214
			22	216
			20	216
			9	216
			31	216
			18.5	216
			8.5	216

			5	216
			4	215
			14.5	215
			11	215
			8.5	215
			24	215
			23.5	217

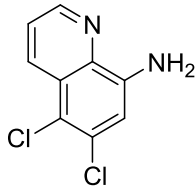
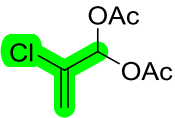
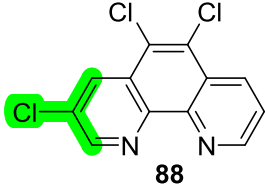
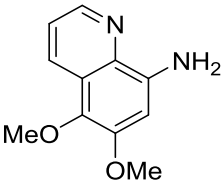
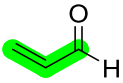
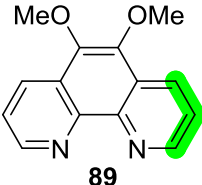
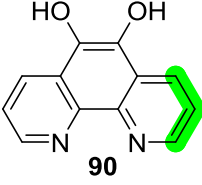
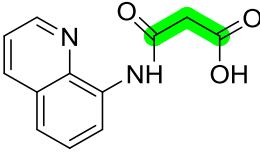
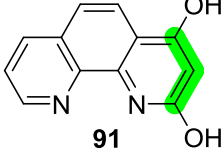
			17.8	217
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The authors continued with a series on ethyl-substituted phen obtained from ethyl-substituted 8-aminoquinoline, with yields varying from 16% to 47% using the same conditions.²¹⁸

The Skraup reaction is not limited to alkyl-functionalized phen_{sub}. Case et al.^{214,219} have synthesized as well a series of chloro-substituted-1,10-phen with yields varying from 3.5%²¹⁴ to 38% (Table 8). The chlorine atoms can be either on the amino-quinoline reactants (**87**) or on the Michael acceptor (**88**). A series of methoxy (and hydroxy) phen can be synthesized with yields varying from 9%²¹⁹ to 74% (Table 8) using in those conditions phosphoric acid instead of sulfuric acid.²²⁰ The methoxy groups can be grafted to 8-aminoquinoline reactants (**89-91**). The obtained methoxy-phen are hydrolyzed in the corresponding hydroxyphen using hydrogen iodide (**89-91**, Table 8). Thus, phen bearing further functionalizable groups can be successfully obtained in the Skraup's conditions.

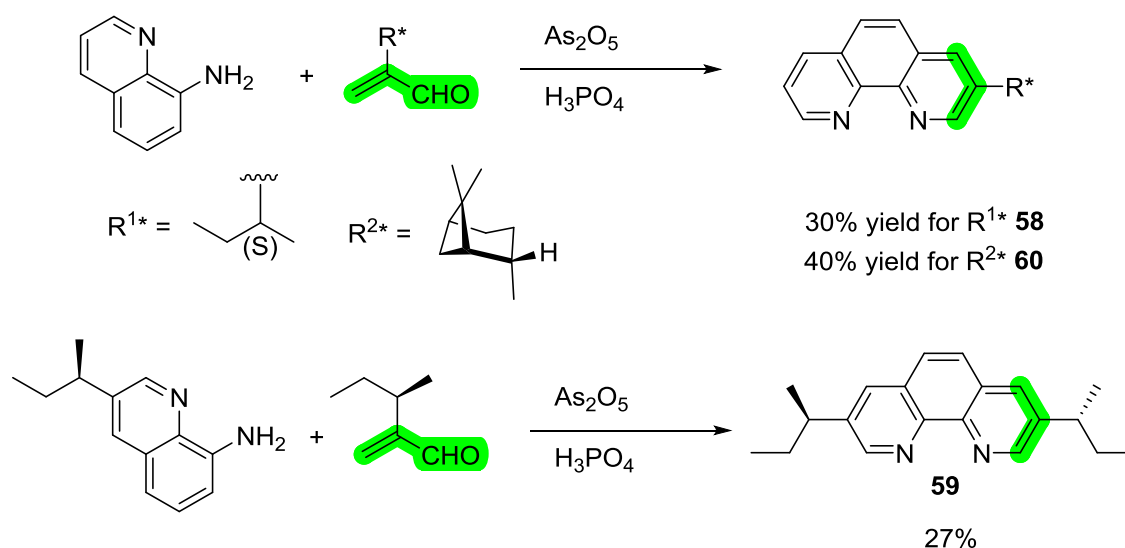
Table 8. Reagents used to yield chloro or hydroxy-polyfunctionalized phen. The fragments of the final phen_{sub} coming from the reagent (glycerol or derivatives) are highlighted in green.

Substituted quinoline	Reagent for the Skraup reaction	Phenanthroline	Yields (%)	Ref
			38	219

		 <p style="text-align: center;">88</p>	7.9	219
		 <p style="text-align: center;">89</p> <p style="text-align: center;">After hydrolysis,</p>  <p style="text-align: center;">90</p>	33	220
	-	 <p style="text-align: center;">91</p>	74	220

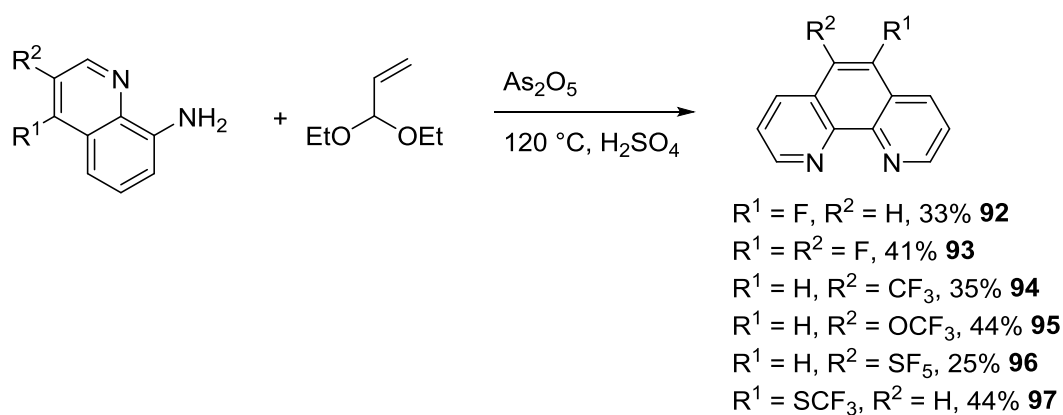
Since this pioneering work, the Skraup reaction has been tremendously used and improved.^{17,83,148,198,221–237} In the following, only selected examples will be presented.

Gladiali et al.^{17,148,222} have synthesized optically active phenanthroline using a Skraup reaction. In that regard, they heated 8-aminoquinoline with chiral acrolein derivatives in phosphoric acid and in the presence of arsenic acid (Scheme 5) that yielded chiral phenanthrolines. Those chiral ligands were used in rhodium-catalyzed asymmetric transfer hydrogenation of acetophenone.



Scheme 5. Optically active phen_{(3,8)sub} obtained by a Skraup reaction

From the perspective of green chemistry, the elimination of toxic reagents like arsenic oxide, the adoption of water as a sustainable solvent, and the advancement of alternative microwave irradiation techniques were undertaken. Saggadi et al.²³⁴ have performed the Skraup reaction with substituted 8-aminoquinoline and glycerol in water and used sulfuric acid instead of arsenic oxide activated by microwave to obtain phen_{sub} in 15 min with 15% yield. Lüdtkke et al.²³⁵ have synthesized fluorine containing phen using acrolein diethyl acetal for 90 min at 120 °C and the yields range from 25 to 44% (Scheme 6). By substituting glycerol (as proposed in the original procedure) with acrolein diethyl acetal, it became feasible to reduce the reaction temperature and shorten the overall reaction time allowing the synthesis of **94** for example. Conversely, in the classical Skraup conditions (higher temperature, use of concentrated sulfuric acid and longer time) the CF₃ group was hydrolyzed.

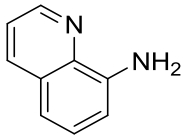
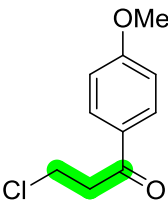
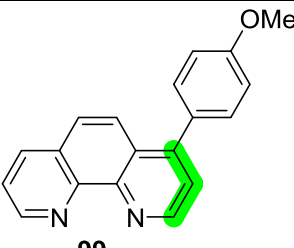
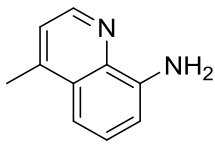
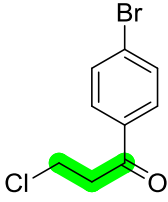
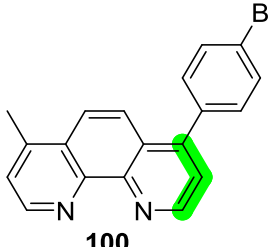
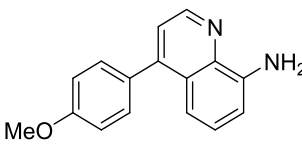
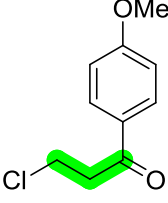
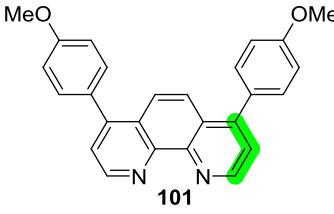
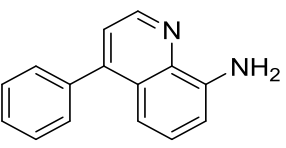
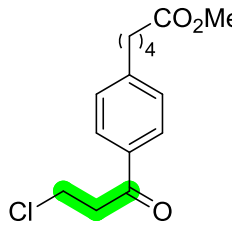
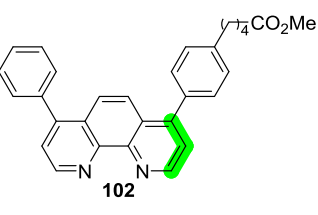
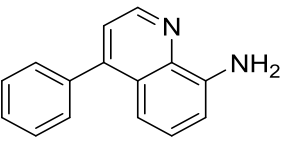
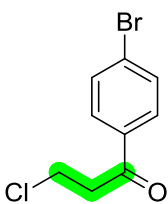
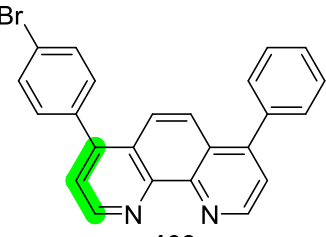


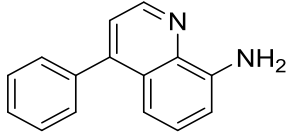
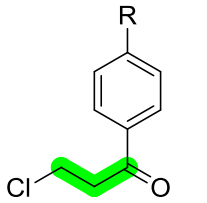
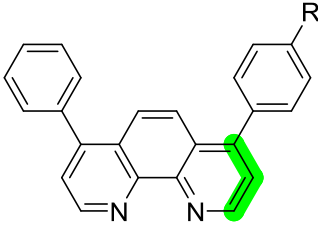
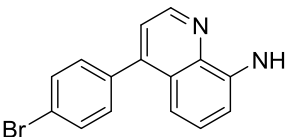
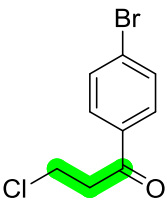
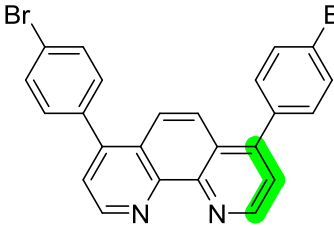
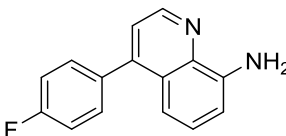
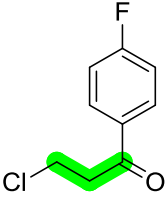
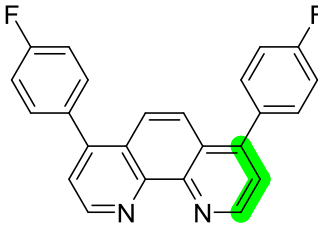
Scheme 6. Synthesis of fluorine containing phen

Finally, some other examples are summarized in Table 9 and show the limitless diversity of the structures which can be obtained from the Skraup synthesis. In those examples, 8-aminoquinolines are reacted in presence of 3-chloro-1-phenylpropan-1-one derivatives. The mechanism remains the same and begins with the formation of an imine and subsequent intramolecular cyclization and HCl elimination.

Table 9. Reagents used to yield various polyfunctionalized phen using Skraup reaction

Substituted quinoline	Reagent for the Skraup reaction	Phenanthroline	Yields (%)	Ref
		<p style="text-align: center;">98</p>	52	223,224

		 <p style="text-align: center;">99</p>	25	225
		 <p style="text-align: center;">100</p>	71	226
		 <p style="text-align: center;">101</p>	67	198
		 <p style="text-align: center;">102</p>	73	227
		 <p style="text-align: center;">103</p>	55	228

	 R ¹ = C ₃ H ₆ OH R ² = C ₃ H ₆ CO ₂ H	 R ¹ = C ₃ H ₆ OH 104 R ² = C ₃ H ₆ CO ₂ H 105	R ¹ = 65 R ² = 60	229
		 106	60	230,231, 237
		 107	67	236

2.1.2. Doebner Von-Miller reactions

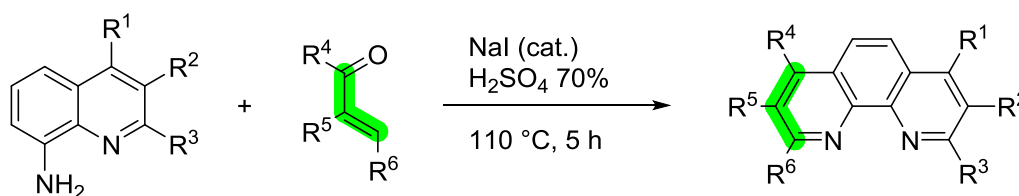
The Doebner and Von Miller reaction²³⁸ is very similar to the Skraup reaction but in this case the acroleine precursors (like glycerol) have been replaced by an α,β -unsaturated ketones or aldehydes that react with 8-aminoquinoline or o-phenylenediamine in acidic media. Sodium iodide can be added as a catalyst and the reaction is called in this case the Bucherer reaction.²³⁹ This reaction is often considered when the Skraup reaction is unsuccessful, or affords the target phen in low yields.

Butt et al.²⁴⁰ have succeeded in the 80's to obtain **3**, **7** or **5** from condensing α,β -unsaturated ketones with o-phenylenediamine at reflux in concentrated acidic media overnight. For

example, phen_{sub} **2** was obtained from reacting o-phenylenediamine and 2-methylacrylaldehyde at 110 °C in 70% H₂SO₄ solution for 16 h with sodium iodide as a catalyst with very low yield.²⁴¹

Aminoquinolines can be used as well. In the 1950's, Case et al.²¹⁹ have reacted 3 or 6-chloro-8-aminoquinoline with α-chloroacrolein diacetate in concentrated HCl and in presence of arsenic acid and zinc chloride. They have obtained 3,8- and 3,5-dichloro-1,10-phenanthroline with very low yields (2.5 and 2%, respectively). They applied the same conditions²¹⁷ on substituted 8-aminoquinolines with either tiglic acid (2-methylbut-2-enoic acid) or crotonaldehyde diacetate to obtain 2,3,8,9- or 2,5,6,9-tetramethyl-1,10-phenanthroline with 7.6 and 17.2% yields, respectively.

Belser et al.²⁴² synthesized various mono and dialkylated-phen in satisfying yields using 8-aminoquinoline or substituted 8-aminoquinoline as the starting material with crotonic aldehyde or methacrolein or methylvinylketone at reflux for 5 h in sulfuric acid and with sodium iodide as a catalyst (Scheme 7).



Phen	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Yield (%)
108	H	H	H	H	H	CH ₃	55
109	H	H	H	H	CH ₃	H	81
74	H	H	H	CH ₃	H	H	51
110	H	H	CH ₃	CH ₃	H	H	75

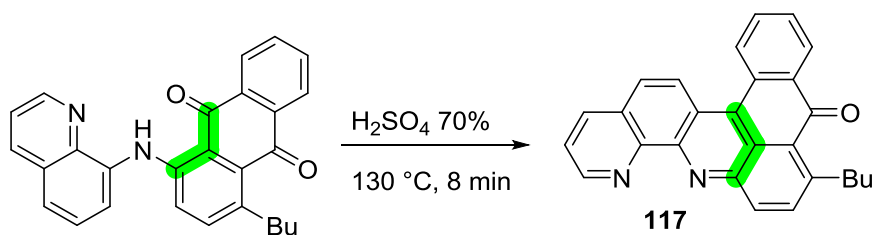
111	H	CH ₃	H	H	H	CH ₃	70
2	H	CH ₃	H	H	CH ₃	H	81
112	H	CH ₃	H	CH ₃	H	H	70
113	H	<i>t</i> Bu	H	H	<i>t</i> Bu	H	82
114	H	<i>n</i> Bu	H	H	<i>n</i> Bu	H	70
115	H	<i>t</i> Bu	H	H	CH ₃	H	91

Scheme 7. Convergent synthesis to obtain substituted phen described by Belser et al.²⁴²

The synthesis of **109** was as well reported by Thiele et al.²⁴¹ in similar conditions but with only 12% yield after 16 h of reflux.

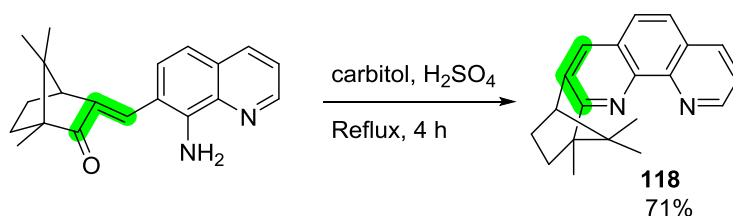
The reaction conditions are compatible with a number of functional groups appended on the different reactants and reagents. For example, with the same conditions as described above, Mobian et al.^{243,244} have synthesized the 3-bromo-7-methyl-1,10-phenanthroline with 67% yield by reacting 8-amino-3-bromoquinoline with methylvinylketone at reflux for 1 h, proving that the reaction conditions are harmless towards brominated aminoquinoline reactants. This ligand was then involved in a Suzuki reaction and the obtained ligand was further used to design catenanes. Pearson et al.²⁴⁵ synthesized with 21% yield 4-methyl-2-trifluoromethylated-1,10-phenanthroline using 8-aminoquinoline and trifluoro-3-penten-2-one.

Sarkar et al.²⁴⁶ described the cyclisation of quinolinylaminobutyl-anthraquinone **116** at 130 °C in acidic media to form the substituted phen **117** (Scheme 8).



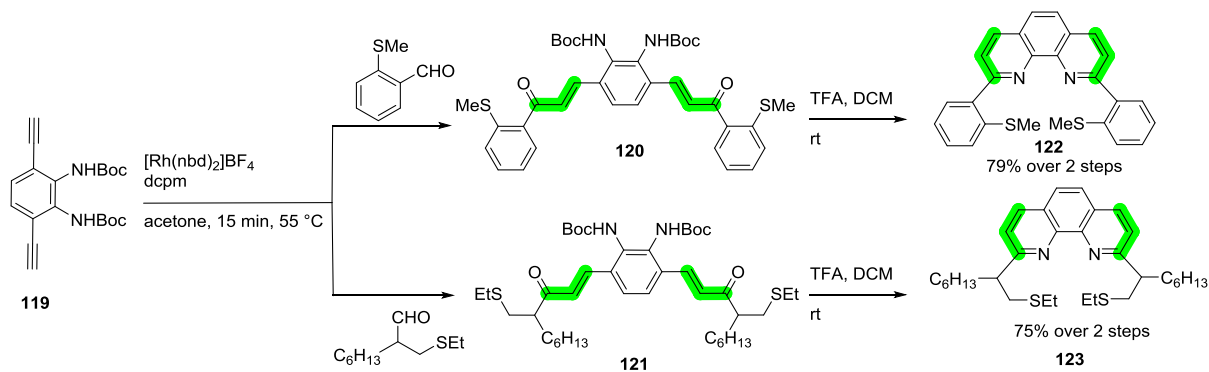
Scheme 8. Convergent synthesis to obtain phen **117**

Intramolecular Doebner-Von Miller reactions are feasible if the 8-aminoquinoline starting reactant is appropriately functionalized by an α -enone moiety. For instance, Chelucci et al.²⁴⁷ synthesized the camphor-fused phen_{(2,3)sub} **118** in refluxing carbitol (ca. 200 °C) and in the presence of a small amount of sulfuric acid (Scheme 9).



Scheme 9. Convergent synthesis to obtain a camphor-fused phen **118**

A remarkable double-intramolecular Doebner-Miller reactions has been reported by Neuhaus et al.²⁴⁸ who have synthesized phen_{(2,9)sub} from BOC-protected 3,6-diethynyl-ortho-phenylenediamine **119**. The Rh-catalyzed condensation of the latter with aldehydes leads to bis- α -enones **120** and **121** which are then submitted to acidic treatment in dichloromethane, leading in very mild conditions to new tetradentate phen **122** and **123** (Scheme 10). TFA proves here a very efficient catalyst for the reaction.



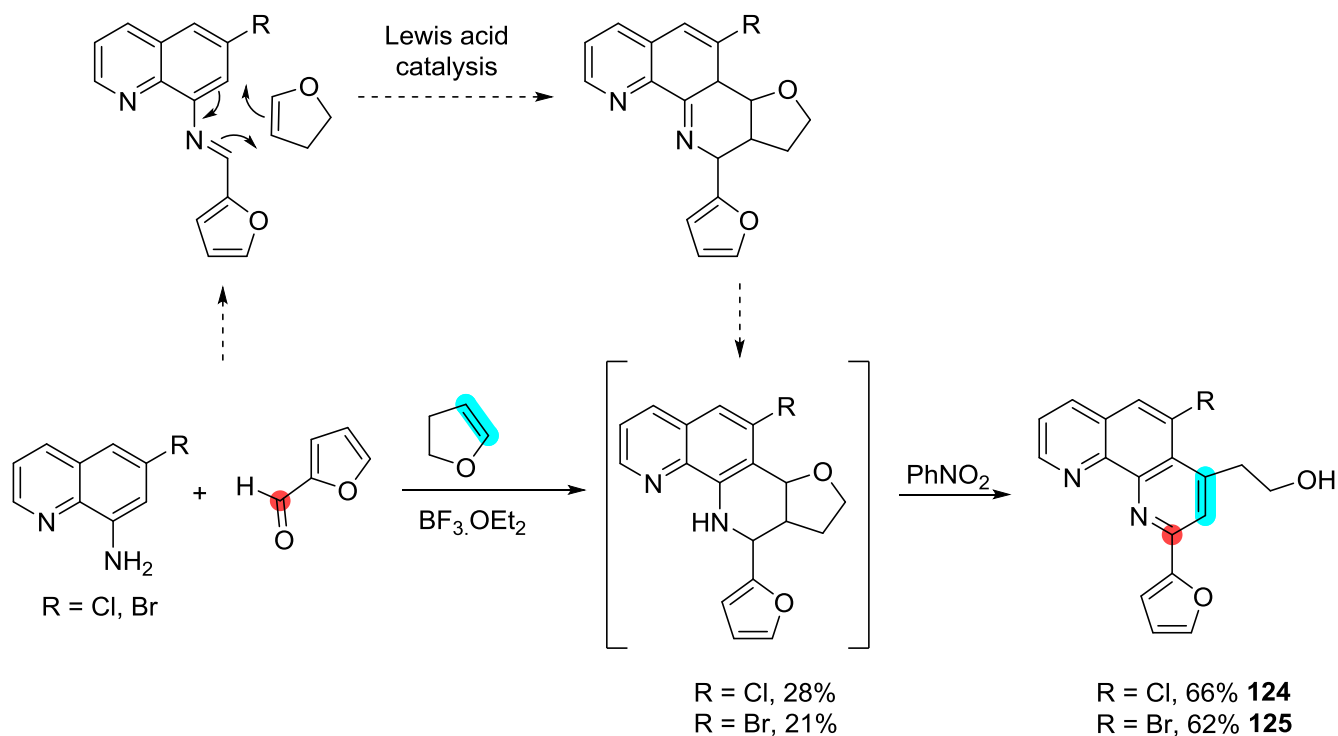
Scheme 10. Tetradentate phen **122** and **123** obtained through a double Doebner-Miller reaction reaction.²⁴⁸

2.2. Povarov reaction

The Povarov reaction, called the imino Diels-Alder reaction, is usually described as a cycloaddition between an aromatic imine and a dienophile (alkene or alkyne) in acidic conditions.²⁴⁹ The aromatic imine is usually formed from an aromatic amine in presence of an aldehyde. This methodology is widespread in heterocyclic chemistry, especially for the formation of quinolines.^{250,251} Furthermore, this reaction has been applied for the convergent formation of phen_{sub} using either o-phenylenediamines or aminoquinolines as starting material.

2.2.1. Alkenes as the dienophiles

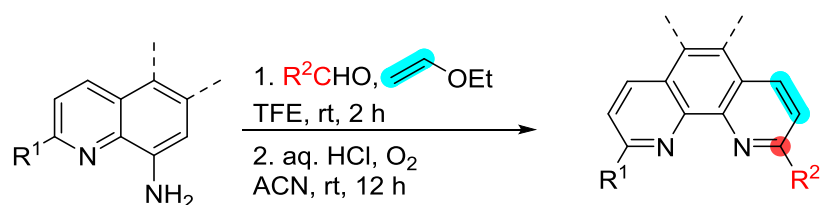
Zaitsev et al.²⁵² have performed a Povarov reaction on 8-amino-6-bromo and 8-amino-6-chloroquinolines with furfural that is further converted by cyclocondensation with 2,3-dihydrofuran and have performed oxidation in the last step (aromatization) to obtain two phen_{(2,4,5)sub} (Scheme 11). In this case, BF₃ has been used to catalyze the reaction. The Lewis acid assists the reaction by bonding to the nitrogen atom of the imine facilitating the addition of the alkene.



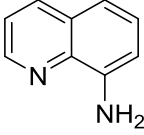
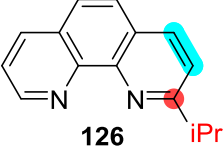
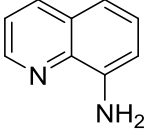
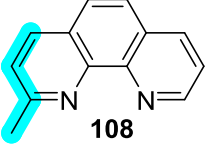
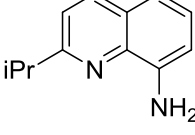
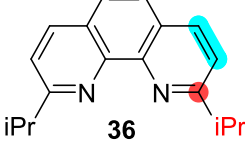
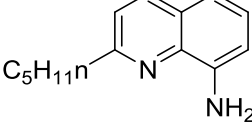
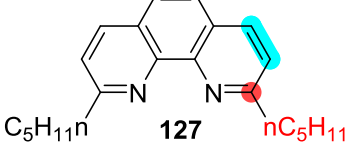
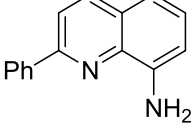
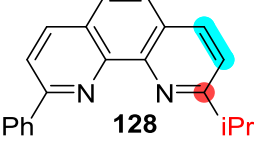
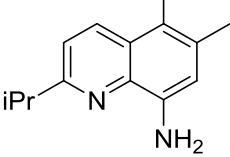
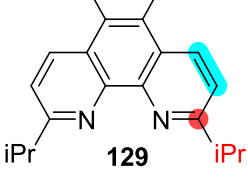
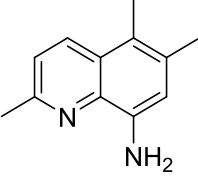
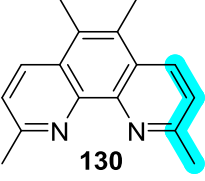
Scheme 11. Povarov reaction developed by Zaitsev et al.²⁵²

De et al.²⁵³ have proposed to perform the reaction in trifluoroethanol (TFE) instead of using a Lewis acid in presence of a ethyl vinyl ether (EVE) as dienophile and the cycloaddition proceeds in a more efficient way. In the last step, the non-aromatic intermediate is oxidized with O₂ for 12 h to obtain different substituted phen_{sub} (Table 10).

Table 10. Synthesis of substituted Phen_{sub} using the Povarov reaction (adapted from reference ²⁵³).



Aminoquinoline	Aldehyde	Phen	Yield (%)

	iPr-CHO		49
	None		43
	iPr-CHO		40
	nC ₅ H ₁₁ -CHO		33
	iPr-CHO		50
	iPr-CHO		44
	None		40

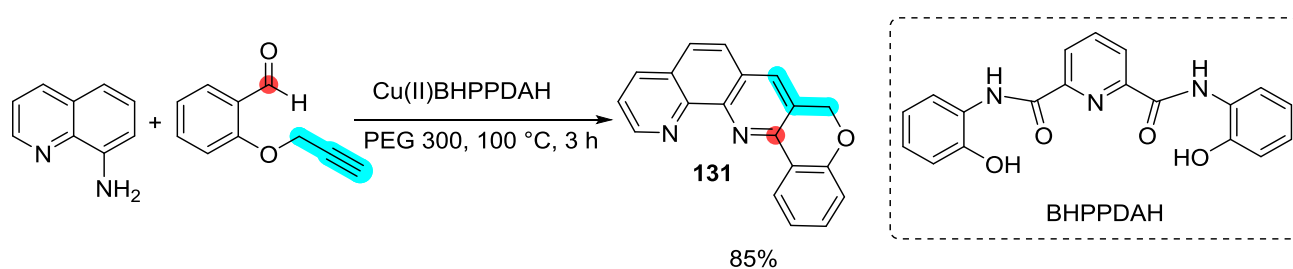
The authors have discovered when HFIP (hexafluoroisopropanol) is used as a solvent, EVE could serve as an acetaldehyde equivalent. When an excess of EVE was present in HFIP,

aniline underwent conversion into an imine, which subsequently underwent further reaction with EVE, leading to the formation of the corresponding tetrahydroquinoline that was further oxidized. The same happened with quinoline to yield phenanthroline.

2.2.2. Alkynes as one of the components

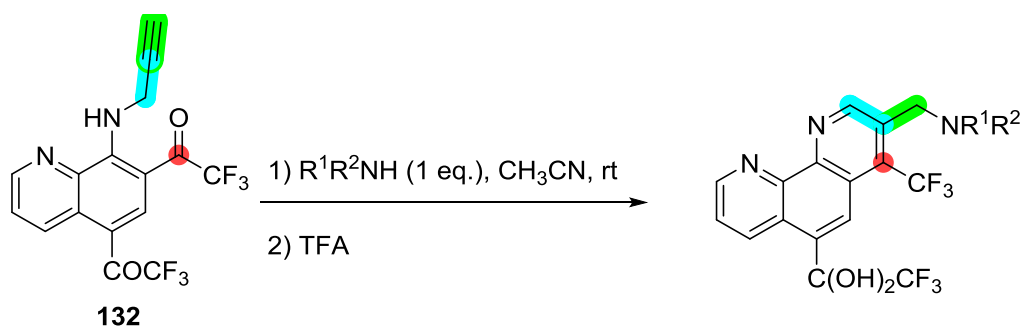
Another method to obtain substituted phen by the Povarov reaction is to react alkyne derivatives with 8-aminoquinolines or ortho-phenylenediamines.

For example, Shargi et al.²⁵⁴ have synthesized the substituted phen **131** by reacting O-propargylated salicylaldehyde with 8-aminoquinoline catalyzed by a copper(II) complex (Cu(II)BHPPDAH, where BHPPDAH = N,N-bis(2-hydroxyphenyl)pyridine-2,6-dicarboxamide) in PEG at 100 °C (Scheme 12).



Scheme 12. Povarov reaction developed by Shargi et al.²⁵⁴

Shibata et al.^{255,256} have reported the synthesis of N-propargyl-5,7-bis(trifluoroacetyl)-8-quinolyamine **132** that can react with various amines to form fluorine-containing phen (Scheme 13) with good yields (Table 11). In this case the reaction has been adapted, probably to avoid the use of highly explosive propargylaldehyde.



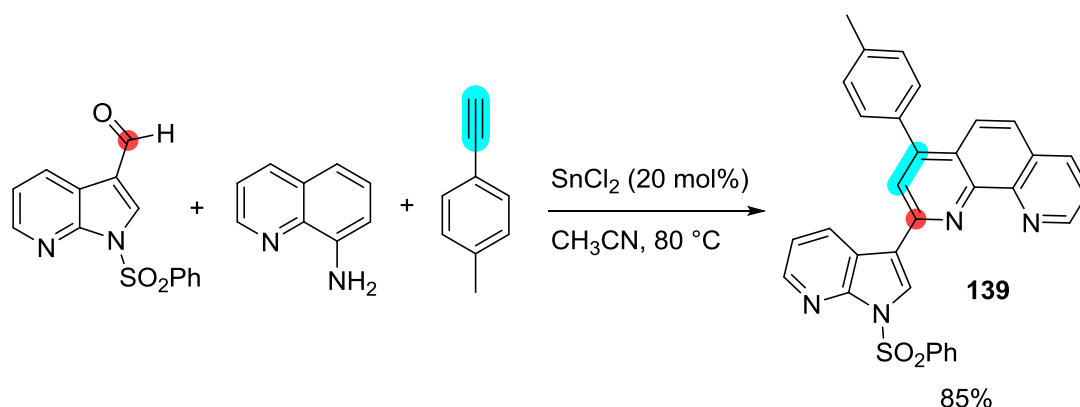
Scheme 13. Povarov reaction developed by Shibata et al.^{255,256}

Table 11. Synthesis of phen_{sub} using the Povarov reaction (adapted from reference²⁵³).

Phen number	First step		Second step				
	R ¹ R ² NH	Time (h)	TFA (eq)	Temp.	Time (min)	Solvent	Yield (%)
133	Me ₂ NH (aqueous solution 50%)	2	54	Reflux	30	None	62
134	Et ₂ NH	2	54	Reflux	30	None	60
135	Piperidine	1	1	rt	30	CHCl ₃	63
136	t-BuNH ₂	4	5	rt	5	CH ₃ CN	58
137	4-MeOC ₆ H ₄ NH ₂	4	5	rt	5	CH ₃ CN	51
138	4-ClC ₆ H ₄ NH ₂	4	5	rt	5	CH ₃ CN	58

Finally, a Suresh et al.²⁵⁷ reacted 7-azaindole-3-carboxaldehyde with 8-aminoquinoline and 4-methylphenylacetylene at reflux in acetonitrile with stannous chloride as the catalyst. The

reaction proceeds smoothly and the 2,4-substituted phen is obtained with 85% yield (Scheme 14).

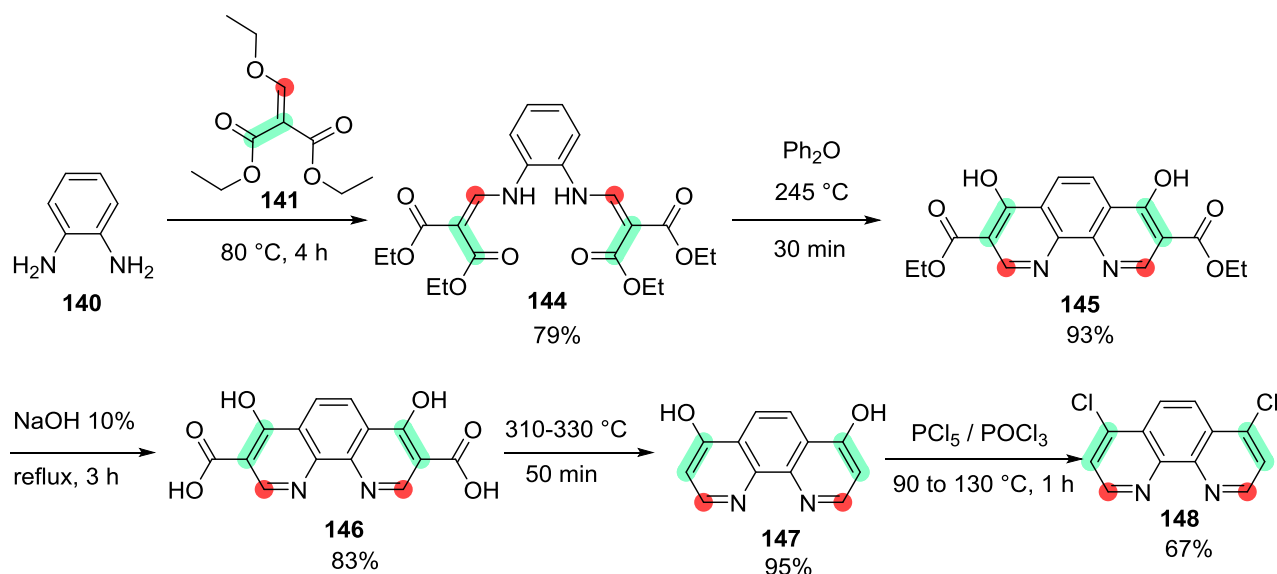


Scheme 14. Povarov reaction developed by Suresh et al.²⁵⁷ to obtain phen **139**

2.3. Convergent reaction with α,β -unsaturated ester

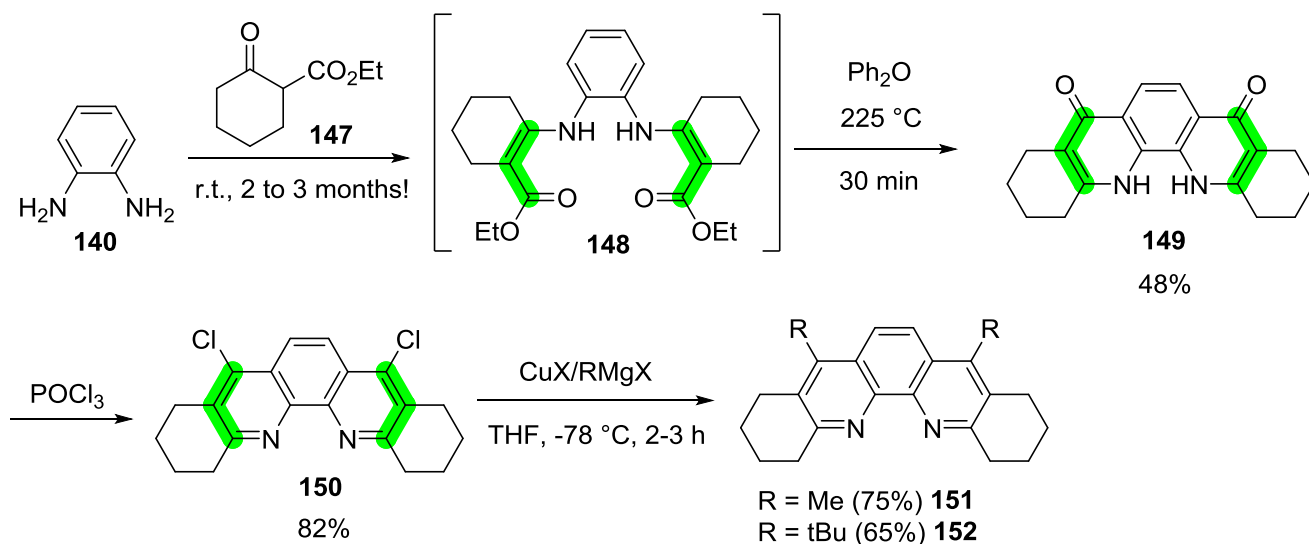
2.3.1. *o*-phenylenediamine as the starting material

In 1946, Snyder et al. mixed ethoxymethylenemalonic ester **141** and *o*-phenylenediamine **140** to obtain *o*-bis(2,2-dicarbethoxyvinylamino)benzene **142**. This compound is then heated at high temperature (reflux in diphenylether) in order to trigger a double intramolecular cyclization, producing 3,8-dicarbethoxy-4,7-dihydroxy-1,10-phenanthroline **143**. Then, after saponification and decarboxylation, the 4,7-dihydroxy-1,10-phenanthroline **145** is obtained and is further transformed with a mixture of POCl₃/PCl₅ into 4,7-dichloro-1,10-phenanthroline **146** (Scheme 15).²⁵⁸



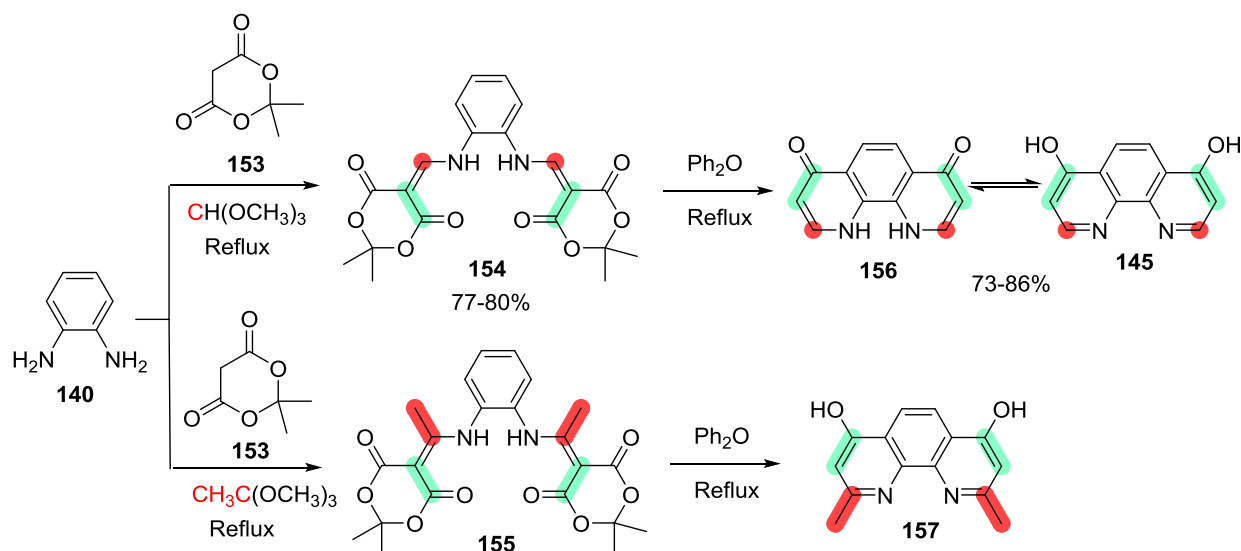
Scheme 15. Convergent synthesis of 4,7-dichloro-1,10-phenanthroline **146**

In 1983, Molock²⁵⁹ has performed the same synthesis and improved the yield of the chlorination reaction using only POCl₃ (93% versus 67% for Snyder). **147** and **148** are particularly important phen_(4,7)sub building blocks, as will be demonstrated later in this review. Following a similar strategy but replacing ethoxymethylenemalonic ester by the simpler ethyl 1-oxocyclohexane-2-carboxylate ketoester **147**, Bell et al.²⁶⁰ have isolated phen_(2,3,4,7,8,9)sub **150**. The neat mixture of o-phenylenediamine **140** and ketoester **147** is first stored at reduced pressure over P₂O₅ (for 2-3 months!) and then, the intermediate **148** was cyclized at high temperature in diphenylether leading to **149**. Reaction of the latter with POCl₃ leads to the hexasubstituted phen_(2,3,4,7,8,9)sub **150**. Interestingly, alkylation of the C_{4,7}-Cl bonds by transition-metal-catalyzed coupling of Grignard reagent (with different catalysts Ni(II)-phosphine catalysts for instance) is reported to fail. This is probably due to a ligand exchange between the phosphine and chlorinated phen. Using an excess of Grignard reagent with cuprous bromide as catalyst finally leads to the successful alkylation with good yields (Scheme 16).



Scheme 16. Convergent synthesis of phen_(2,3,4,7,8,9) **150**²⁶⁰

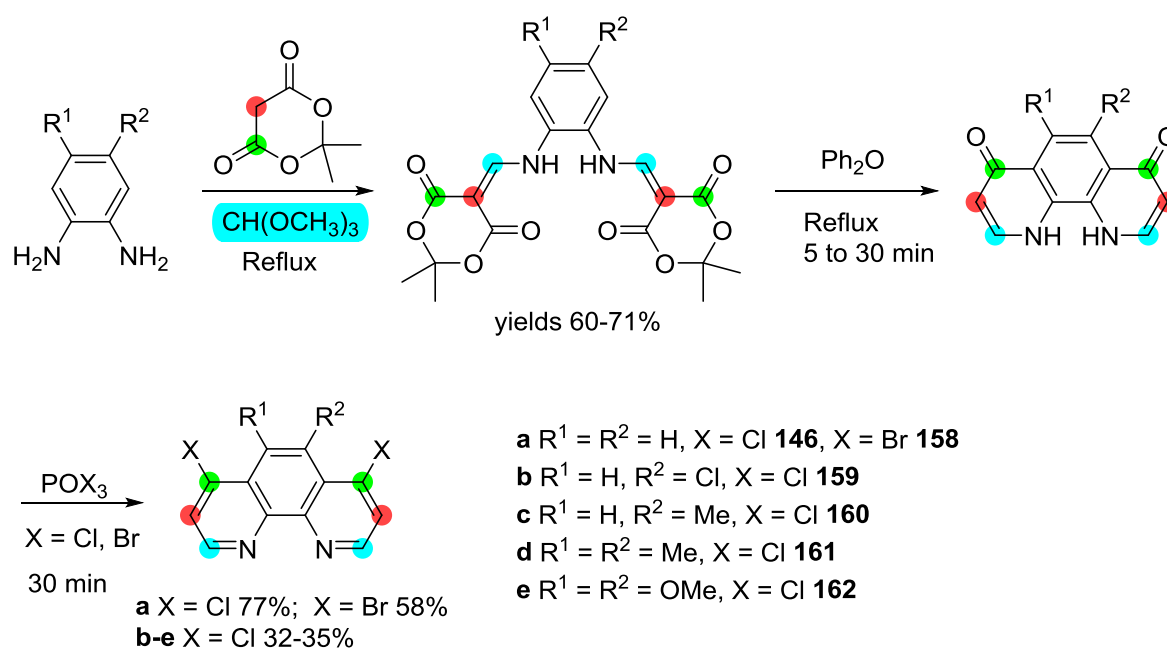
Following those seminal works, a more convenient three-component synthesis of 4,7-dihydroxyphenanthroline **145** has been proposed, based on a mixture of *o*-phenylenediamine **140**, Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) **153** and trimethylorthoformate (Scheme 17).^{86,261–264} The latter forms an imine with *o*-phenylenediamine onto which Meldrum's acid efficiently condense leading to intermediate **154**. The latter is submitted to a thermal treatment at high temperature leading to intramolecular cyclization and resulting in the formation of **156**, tautomer form of phen_(4,7) **145**.



Scheme 17. Convergent synthesis of 4,7-dihydroxyphenanthroline **145** and 2,9-dimethyl-4,7-dihydroxy-1,10-phenanthroline **157** using Meldrum's acid **153**.

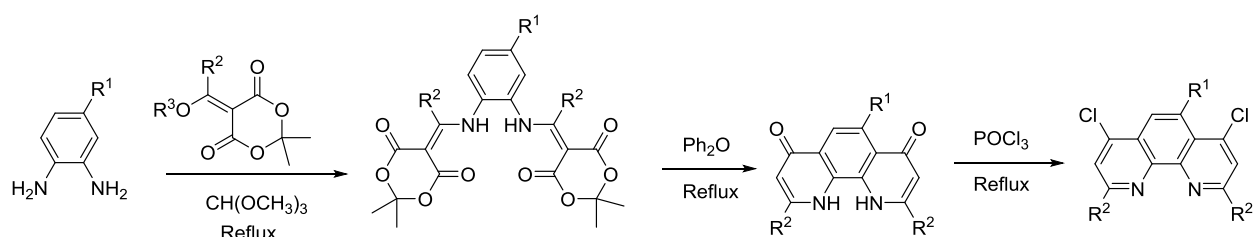
It is important to point out that when performing the first step using trimethylorthoacetate instead of trimethylorthoformate, followed by thermal-cyclization-decarboxylation, tetrasubstituted 2,9-dimethyl-4,7-dihydroxy-1,10-phenanthroline **157** is obtained. This synthon is further transformed and used in the field of coordination gel polymers,²⁶⁵ can possess potential G-quadruplex stabilizing effects when further derivatized²⁶⁶ or can be used as a ligand in the nickel-catalyzed allyl-alkyl coupling reaction.²⁶⁷ This molecule can be further used to build a Cu(I) supramolecular gel-like material, used to form colored Cu(I) complexes that have applications in solution-processed OLED²⁶⁸ or used after further transformation as a radiotracer of actinides(III) and lanthanides(III).²⁶⁹ The wide range of topics covered demonstrates again the vast field of potential applications for phenanthrolines. Then, 4,7-dihalogeno-5,6-substituted-1,10-phenanthroline derivatives can be prepared in a similar way: from thermocyclization of various substituted o-phenylenediamine using Meldrum's acid,²⁷⁰ different adducts are obtained and after decarboxylation/cyclization in

refluxed diphenyl ether and subsequent treatment with POX_3 (Scheme 18), the various substituted phen are synthesized.



Scheme 18. Convergent 4,7-dihalo-1,10-phenanthroline synthesis from thermocyclization of various o-phenylenediamine using Meldrum's acid²⁷⁰

The same strategy has been used by Nycz et al..²⁷¹ However the authors have used substituted Meldrum's acid which allows to obtain $\text{phen}_{(2,9)\text{sub}}$ after the thermal and POCl_3 treatments. If, in addition, substituted o-phenylenediamine are used, $\text{phen}_{(2,5,9)\text{sub}}$ can be obtained (Scheme 19). Yields vary from 32% to 92%. The lower yields were observed with $\text{R}_1 = \text{CN}$ or CO_2Et because those substituents were hydrolyzed during the POCl_3 treatment. This shows that the drawback of this method is the rather harsh conditions which are necessary to complete the reaction.



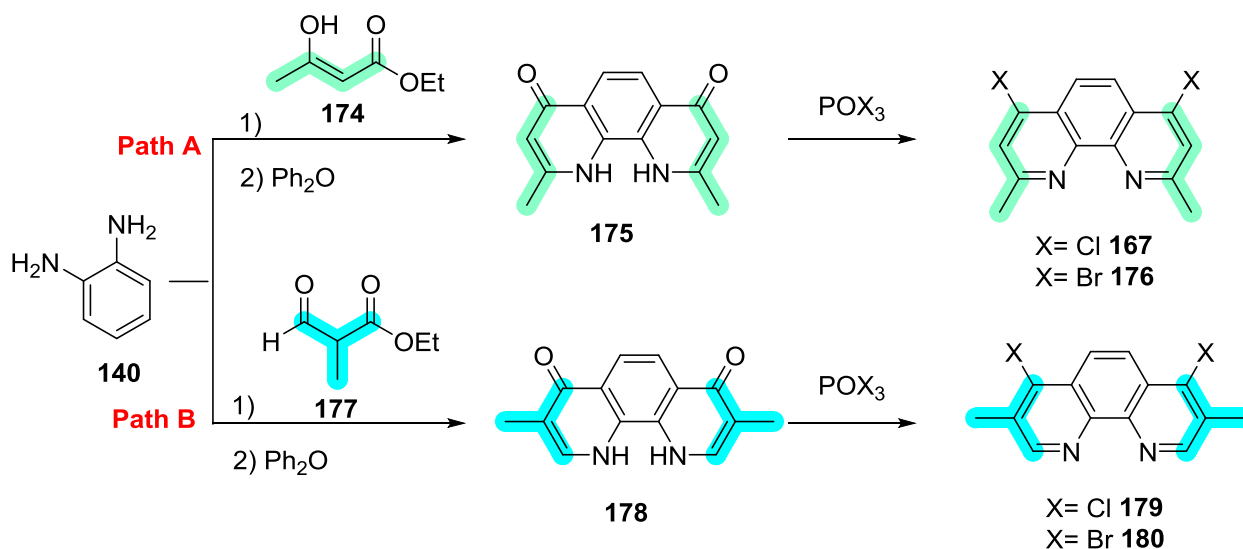
R² = H and R¹ = H **146** (84%), F **163** (85%), Cl **164** (75%), CH₃ **165** (91%), CN **166** (48%)
 R² = CH₃ and R¹ = H **167** (92%), F **168** (93%), Cl **169** (78%), Br **170** (68%), CH₃ **171** (86%), CN **172** (32%), COOEt **173** (38%)

yields from substituted o-phenylenediamine

Scheme 19. Convergent synthesis of 2,6,9-substituted-4,7-dichloro-1,10-phenanthroline using substituted Meldrum's acid.

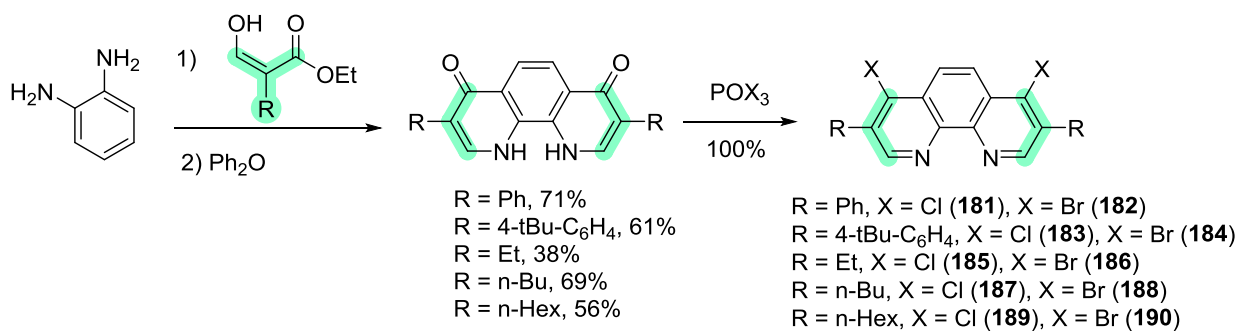
Summarily, the convergent method using Meldrum's acid is particularly versatile because it leads to diversely functionalized phen_{sub}, where the functional groups can be positioned on three different reactants: Meldrum acid itself (Scheme 19), the o-phenylenediamine (Scheme 18) or even the trimethoxyalkane (triethylorthoformate or triethylorthoacetate, Scheme 17).

Finally, other 1,3-dioxo compounds have been reacted with o-phenylenediamines to achieve the synthesis of phen_{sub}. For example, the reaction of o-phenylenediamine **140** with (Z)-ethyl 3-hydroxybut-2-enoate **174**, followed by thermal cyclisation in diphenylether gives 2,9-dimethyl-1,10-phenanthroline-4,7-dione **175** (path A, Scheme 20). When using ethyl 2-methyl-3-oxopropanoate **177** before cyclization, 3,8-dimethyl-1,10-phenanthroline-4,7-dione **178** was obtained (path B Scheme 20). Both intermediates then reacted with POX₃ to give the corresponding halogenated-1,10-phenanthroline.^{202,272,273}



Scheme 20. Convergent synthesis of 2,9-disubstituted-4,7-dihalogeno-1,10-phenanthroline (path A) or 3,8-disubstituted-4,7-dihalogeno-1,10-phenanthroline (path B).

The same strategy has been used by Schmittl et al.²⁷⁴ to obtain 4,7-dihalogenated phen possessing as well various groups in the 3,8-positions (Scheme 21).



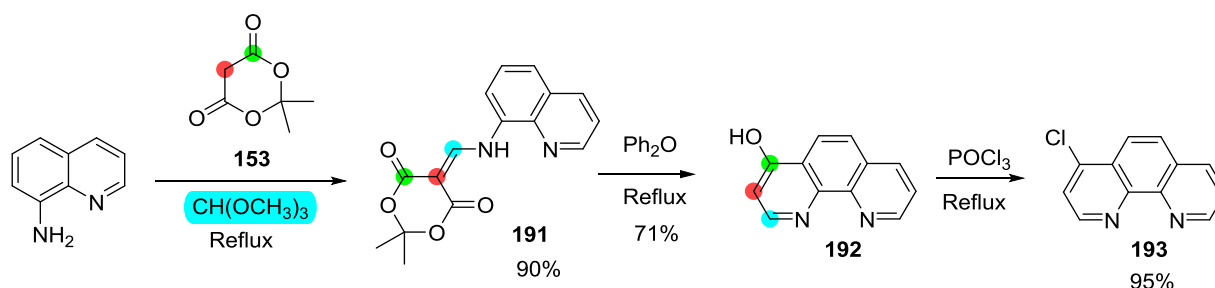
Scheme 21. Convergent synthesis of 3,8-disubstituted-4,7-dihalogeno-1,10-phenanthroline.

Incidentally, Köning et al.²⁷³ mention that the most crucial part in this synthesis is the step involving POX₃ (X = Cl or Br). In particular, the work-up of this last step must be carefully performed: when the hot reaction mixture is poured into icy water, it is important to control

the temperature should not exceed 45-50 °C when quenching the mixture with NaOH to reach pH 14.

2.3.2. Aminoquinoline as the starting material

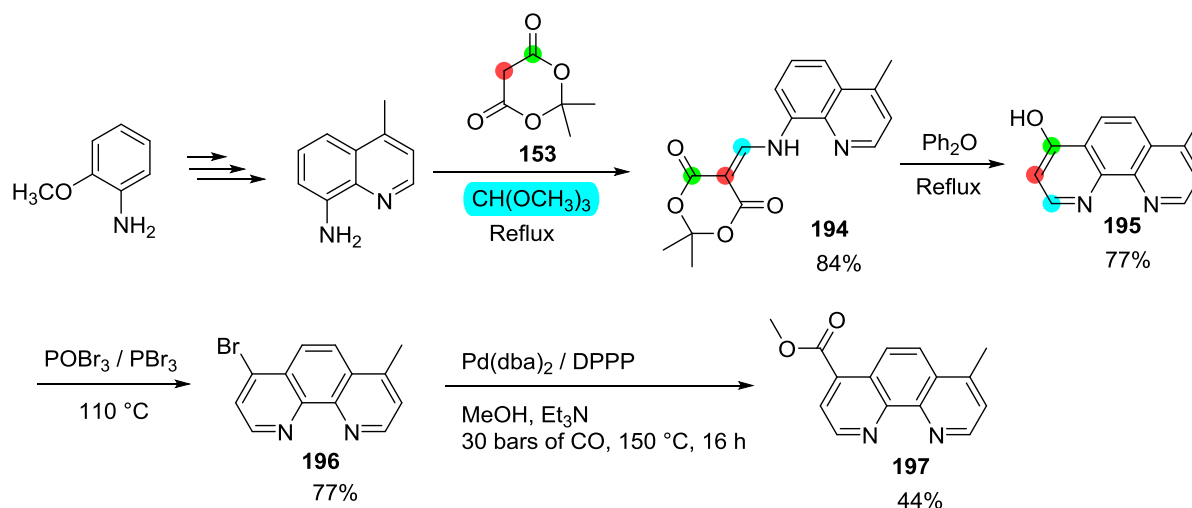
Starting from o-phenylenediamine, the previously described method leads to symmetrical phen_{sub} molecules. Accessing non-symmetrical ones is feasible, when starting from aminoquinoline. For example, 4-chlorophenanthroline **193** is prepared using 8-aminoquinoline and Meldrum's acid **153** that are refluxed in trimethylorthorformate to form an intermediate that cyclizes into 4-hydroxyphenanthroline in refluxing diphenyl ether. Then the use of POCl₃ leads to the 4-chlorophenanthroline **193** that can be further treated with sodium methylate to yield 4-methoxyphenanthroline or with DMF, or piperidine^{261,275} (Scheme 22).



Scheme 22. Convergent 4-chloro-1,10-phenanthroline synthesis using Meldrum's acid.²⁷⁵

To obtain dissymmetric halogeno phenanthroline, a Skraup reaction onto 2-aminoanisole followed by hydrolysis of the methoxy group and substitution by an amino group to form 8-amino-4-methylquinoline can be performed.²⁷⁵ The latter is then engaged in the same conditions described above : (i) first reaction with Meldrum's acid **153**, then (ii) thermocyclization in diphenylether followed by halogenation with POBr₃ that yields 4-bromo-7-methylphenanthroline **196** in an overall yield of 49.8% for the last three steps. Finally, the

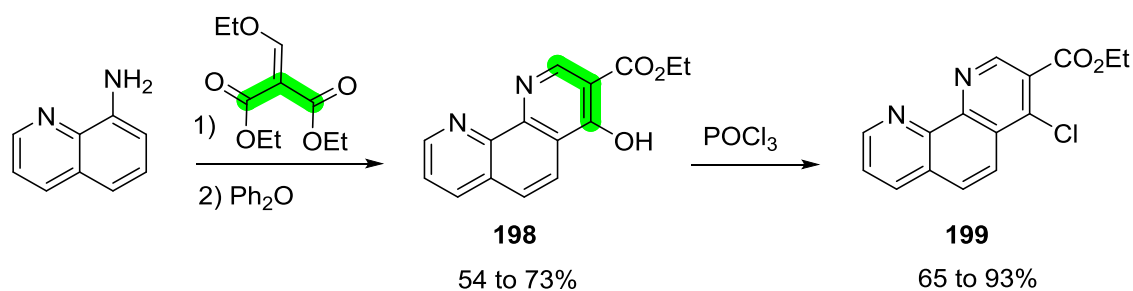
authors could perform a carbonylation of the C₄-Br bond using a pallado-catalyzed synthesis under 30 bars of CO in MeOH to yield 4-carbomethoxy-7-methyl-1,10-phenanthroline **197** (Scheme 23). Phen_{(4)sub} **197** has been used as ligand in a palladium-catalyzed reductive carbonylation reaction transforming nitrobenzene into methyl phenylcarbamate.²⁷⁵



Scheme 23. Convergent 4-bromo-7-methyl-1,10-phenanthroline **196** synthesis using Meldrum's acid²⁷⁵

When 8-amino-2-methylquinoline is reacted with Meldrum's acid in trimethylorthoacetate and after cyclization in diphenylether followed by halogenation with POCl₃, 4-chloro-2,9-dimethyl-1,10-phenanthroline is obtained with a 35% overall yield.²⁷⁶

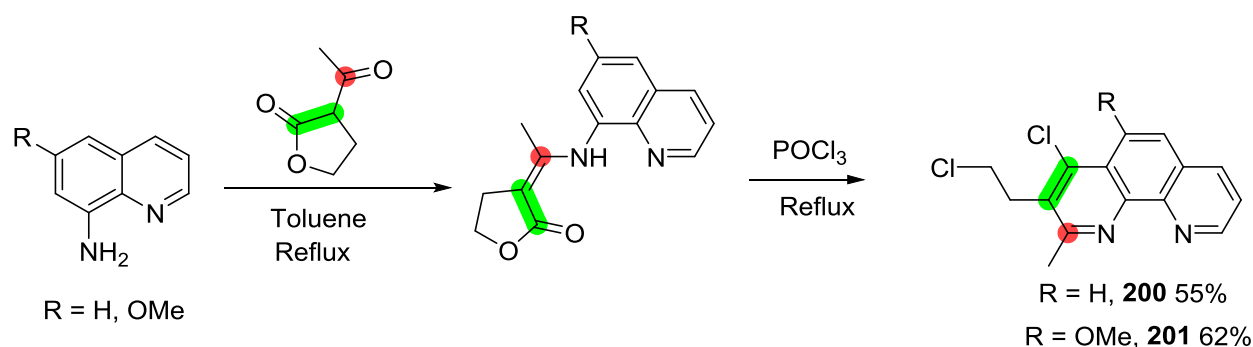
Like in the case of *o*-phenylenediamines as starting materials, other 1,3-dioxo compounds than Meldrum's acid can be used. For example, when 8-aminoquinoline is used as the starting material and reacted with diethyl ethoxymethylenemalonate followed by cyclization in refluxing diphenylether, the corresponding dissymmetric 3,4-disubstitued phenanthroline **198** and **199** are obtained (Scheme 24).²⁷⁷⁻²⁷⁹



Scheme 24. Convergent synthesis of 3,4-disubstitued-1,10-phenanthroline from 8-aminoquinoline.

Finally, when substituted 8-aminoquinoline is reacted with 2-acetylbutyrolactone followed by cyclization in refluxing POCl_3 , phen_(2,3,4,5)sub **200** and **201** are obtained (Scheme 25).^{280–282}

Those molecules have been designed in the purpose of obtaining analogs of primaquine, an antimalarial drug.



Scheme 25. Convergent synthesis of phen_(2,3,4,5)sub from 8-aminoquinoline.

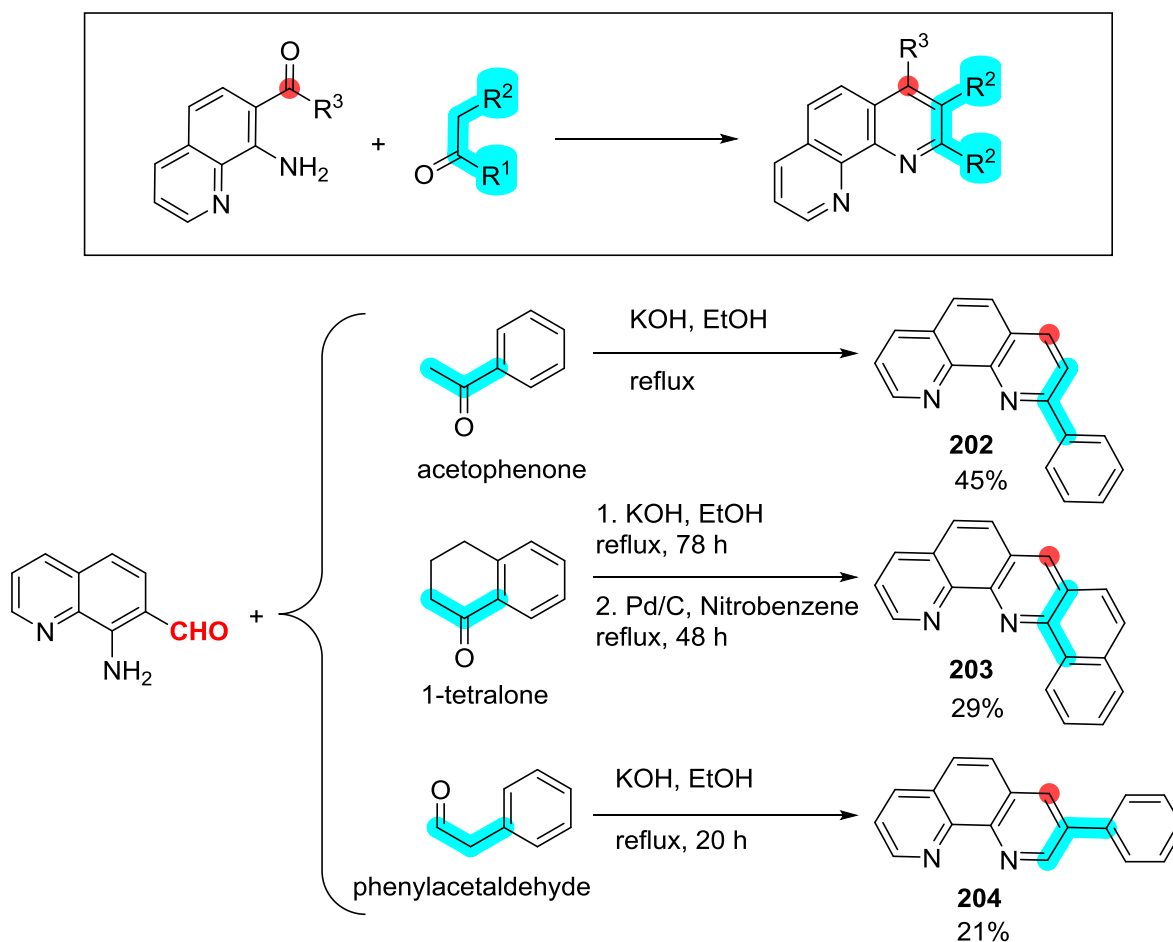
2.4. Friedländer reaction

The Friedländer reaction is diametrically opposed to the previous syntheses because it is performed in basic medium, and relies on the condensation of enolizable aldehydes or ketones ((i.e. ketones and aldehydes bearing a C-H group in α of the C=O carboxy function)) on 8-carbonyl substituted aminoquinolines (e.g. 8-amino-7-quinolinecarbaldehyde, which is a very

abundantly used synthon in the Friedländer condensation) followed by oxidation in basic conditions.

Thummel and his group have applied this reaction to obtain various phen_{sub} that can be further on coordinated with various metal ions. The authors have studied their photophysical properties^{283–296} and more recently the application of cobalt complexes as catalyst for proton reduction into H₂ under visible light.^{297,298} Other groups have used as well this condensation for the formation of various phen_{sub}.^{149,245,299–310} This reaction has been largely employed thus, in the following, only selected examples will be presented.

For instance, simple mono-substituted phen_{sub} **202–204** are prepared from 8-amino-7-quinolinecarbaldehyde, at reflux in saturated ethanolic KOH, with either acetophenone, 1-tetralone (followed by a catalytic dehydrogenation) or with phenylacetaldehyde (Scheme 26).^{284,296}

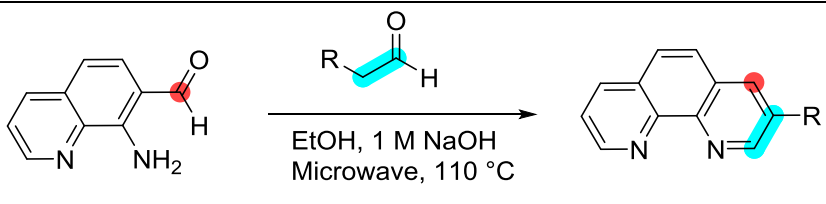
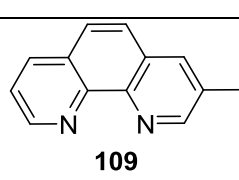
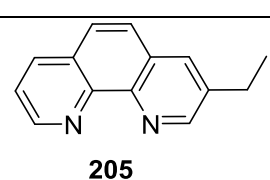


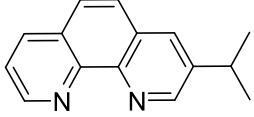
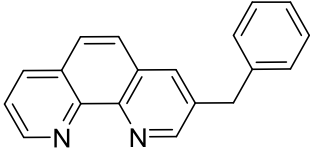
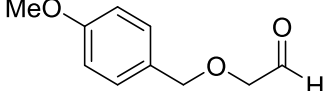
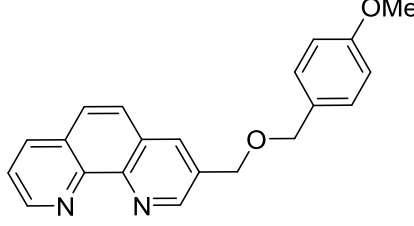
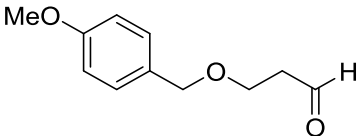
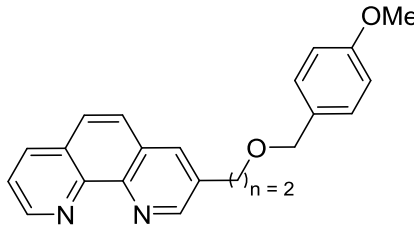
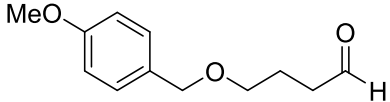
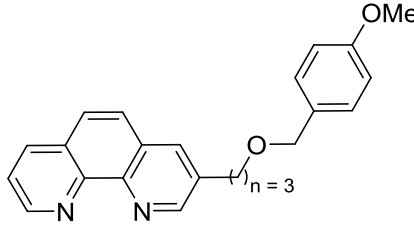
Scheme 26. Friedländer condensation to obtain various mono-substituted phen²⁸⁴

A microwave assisted Friedländer condensation has been developed by Dennison et al.³⁰⁸

Unsymmetrical phen_{(3)sub} have been obtained with high conversions in significantly shorter time than conventional heating (Table 12).

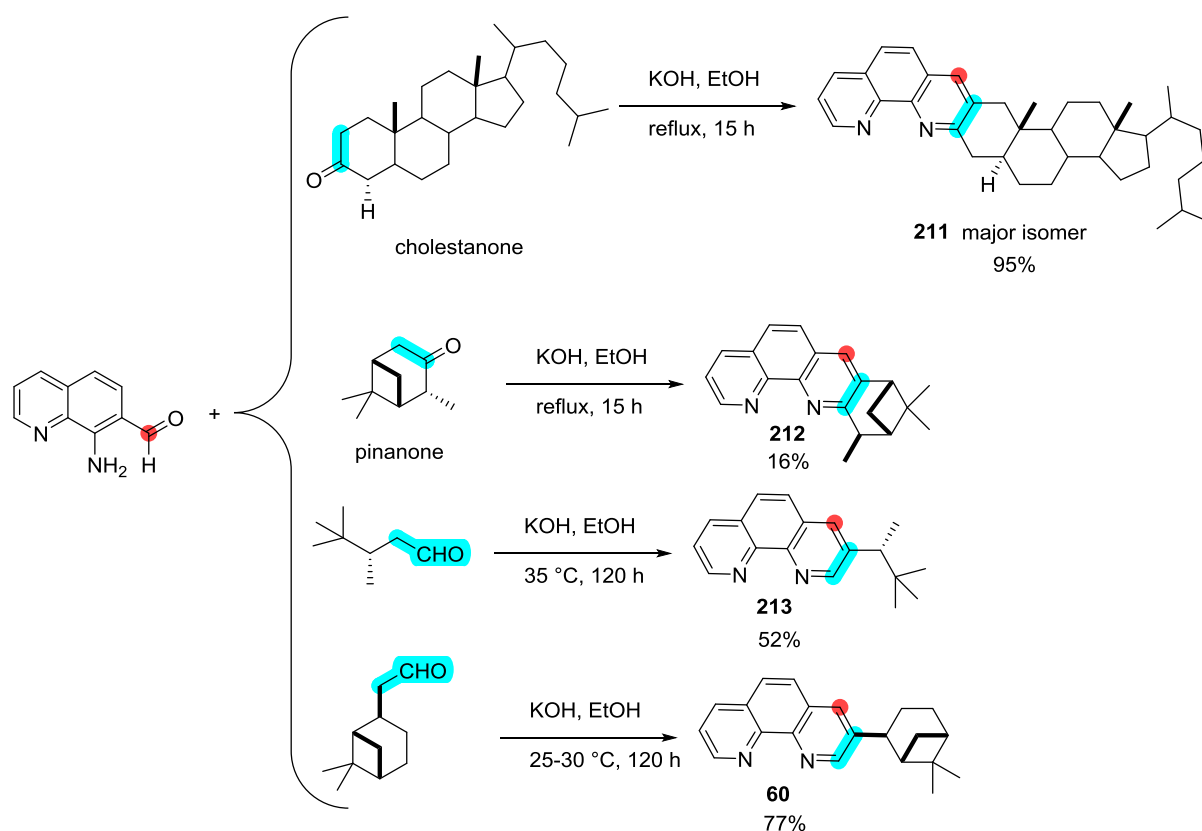
Table 12. Microwave assisted base-catalyzed Friedländer condensation to access phen_{(3)sub}

			
Aldehydes (R-CHO)	Time (min)	Conversion (%)	Product
Me-CHO	6	100	 109
Et-CHO	6	100	 205

i-Pr-CHO	6	70	 206
Benzyl-CHO	6	93	 207
	10	82	 208
	10	83	 209
	10	0	 210

A straightforward approach to obtain chiral alkyl-substituted phen has been developed by Gladiali et al.²⁸⁶ using a Friedländer condensation. Starting with 8-amino-7-quinolinecarbaldehyde and chiral enolizable ketones or aldehydes *via* base-catalyzed

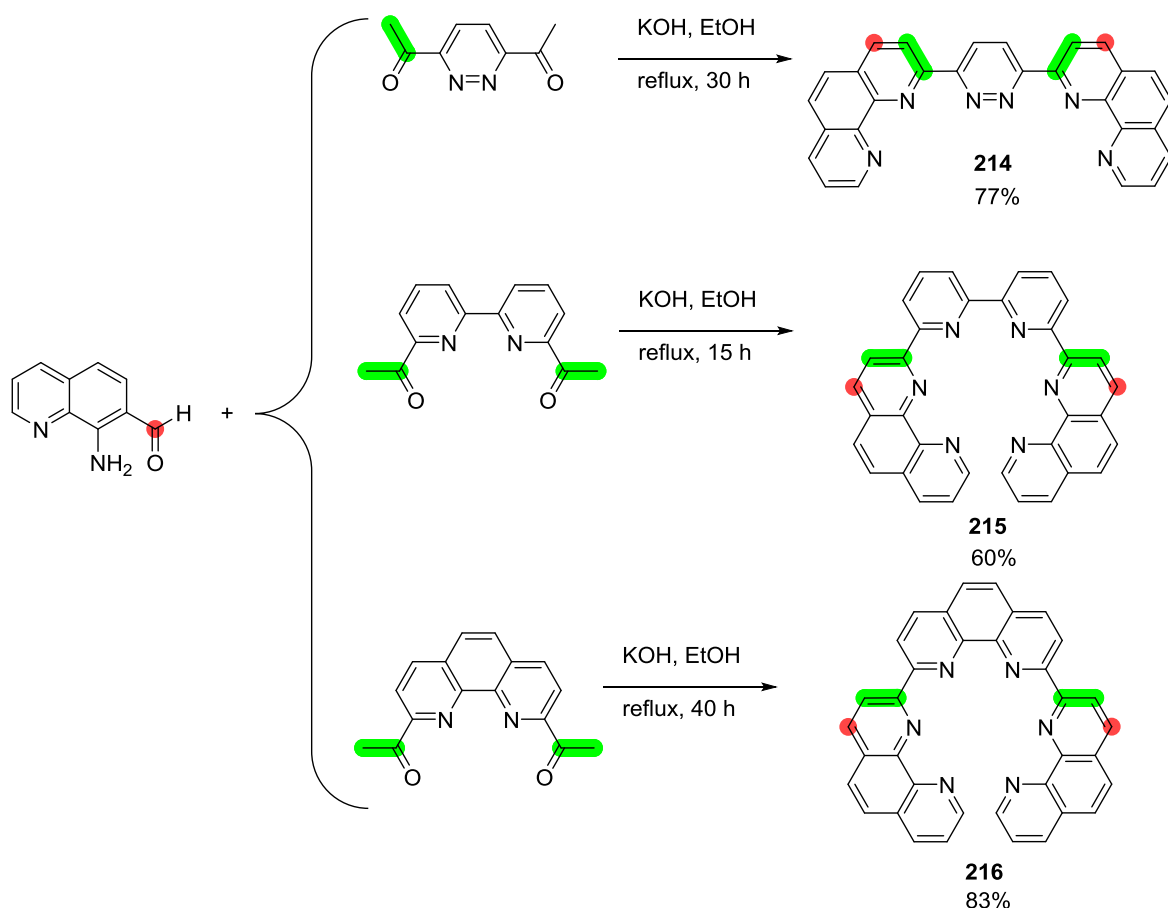
condensation, the authors have synthesized various [x,y-b]-cycloalkeno-condensed phen_{sub}. Some examples are presented in Scheme 27.



Scheme 27. Friedländer condensation to obtain various chiral phen²⁸⁶

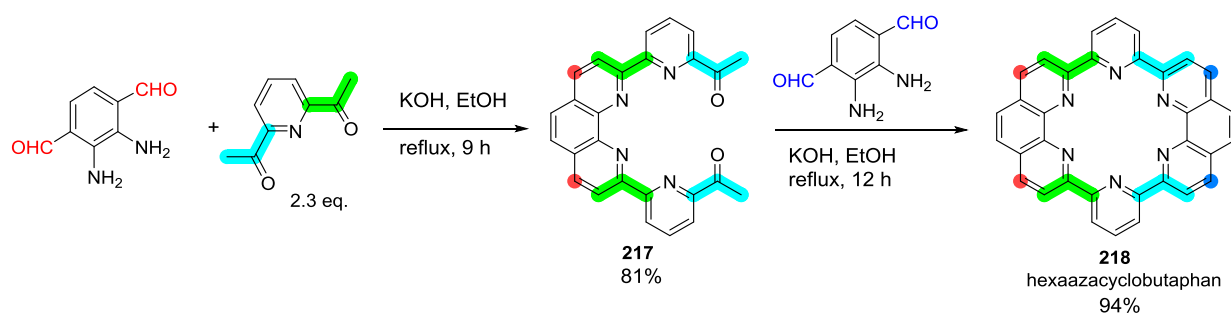
The same strategy has been employed to develop other chiral phen^{149,309,310} and those molecules were proven to be efficient chiral ligands for palladium in the enantioselective Pd-catalyzed allylic substitution¹⁴⁹ or Pd-assisted asymmetric 1,4-addition reactions.³¹⁰ Incidentally, the Friedländer condensation has been used as well to form chiral helicene-like phen and their chiroptical properties have been studied.^{299,301}

The Friedländer reaction, when performed on diketones, leads to the formation of phen oligomers. For example, polypyridyl ligands **214** to **216** can be obtained from 8-amino-7-quinolinecarbaldehyde through a Friedländer condensation that proceeds smoothly, the most difficult synthons to obtain being the precursor diketones.²⁹³ Some examples are presented in Scheme 28.



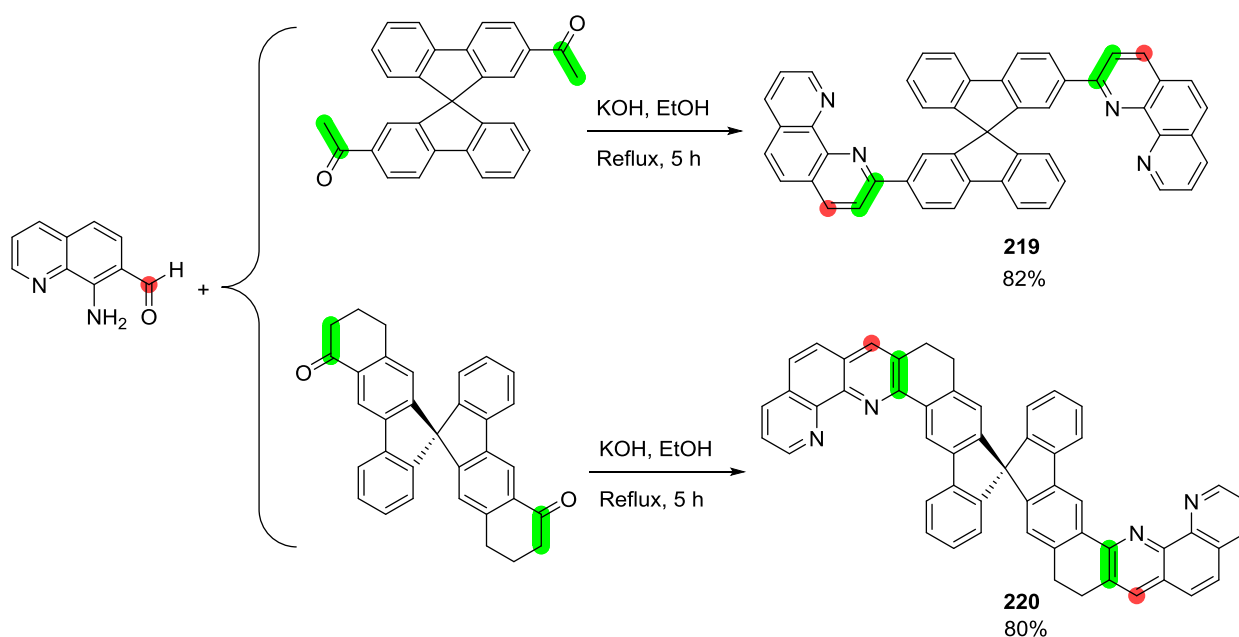
Scheme 28. Friedländer condensation to obtain phen dimers or trimers²⁹³

In the most frequent examples of Friedländer reactions, the starting reagent is the 8-amino-7-quinolinecarbaldehyde but 1,2-diamino benzene molecules can be used too. For instance, 2,3-diaminobenzene-1,4-dicarbaldehyde was synthesized and used as a synthon in a double Friedländer condensation with 2,6-diacetylpyridine to obtain a hexaazacyclobutaphan **218** in very good yield (Scheme 29).³⁰⁰



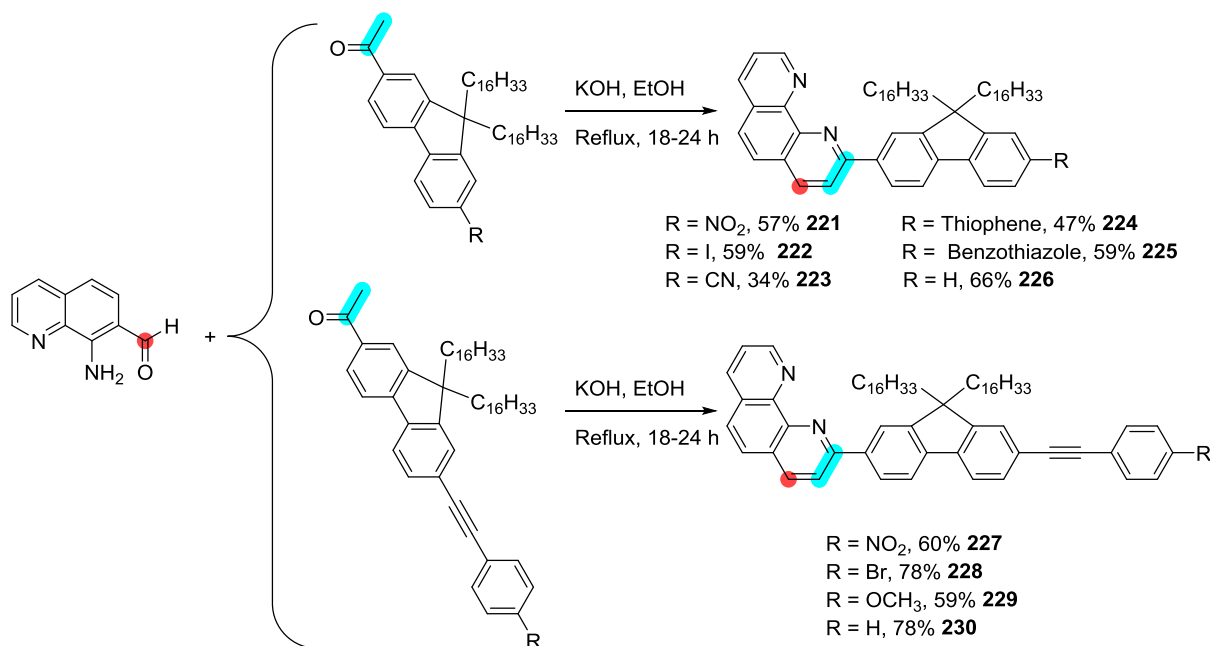
Scheme 29. Double Friedländer condensation to obtain a hexaazacyclobutaphan **218**.³⁰⁰

9,9'-spirobifluorene-derived phen **219** and **220** are synthesized by employing a Friedländer condensation between 9,9'-spirodifluorene-skeleton compound with 8-amino-7-quinolinecarbaldehyde^{305,306} for organic electronics and some examples are presented in Scheme 30.



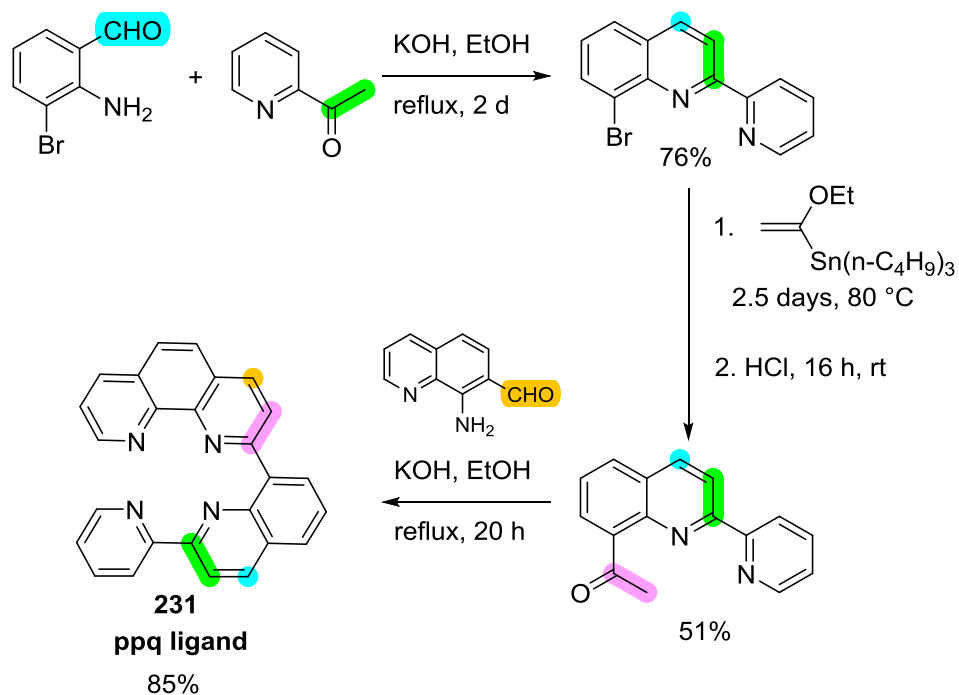
Scheme 30. 9,9'-spirobifluorene-derived phen obtained after a Friedländer condensation.^{305,306}

Liu et al.^{303,304} developed platinum(II) complexes based on fluorenyl-derived phen (Scheme 31), in order to increase the π -donating ability of the aryl ring to improve the non-linear absorption properties of the corresponding complexes.



Scheme 31. Platinum(II) complexes based on fluorenyl-derived phen obtained after a Friedländer condensation.^{303,304}

As mentioned above, Thummel and his coworkers focus on Co(II) polypyridine complexes for the hydrogen production from water. The preparation of some ligands used for the coordination of cobalt ions necessitates a double Friedländer condensation. A first Friedländer condensation is performed between 3-bromo-2-aminobenzaldehyde and 2-acetylpyridine to afford 2-pyridyl-8-bromoquinoline which features the molecular skeleton of bpy. The latter is further transformed by a Stille reaction into 2-pyridyl-8-acetylquinoline, which is basically a bpy derivative bearing an enolizable ketone. In other words, a bpy-like adequate synthon for the synthesis of a phen derivative *via* the Friedländer condensation. Thus, the second Friedländer condensation is carried out using 8-amino-7-quinoline carbaldehyde and the tetracoordinating mixed phen-bpy ligand 8-(1''-10''-phenanthrol-2''-yl)-2-(pyrid-2'-yl)quinoline **231** (ppq) was obtained with a 33% overall yield (Scheme 32).²⁹⁷



Scheme 32. Double Friedländer condensation to obtain the ppq ligand **231**²⁹⁷

Using the same strategy, the same group has achieved the synthesis of two more rigid ligands **221** and **222** (Figure 21) for the design of square planar Co(II) complexes.²⁹⁸

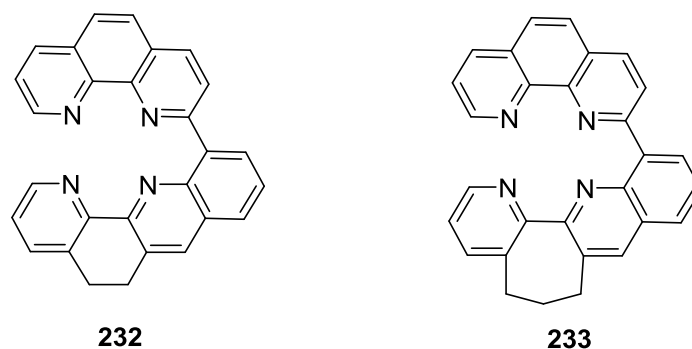


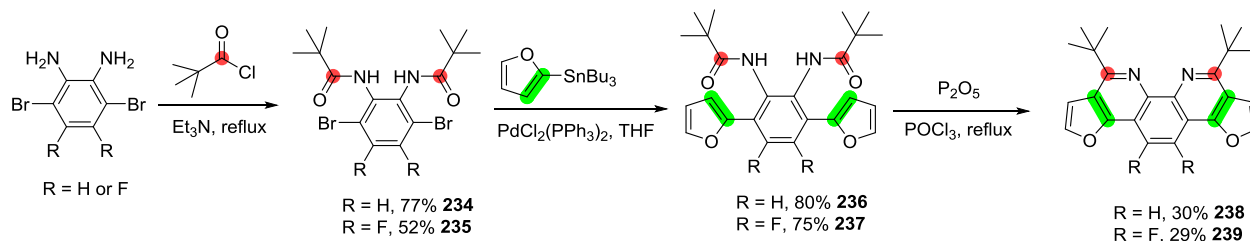
Figure 21. Two ligand used in the formation of Co(II) catalyst active in the proton reduction from water under visible light.

Those three complexes were proven to catalyze light-driven H₂ evolution in aqueous medium with TOF up to 2125 h⁻¹.

2.5. Miscellaneous reaction

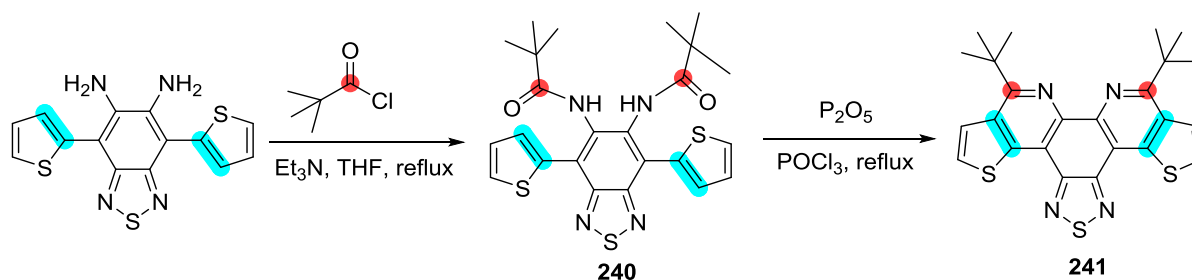
The formation of phen by convergent methods can be performed by other reactions whose characteristics and conditions do not fully fit with the above mentioned main strategies. A sample of those original reactions is presented in the following.

Liu et al.³¹¹ developed furan-fused phen **238** and **239** using the Bischler-Napieralski cyclization. The synthesis starts classically by the bis-amidation of 5,6-dibromo-orthophenylenediamine derivatives. The C-Br bonds of amides **234** and **235** are then functionalized through a Stille cross-coupling allowing to append two furan moieties (**236** and **237**). The cyclization reaction is then performed by refluxing **236** and **237** in POCl₃ employing P₂O₅ as a catalyst (Scheme 33). **238** and **239** are actually octafunctionalized phen_{(2,3,4,5,6,7,8,9)sub} obtained in only three steps from the starting diamine. **238** and **239** were further modified to form new donor-acceptor-donor molecules and the photophysical and electrochemical properties were discussed with respect to the influence of the fluorine atom, whether they are present or not.



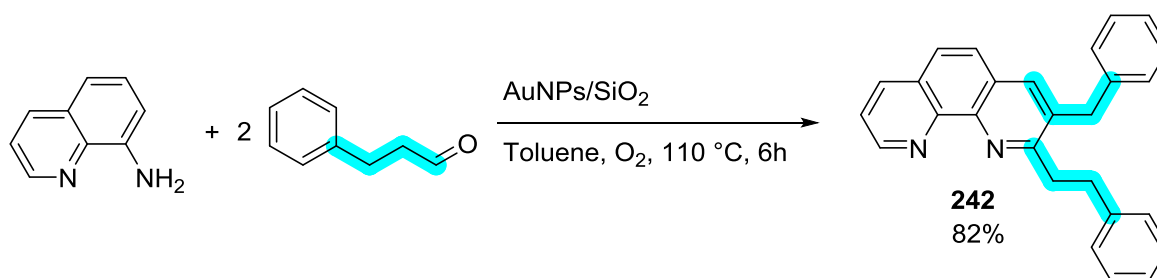
Scheme 33. Bischler-Napieralski cyclization to obtain furan-fused phen **227** and **228**³¹¹

In the same approach, Yuan et al.^{312,313} have synthesized thiophene fused 1,10-phenanthroline **241** with Bischler-Napieralski cyclization and went one step further by adding a S,N-containing heterocycle (Scheme 34). This S,N-containing heterocycle can then be reduced to furnish the corresponding diamine bearing phen_{(2,3,4,5,6,7,8,9)sub} able to condense on diketones and yield polycyclic aromatic hydrocarbons.



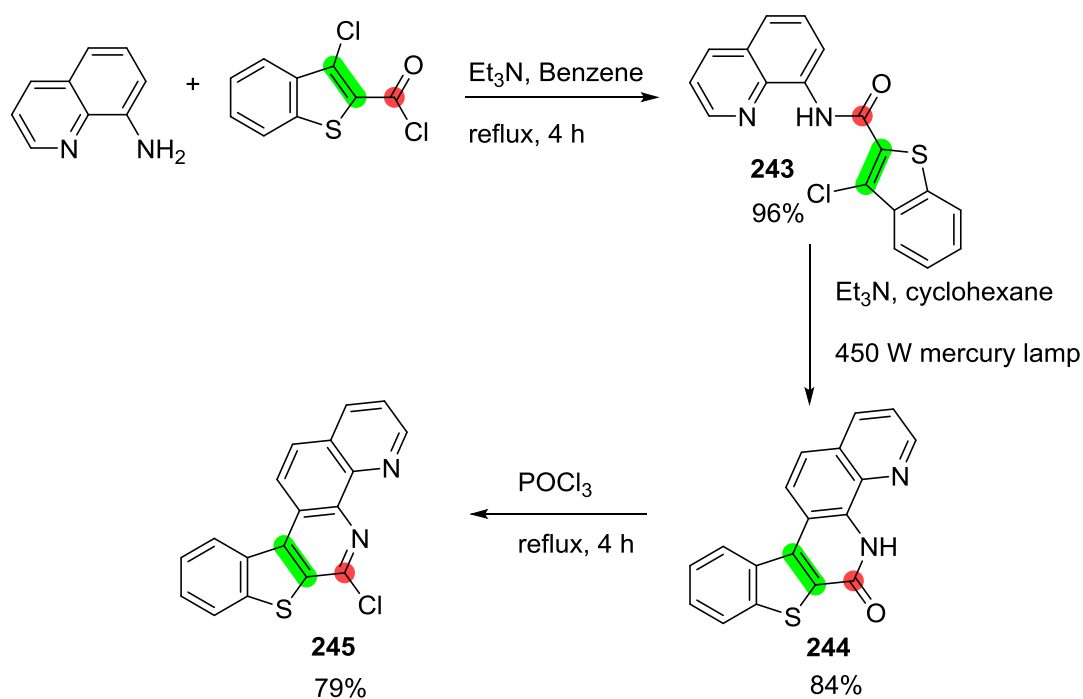
Scheme 34. Bischler-Napieralski cyclization to obtain thiophen-fused phen

So et al.³¹⁴ have developed a silica supported gold nanoparticles (NPs) catalyst which, in presence of O₂, is able to perform oxidative cyclization of 8-aminoquinoline with two equivalents of aldehyde to obtain the 2,3-disubstituted phen **242** (Scheme 35).



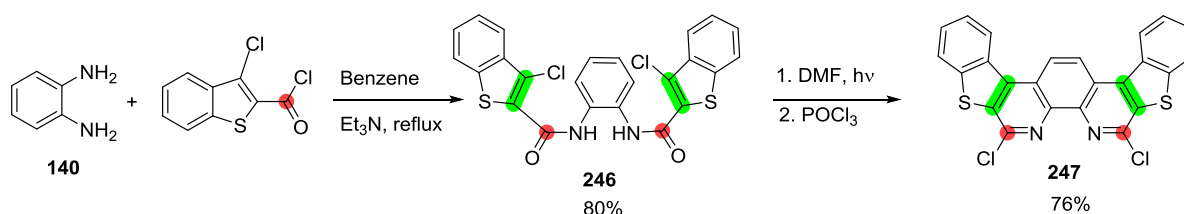
Scheme 35. Oxidative cyclization of quinoline using AuNPs/SiO₂ catalyst with O₂

Halverson et al.³¹⁵ synthesized 6-chloro[1]benzothieno[2,3-c]phen **245** from 8-aminoquinoline and 3-chlorobenzothiophene-2-carbonylchloride using a photo-assisted Skraup-Doebner-Von Miller reaction. The photocyclization is performed on the amide **243** with a 450 W mercury lamp affording tricyclic derivative **244**. Refluxing in POCl₃ gives as usual the desired phen_{(3,4)sub} **245** (Scheme 36).



Scheme 36. Photocyclisation developed by Halverson et al.³¹⁵ to obtain substituted phen **245**

Another example of photocyclization from phenylenediamine **140** was described by Abou Elmaaty et al.³¹⁶ to form bis-fused phen **247** (Scheme 37).



Scheme 37. Double photocyclisation developed by Abou Elmaaty et al.³¹⁶ to obtain bis-fused phen

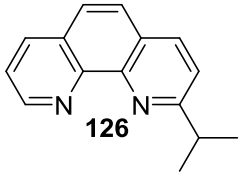
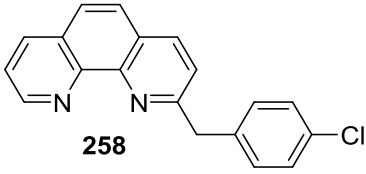
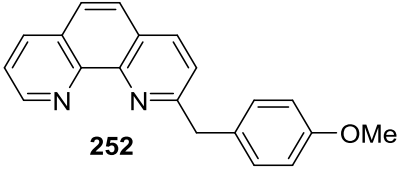
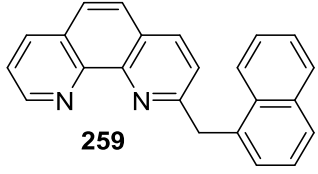
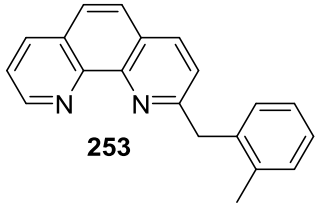
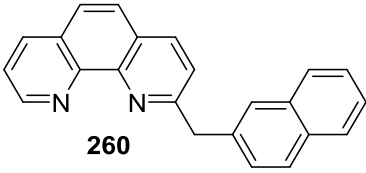
Cheng et al.³¹⁷ developed a new approach to obtain unsymmetrical phen using a [3+3'] annulation between 3-ethoxycyclobutanones and 8-aminoquinolines and catalyzed by a Lewis acid (Table 13). In fact, the cyclobutanone adds on the 8-aminoquinoline to form an imine, and the C₄ cycle opens in presence of a Lewis acid. As such, this original method can be seen

as a variant of the Skraup-Doebner-Von Miller method, where the Michael acceptors are replaced by the cyclobutanone derivatives.

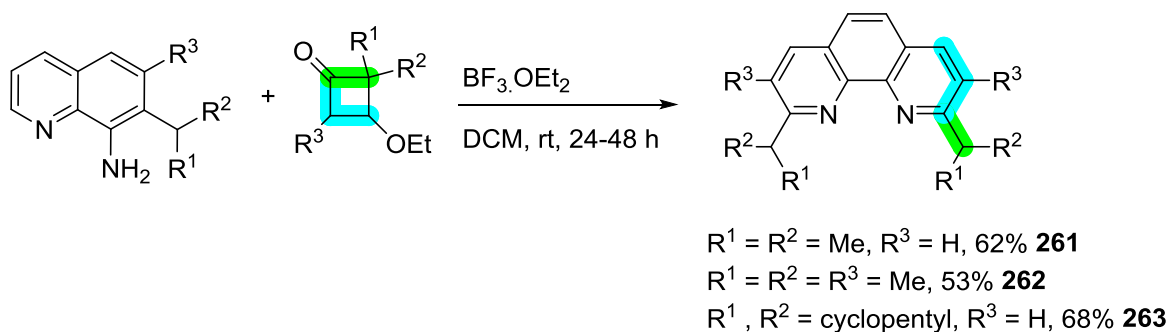
Table 13. Synthesis of unsymmetrical phen



Products	Yields	Products	Yields
<p>248</p>	76	<p>254</p>	66
<p>249</p>	82	<p>255</p>	79
<p>250</p>	85	<p>256</p>	50
<p>251</p>	67	<p>257</p>	52

	75		64
	74		47
	76		44

The same authors have performed this reaction on substituted 8-aminoquinolines to obtain phen_{(2,3)sub} **261** to **263** (Scheme 38).

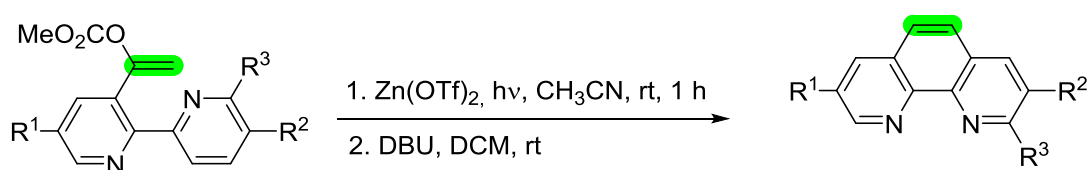


Scheme 38. Annulation with cyclobutanone derivatives to obtain phen_{(2,3)sub}.

Other original chelation-assisted photochemical electrocyclic reactions of 3-alkenyl-2,2'-bipyridines are described in the literature, to obtain efficiently various phen derivatives (Table 14).³¹⁸ This method allows to convert an appropriately functionalized bpy into phen. The metal chelation forces the bpy derivative to adopt the *cis* geometry, and the photochemical

electrocyclization reaction can then occur regioselectively, leading to the target phen_{sub} ligand after decarboxylation.

Table 14. Photochemical electrocyclic reactions of 3-alkenyl-2,2'-bipyridines to obtain substituted phen



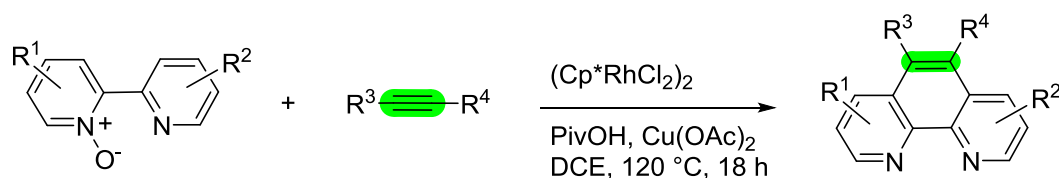
Starting material	Products	Yields
	 Phen	68
	 264	59
	 109	72
	 74	59

	 265	74
	 204	70
	 266	69

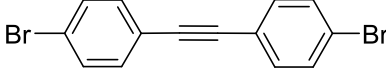
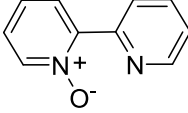
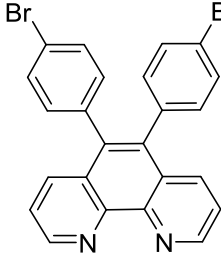
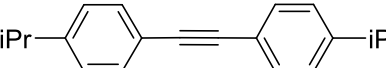
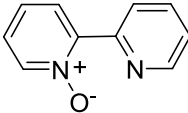
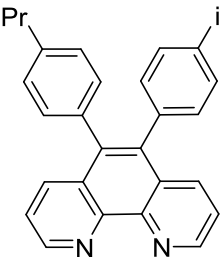
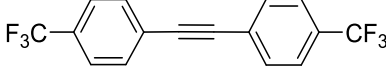
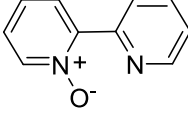
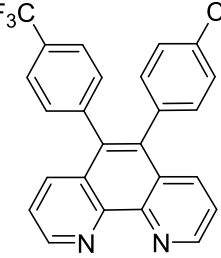
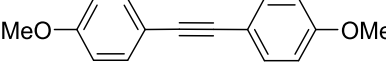
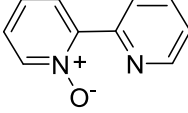
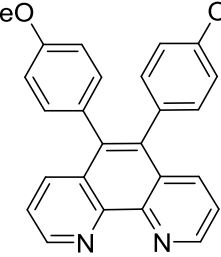
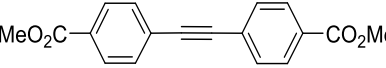
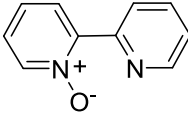
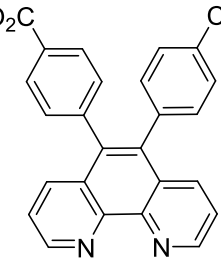
All those phen_{sub} are interesting synthons useful for further transformation and ligand design. For example, Cheng et al.³¹⁹ have performed a Sonogashira coupling in classical conditions on the 3-ethynylphenanthroline (Table 14, phen **266**) developed by Takahashi et al.³¹⁸ with various iodinated binol derivatives. The obtained ligands can be further treated with zinc ions and self-assemble into metallogages. One of the metallogage exhibits catalytic activity for the Knoevenagel condensation.

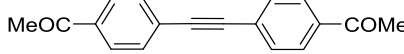
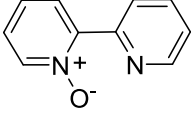
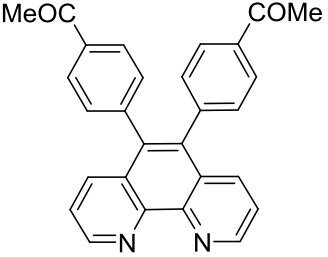
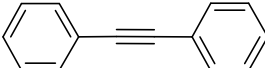
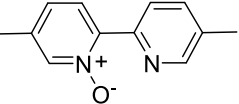
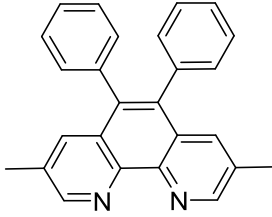
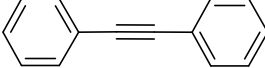
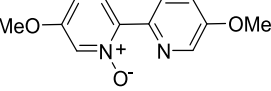
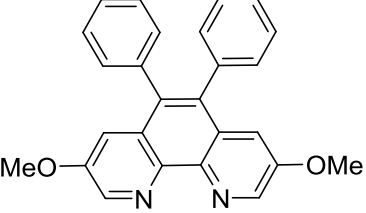
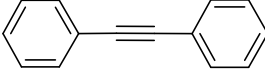
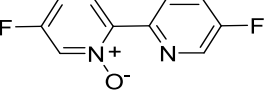
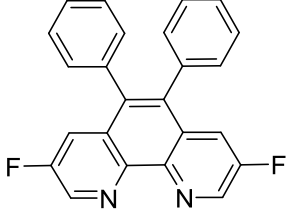
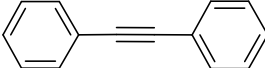
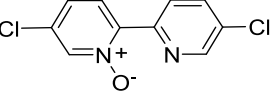
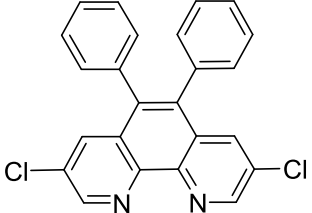
Another method to convert bpy into phen has been reported by Xu et al.³²⁰ Indeed, the oxidative annulation of 2,2'-bipyridine N-oxides with alkynes catalyzed by Rh(III) gives access to a collection of various phen_{sub} (Table 15).

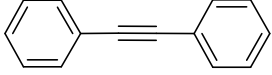
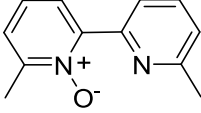
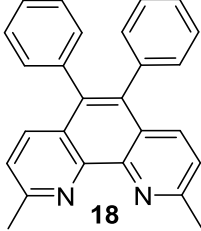
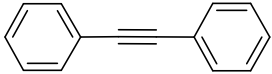
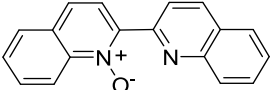
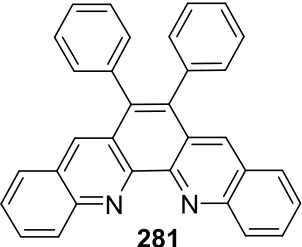
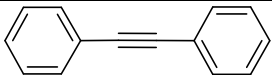
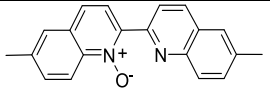
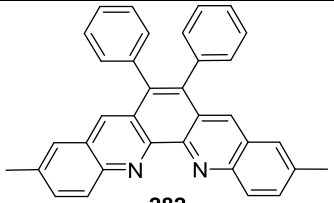
Table 15. Rh(III) catalyzed oxidative annulation of 2,2'-bipyridine N-oxides with alkynes



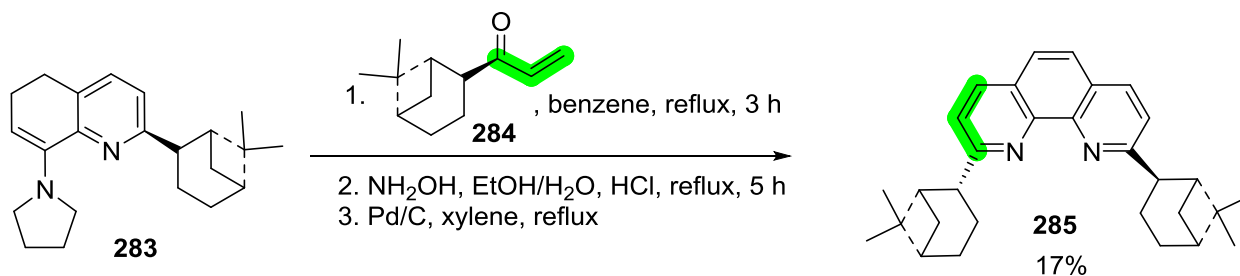
Alkyne	2,2'-bipyridine N-oxide	Products	Yield (%)
		<p style="text-align: center;">267</p>	85
		<p style="text-align: center;">268</p>	91
		<p style="text-align: center;">269</p>	80
		<p style="text-align: center;">270</p>	84

		 <p style="text-align: center;">271</p>	83
		 <p style="text-align: center;">272</p>	80
		 <p style="text-align: center;">273</p>	76
		 <p style="text-align: center;">274</p>	81
		 <p style="text-align: center;">275</p>	79

		 <p style="text-align: center;">276</p>	85
		 <p style="text-align: center;">277</p>	74
		 <p style="text-align: center;">278</p>	76
		 <p style="text-align: center;">279</p>	58
		 <p style="text-align: center;">280</p>	61

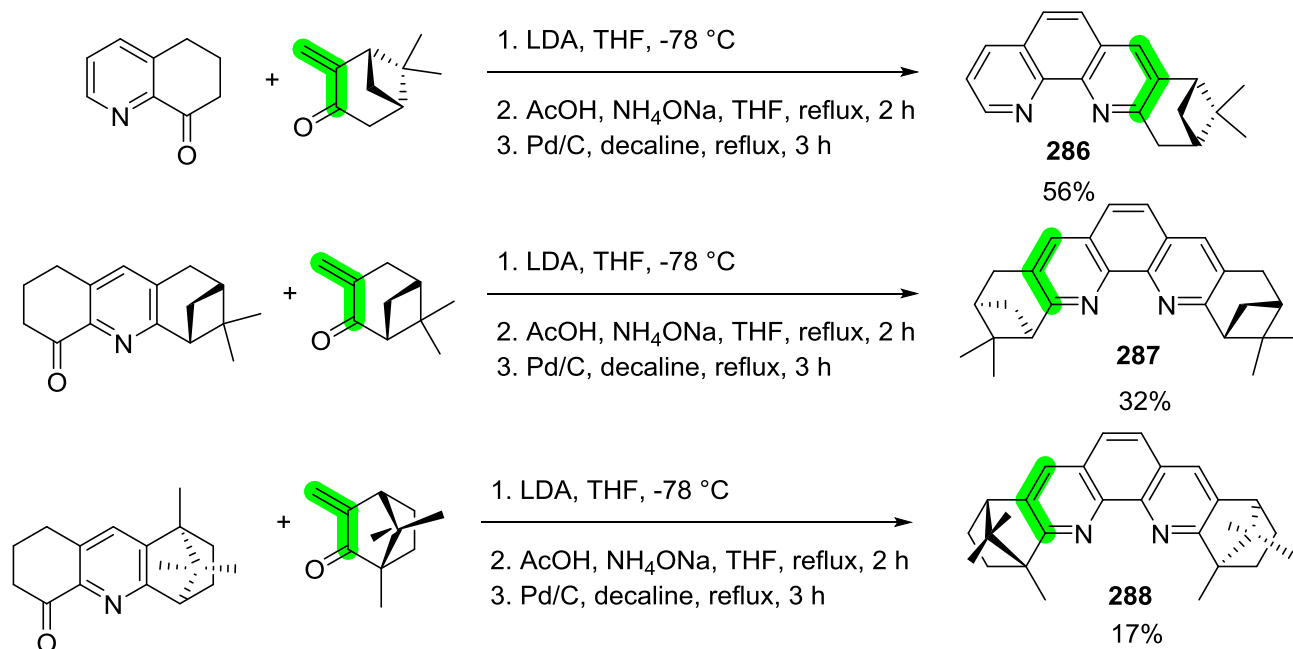
			81
			69
			72

Chelucci et al. have developed various pathways to obtain chiral phen. For example, phen **285** bearing the 6,6'-dimethylnorpinan-2-yl group has been obtained after performing the heteroannellation of **283** on ((1S,2S)-6,6-dimethylbicyclo[3.1.1]hept-2-yl)-2-propen-1-one **284** (Scheme 39). This method differs from conventional reactions in that the starting material **283** is a 5,6-hydrogenated quinoline derivative and to get **285** a dehydrogenation step is needed.³²¹



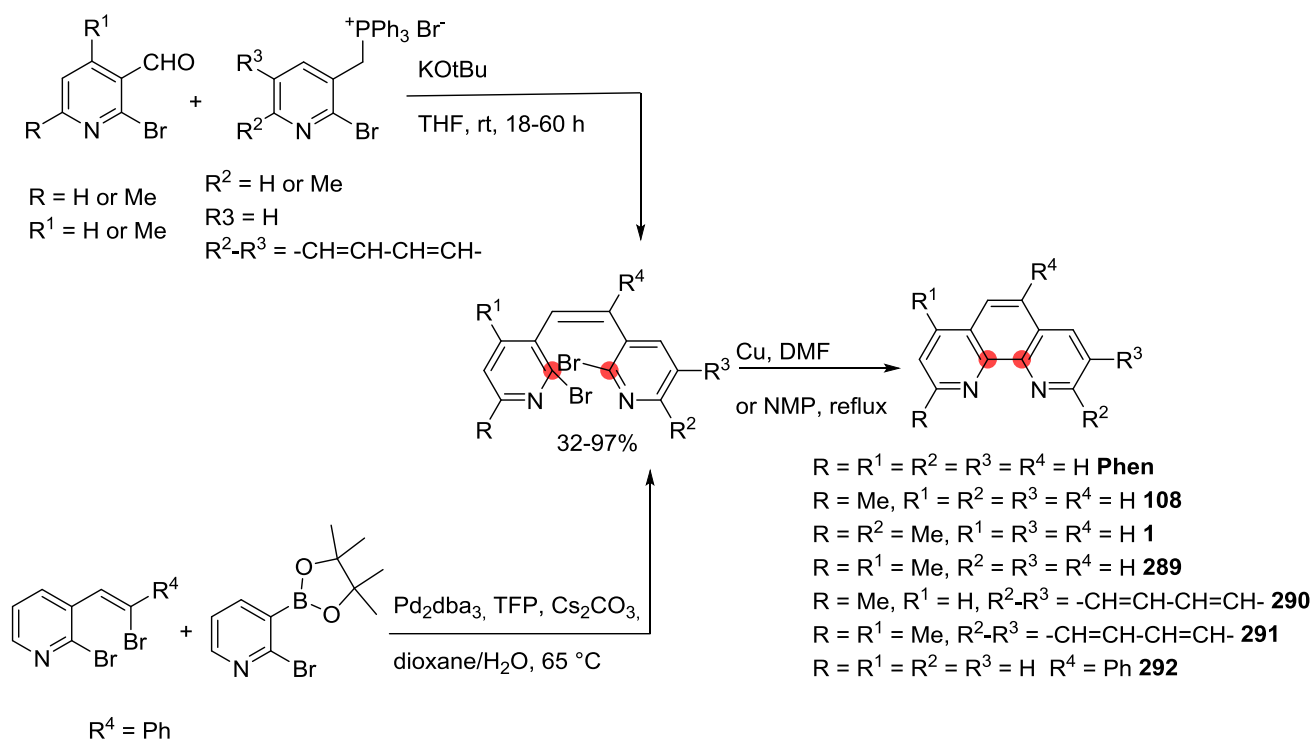
Scheme 39. Synthesis of phen **285** bearing the 6,6'-dimethylnorpinan-2-yl group

The authors have obtained chiral phen **286** to **288** bearing chiral pinene copula (Scheme 40).^{322–324} Those chiral ligands are efficient in asymmetric copper(I)-catalyzed allylic substitution and oxidation.



Scheme 40. Synthesis of chiral phen **286–288** bearing chiral terpene type copula

Finally, the same authors have studied a new approach to obtain substituted phen,^{325,326} consisting in reacting two substituted pyridine rings immobilized in a pyridine-dimer through an intramolecular Ullmann reaction (Scheme 41). The pyridine conjugated dimer is obtained by a Wittig reaction. For the Ullmann coupling, DMF (N,N-dimethylformamide) or NMP (1-methyl-2-pyrrolidinone) were tested as solvents, and NMP was the best in term of time of reaction and yields (Table 16).



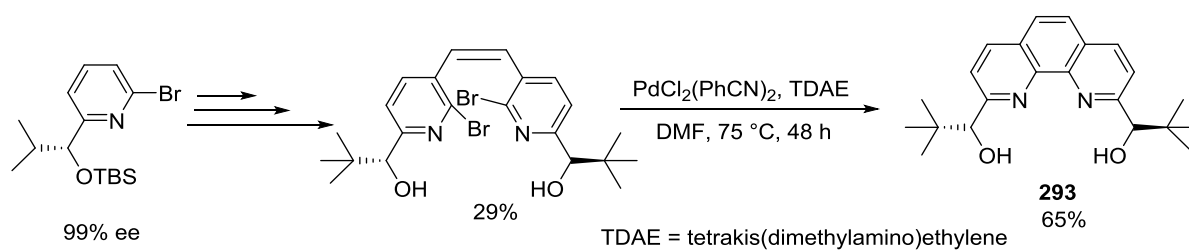
Scheme 41. Synthesis of substituted phen **1**, **108** and **289** to **292** described by Chelucci et al.^{325,326}

Table 16. Intramolecular Ullmann coupling to obtain phen_{sub}

Alkene	Product	Reaction time (h)		Yield (%)	
		DMF	NMP	DMF	NMP
		5	-	67	-
		18	9	75	76

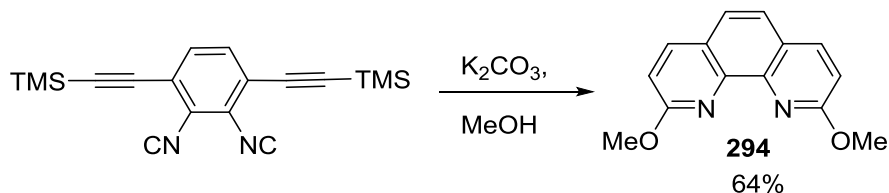
		120	30	32	59
		40	-	24	-
		40	26	24	36
		-	14	-	35
		2	-	72	-

Nandakumar et al.³²⁷ have used the same approach developed by Chelucci et al. to obtain chiral phen_{sub} (Scheme 42). Those new chiral ligands are used in enantioselective ring opening reactions of meso-epoxides and aminations of β -ketoesters.



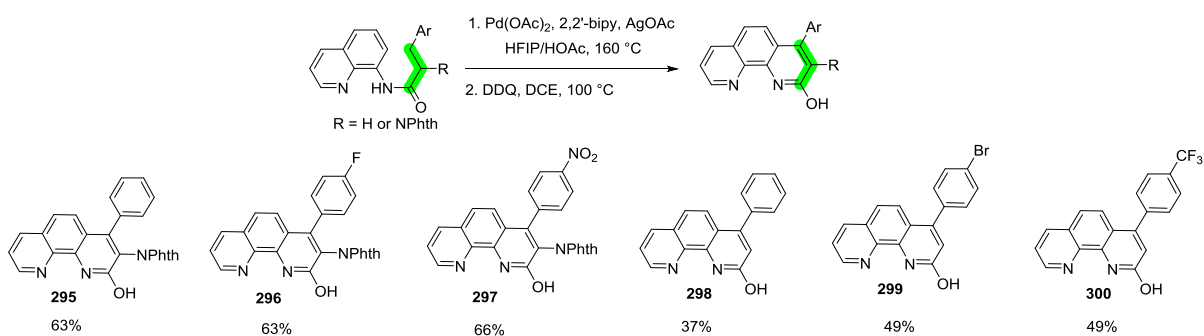
Scheme 42. Synthesis of chiral phen described by Nandakumar et al.³²⁷

Suginome et al.³²⁸ have synthesized the 2,9-dimethoxy-1,10-phenanthroline **294** using dialkynyldiisocyanobenzene as starting material that underwent nucleophile-induced intramolecular cyclization in methanol with 64% yield (Scheme 43).



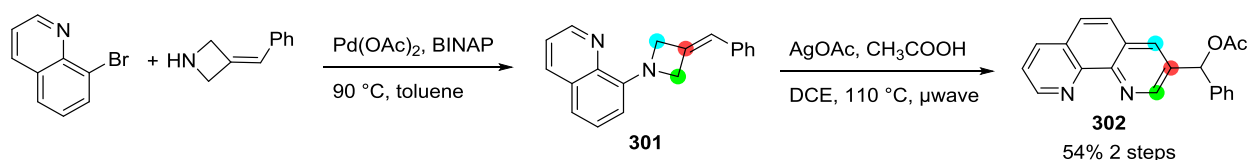
Scheme 43. Nucleophile-induced intramolecular cyclization to obtain the 2,9-dimethoxyphen **294**

Jiang et al.³²⁹ have synthesized various phen_{sub} through a cross-dehydrogenative coupling starting with substituted 8-aminoquinolines catalyzed by palladium acetate followed by oxidation using DDQ (Scheme 44). The same strategy was used by Sun et al.³³⁰ to synthesize various phen_{(2,4,6)sub}.



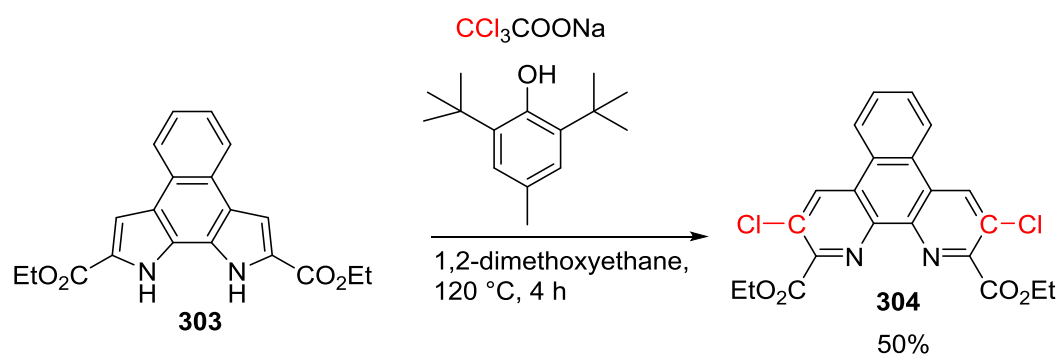
Scheme 44. Cross-dehydrogenative coupling developed by Jiang et al.³²⁹

Cai et al.³³¹ synthesized 3-substituted phen **302** by using an oxidative cascade reaction of N-aryl-3-alkylideneazetidone **301** and acetic acid using silver salt and microwave irradiations (Scheme 45).



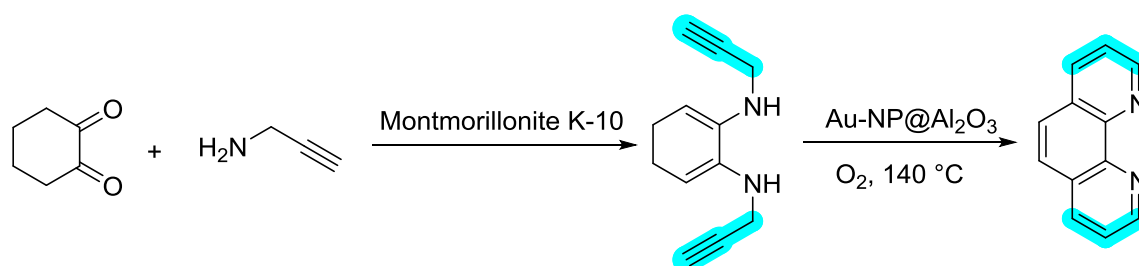
Scheme 45. Oxidative cascade reaction of N-aryl-3-alkylideneazetidines and acetic acid

Very originally, Samala et al.³³² have described a one carbon ring expansion from naphthobipyrrole diester³³³ that allows the formation of the phen core in the presence of dichlorocarbene, generated in situ from sodium trichloroacetate CCl_3COONa (Scheme 46).



Scheme 46. One carbon insertion into naphthobipyrrole diester described by Samala et al.³³²

Finally, 1,10-phenanthroline is obtained in a two-step micro continuous flow system starting with propargylamines and bis-ketones. The synthesis uses two different packed bed capillary reactors filled with two different catalysts. The best results were obtained with Montmorillonite K-10 clay for the first step and alumina supported gold nanoparticles for the second step. Phen was obtained after an aerobic oxidation, with an overall yield of 37.5% (Scheme 47).³³⁴



Scheme 47. 1,10-phenanthroline synthesis using micro continuous flow conditions.

2.6. Concluding remarks

There are many facets to the convergent methods allowing to synthesize phen_{sub}. Apart from the well-established methods described in sections 2.1 to 2.4, there are several original cyclization reactions leading to desired phen_{sub} (section 2.5). Remarkably, the yields have substantially increased from a few percents in the early history of the Skraup reaction applied to 8-aminoquinoline, to above 80% in a several cases. Another remarkable feature of the convergent methods is the complexity of certain structures obtained only in a few steps. Nevertheless, it is important to remind that the synthesis of functionalized 8-aminoquinoline (for the Skraup-Doebner-Von Miller reactions, section 2.1) or 8-amino-7-quinolinecarbaldehyde (for the Friedländer reactions, section 2.4) can be challenging. The reactions involving such starting materials are thus well-adapted to phen_{sub} which are functionalized only on one side (i.e. the side where the cycloaddition takes place). On the other hand, the reactions explored in sections 2.2 (Povarov's method) or 2.3 (use of ketoesters) can be performed on ortho-phenylenediamines, and allow to build substituted phen fragments on each side.

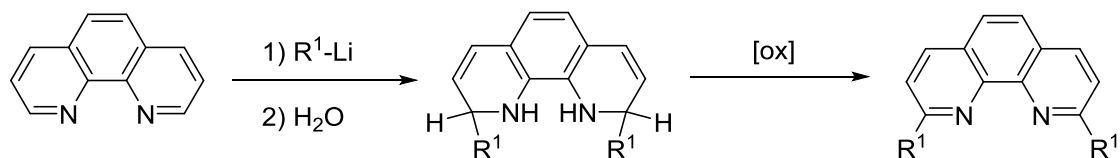
3. Divergent synthesis pathways

3.1. Functionalization of phen in positions 2 or 9 / 2 and 9

As presented in the introduction, the functionalization of phen in α of the chelating nitrogen atoms is the most impactful on the coordination ability of the ligand because substituents in those positions are the closest possible to the N $\widehat{\text{N}}$ cavity. There are numerous strategies to functionalize phen in positions 2 and/or 9, either by starting with naked phen or with pivotal commercially available building blocks (e.g. neocuproine **1**).

3.1.1. Direct functionalization of phen in positions 2 and 9 by organo lithium reagents

Principle and method: naked phen can be easily and selectively functionalized either once in position 2 or twice in positions 2 and 9 by a group R using organolithium reagents R-Li. R is usually either an alkyl or an aryl moiety. The reaction is carried out in two steps. The first one is a nucleophilic attack of R-Li on the carbons in α of the nitrogen atoms. Usually, either commercially available or freshly prepared R-Li (organolithium reagents can be obtained by halogen metal exchange on the corresponding halogenated substrate in presence of lithium sand, *t*BuLi or *n*BuLi) are either funneled on phen suspensions at low temperature or phen suspensions are added into R-Li solutions, yielding dark red solutions which are then abandoned at room temperature under inert atmosphere for very variable durations. The obtained adduct is a hydrogenated phenanthroline which must be re-aromatized in presence of a mild oxidant, usually activated MnO₂ (Scheme 48).



Scheme 48. Mechanism for the functionalization of phen by organolithium reagents.

Sauvage reported the first account of this synthetic strategy on phen in 1982,³³⁵ inspired by the pioneering work of Ziegler and Zeiser on pyridine.^{336,337} Over the years, the overall synthesis protocol has little changed. Nevertheless, several variations of the conditions have been reported.

The most common solvent used for the first step (nucleophilic addition of R-Li on phen) is toluene (e.g. the synthesis of **35**, **305-306**, Scheme 49), but THF (e.g. synthesis of **310**), diethyl ether (e.g. synthesis of **309**) and other aprotic solvents such as hexane have been used.^{335,338} Although the nature of the solvent seems to have little impact on the outcome of

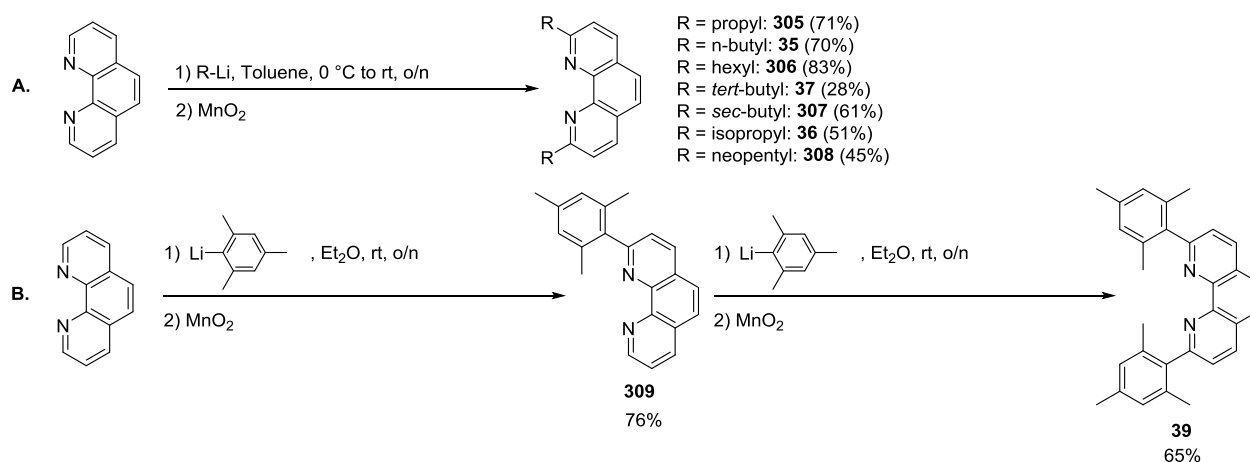
the reaction when simple R-Li are used (such as *n*BuLi or PhLi), Schmittel et al.³³⁹ reported that diethyl ether is more appropriate than toluene when bulky R-Li are used, probably for solubility reasons. In addition, diethyl ether can coordinate lithium ions and increase the reactivity of R-Li.

The impact of the steric bulk of alkyl organolithium reagents on the yield of the reaction is thus very strong. Basically, α -ramified alkyl chains (sec-butyl,¹³⁹ isopropyl³⁰⁹ or *tert*-butyl¹³⁹ yielding **307** (61%), **36** (51%) or **37** (28%) respectively) or particularly bulky aliphatic alkylolithium (e.g. neopentyl,¹³⁹ leading to **308** (45%)) can sometimes prove more difficult to graft on phen (Scheme 49A). It is however possible to improve the yields of those syntheses. For example, increasing the temperature or the duration of the reaction allowed to slightly increase the yield of **37** from 28% to 36%³³⁵ and the yield of **307** from 61 to 78%.³³⁸

Sauvage reports as a general rule that ambient or higher temperatures favor substitution in both positions 2 and 9, while milder temperature (below 10 °C) tend to favor mono-substitution.³⁴⁰ The duration of the addition step is highly dependent on the reactivity of the organo lithium reagent, which is directly related to its steric hindrance. The reaction of non- or little sterically challenged R-Li (e.g. PhLi, *n*BuLi...) on phen is performed in a few hours (Jakobsen³⁴¹ reported that a 5 min reaction time is sufficient for the addition of Phenyllithium on phen) whereas bulky R-Li often require days to reach satisfactory yields.³³⁵ In a few examples, the reaction mixture is even refluxed to help overcome the potentially high activation barriers.³⁴²

Finally, it has been demonstrated that performing the reaction in two steps (i.e. isolating mono substituted 2-R-phen, and reacting it with R-Li to afford 2,9-R₂-phen) leads to better overall reaction yields especially when bulky R-Li are used (see for example the synthesis of **39** via **309**, Scheme 49B).^{339,343} Incidentally, this strategy allows to isolate non-symmetrically substituted phen, bearing two different groups R¹ and R² in positions 2 and 9,³⁴⁴ by making

two subsequent nucleophilic additions/oxidation steps with R^1 -Li first, then R^2 -Li. In this frame, Jakobsen proposed a one-pot method, where organo lithium reagents R^1 -Li and R^2 -Li are introduced one after the other in the same reaction vessel containing phen. A final oxidation step leads to non-symmetrical phen ligands, thus avoiding the potentially unnecessary isolation of mono substituted phen.³⁴¹



Scheme 49. Examples of functionalization of phen in positions 2 and 9 by R-Li

MnO₂ is the most common oxidant used for the re-aromatization step. This oxidation is usually realized in dichloromethane for a few hours in ambient air, at room temperature (although Naganawa et al.^{345,346} used ethyl acetate at 60 °C), under vigorous stirring and with a strong excess of MnO₂. Lüning et al. precise they performed azeotropic distillation of water during oxidation.³⁴³ In some cases, MnO₂ powder was activated by heating under vacuum for a few hours.³⁴⁷ Other typical oxidants (KMnO₄, nitrobenzene) have been tested but proved less efficient.³³⁵ A few works report the use of DDQ^{348,349} and bleach^{350,351} too. However, all soluble oxidants must be removed by extraction or chromatography, whereas MnO₂ requires a simple filtration step.

In the examples given in Scheme 49, the aliphatic or aromatic groups attached to positions 2 and 9 increase the steric hindrance around the chelating nitrogen atoms. This has several

consequences which have been exposed in the introduction. For example, PVC membranes embedding **35** can selectively bind Li^+ ions vs. K^+ or Mg^{2+} .^{335,338}

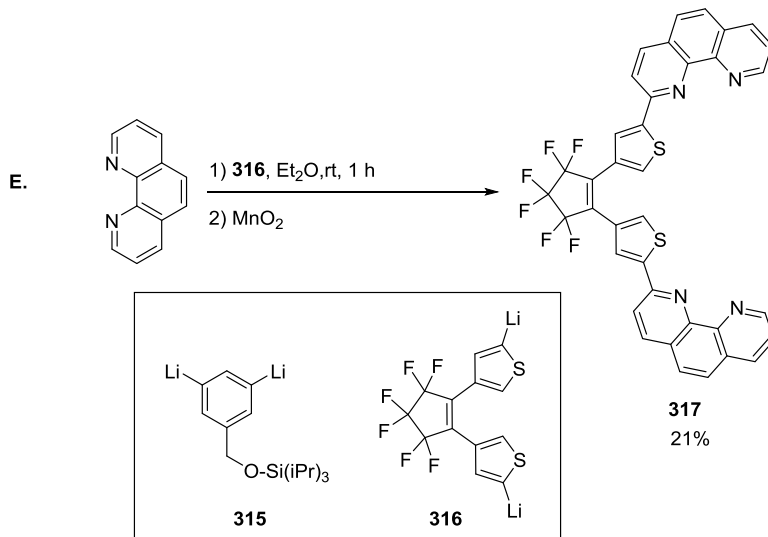
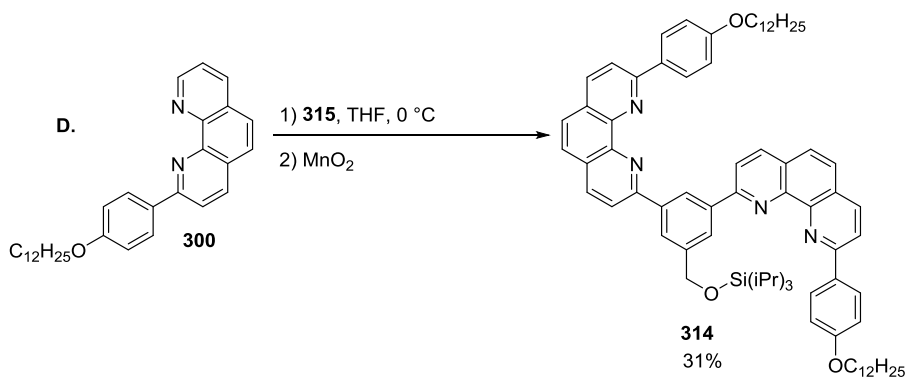
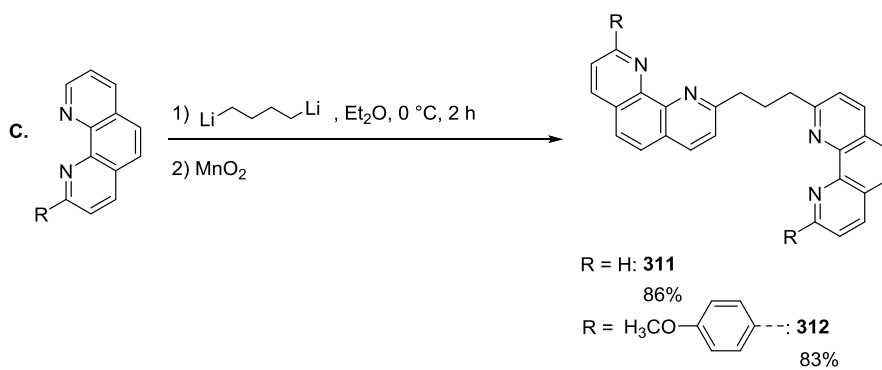
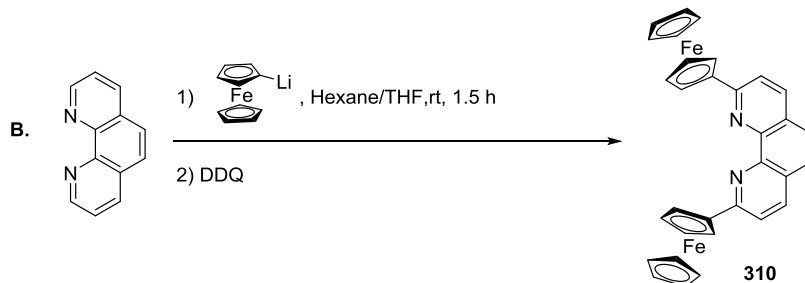
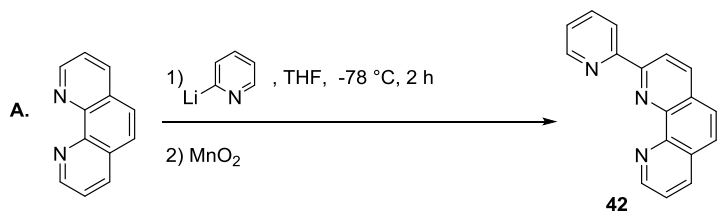
Sterically hindered phen ligands have been abundantly used in the field of copper(I) photochemistry too. The presence of simple alkyl or aryl groups in positions 2 and 9 of phen prevents photo-induced flattening of the coordination sphere and restores the excited state properties.^{133,352} A rule of thumb states therefore that the larger the bulky groups in α of nitrogen atoms, the higher both the emission quantum yield and lifetime. Those complexes and their properties have been explored in a number of contributions which have already been reviewed elsewhere.^{53,54,353}

The chemistry of organolithium reagents is very rich and not limited to the structures exposed in Scheme 48. For example, the use of pyridine lithium reagent¹⁵² has allowed to isolate phen ligand **42** (Scheme 50A) which can be considered as a terpy analogue with increased rigidity. In this case, the coordinating ability of phen is significantly enhanced with a number of metal ions which are accommodated by such a chelating $\widehat{\text{N}}\widehat{\text{N}}\widehat{\text{N}}$ environment (e.g. Pt ,¹⁵² Ru ,^{354,355} Pt ,¹⁵² Co)³⁵⁶.

Original organo lithium reagents such as ferrocene lithium³⁵⁷ or chromium tricarbonyl phenyllithium³⁴⁹ have allowed to synthesize hybrid phen ligands (e.g. **310**, Scheme 50B) where a metal center is covalently bound to phen while preserving its chelating ability.^{349,357} Those original species were developed in the frame of H_2 storage³⁵⁷ (by reduction of phen nucleus) and anti-malarial drug design.³⁴⁹

Bis-lithium reagents can be prepared from bis halogenated aryl or alkyl compounds, and can be used to prepare phenanthroline dimers. For example, 1,4-dilithiobutane in presence of 0.5 eq. of phen lead to **311** and **312** (Scheme 50C), where two phen fragments are connected in positions 2 by a butyl chain.³⁴⁰ Armaroli, Nierengarten et al. used the same strategy to design **314**, from monosubstituted **313** and bis-lithium reagent **315** (Scheme 50D).³⁵⁸ A final

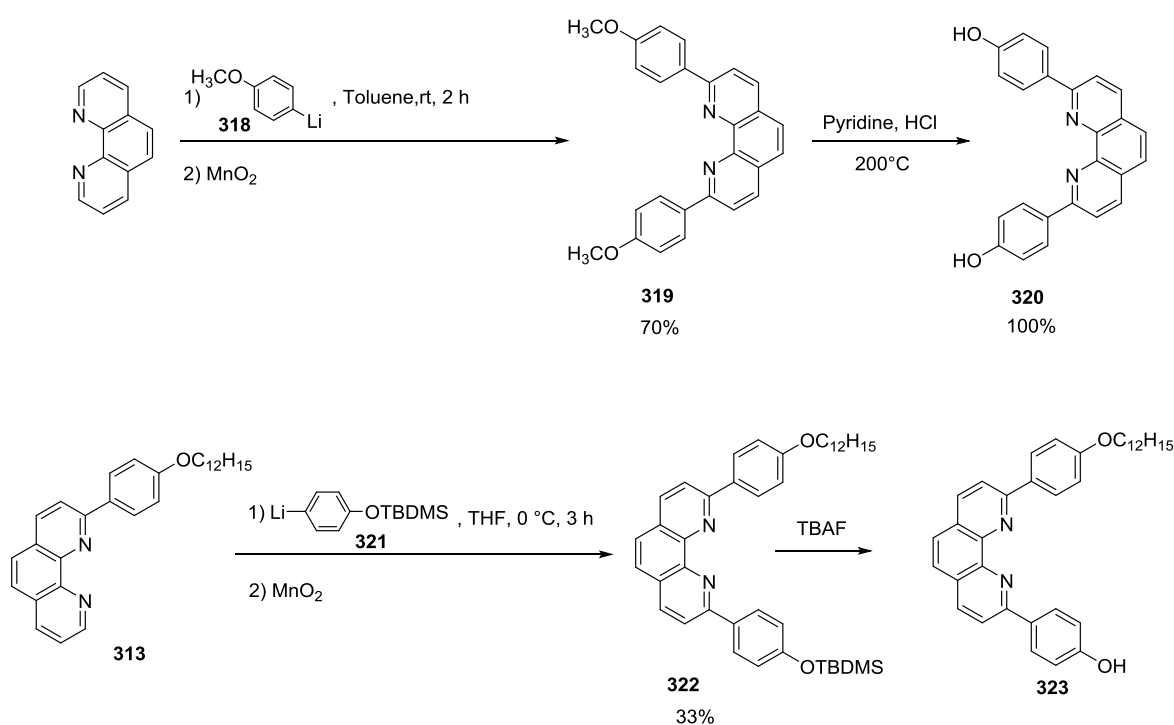
example is the addition of bis lithium bithienylhexafluorocyclopentene **316** (obtained by halogen/metal exchange) on excess phen, which allows to reach photochromic material **317** (Scheme 50E).³⁵⁹



Scheme 50. Action of original organolithium reagents on phen

Organo lithium reagents are very reactive, meaning that only chemically inert R groups can be used to prepare R-Li. This may appear as a limitation to this synthetic method, however many examples can be found where further decoration is feasible. As a matter of fact, it is possible to append several functional groups to phen_{(2,9)sub} using organolithium chemistry: alcohol groups, halogen atoms, aldehydes and amines. In most cases, appropriate protecting groups are used to prepare stable organolithium reagents.

To begin with, there are several alcohol protecting groups which are compatible with organolithium reagents. For example, anisyllithium **318** is stable and reacts with phen as exemplified in Scheme 51, leading to ligand **319**. **319** best known as dap (for 2,9-dianisyl-1,10-phenanthroline) is a famous phen_{(2,9)sub} ligand because the homoleptic complex [Cu(**319**)₂]⁺ is an excellent photosensitizer.^{360,361} As shown in Scheme 51, the methyl groups can be removed by treatment in pyridinium chloride at 200 °C, leading to **320**, which initiated the field of catenanes (see below).³⁶² BBr₃ can be used as well, as demonstrated by Lüning and co-workers (synthesis of **324**, Figure 22).³⁴³



Scheme 51. Synthesis of phenol-bearing phen_{(2,9)sub} ligands through organolithium chemistry

Alternatively, organolithium reagents bearing TBDMS, MOM³⁴⁵ and THP etheroxides³⁶³ have been used to generate phen_{(2)sub} and phen_{(2,9)sub} ligands. For example, the reaction of TBDMS protected organo lithium reagent **321** on **313** is given in Scheme 51. The resulting phen_{(2,9)sub} **322** is subjected to tetrabutylammonium fluoride to afford OH-bearing **323**.³⁶⁴

Summarily, there are numerous phen_{(2,9)sub} and phen_{(2)sub} ligands bearing free OH groups (Figure 22) which have been originally obtained *via* organolithium chemistry.

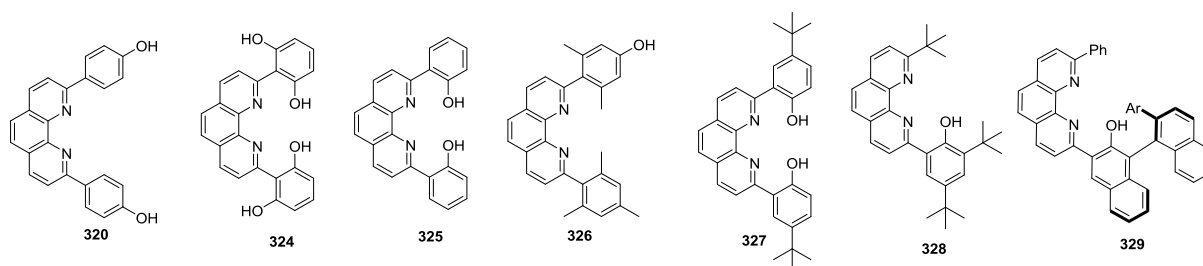
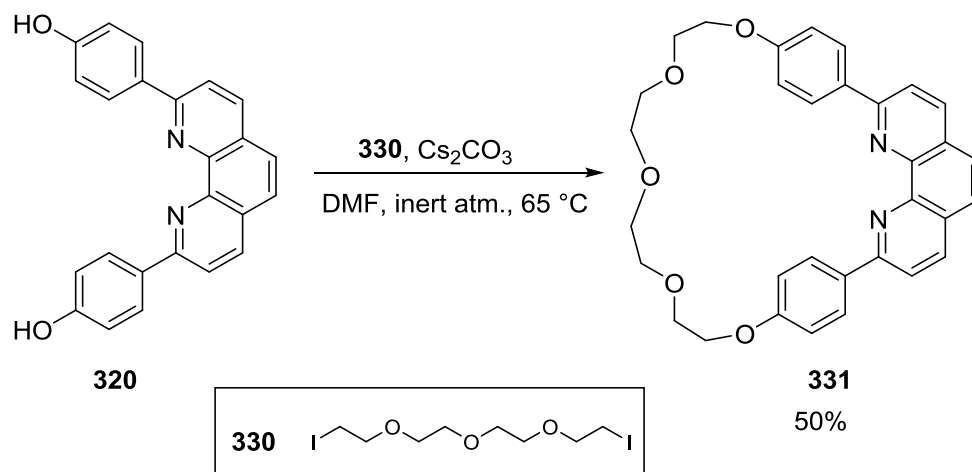


Figure 22. Examples of OH-bearing phen_{(2,9)sub} obtained by deprotection of the corresponding methoxylated derivatives

The reactivity of the free OH groups is not different from the one of phenol. A landmark example is **320** which can be used as nucleophile in presence of **330** to afford macrocycle **331** (Scheme 52). The latter is a pivotal species for the preparation of interlocked molecular rings.³⁶²

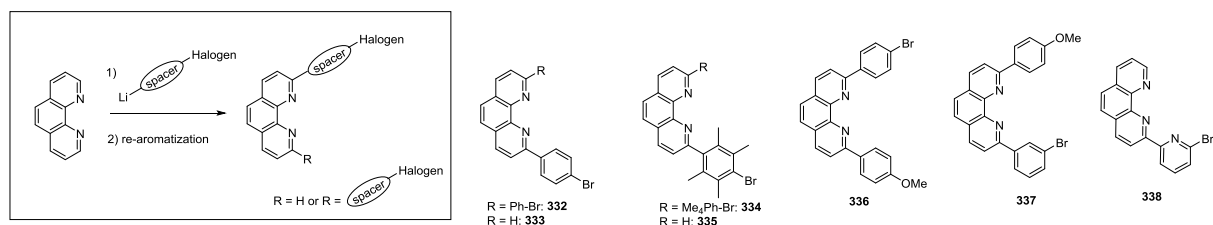


Scheme 52. Example where the reactivity of OH groups on phen_{(2,9)sub} is exploited

The resulting free phenol functions can be used for their reactivity or for their coordinating abilities which significantly modifies the properties of naked phen. For instance, ligand **328** provides an adequate environment for Cu(II) coordination after deprotonation of the OH group mimicking the active site of galactose oxidase.³⁶⁵ **325** shows a salen-like structure where the usual imine groups of salen are replaced by C=N bonds of phen, leading to more stable complexes.³⁴² In **329**, a chiral BINOL moiety has been tethered to position 2 of phen; the mixed phen/phenol chiral coordinating cavity proves a relevant additive for the efficient enantioselective addition of diethyl zinc to aromatic aldehydes and the asymmetric Michael addition of oxindoles (in presence of Ni²⁺).³⁴⁵

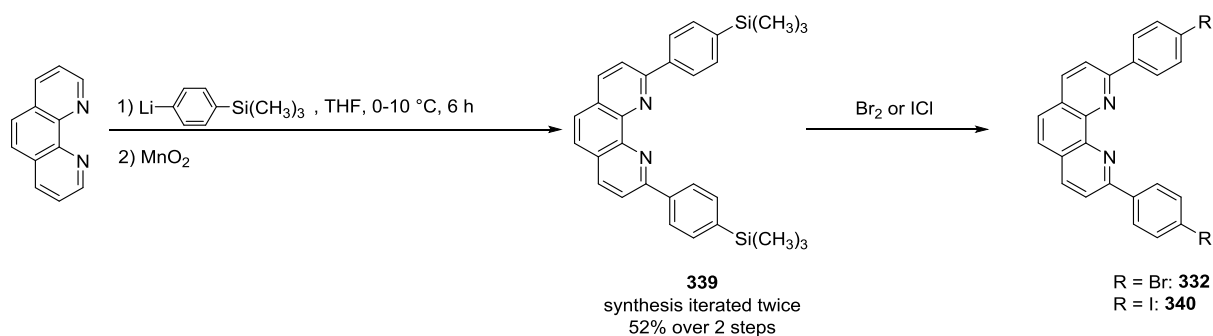
Surprisingly, an organolithium reagent bearing an untouched halogen atom can be prepared directly from a bis halogenated starting material in presence of one equivalent of butyllithium.^{339,366,367} Ligands **332**,³⁶⁸ **333**,^{367,368} **334**,³³⁹ **335**,³³⁹ **336**,³⁶⁷ **337**³⁶⁹ and **338**³⁵⁶ were

obtained by reaction of such halogenated organo lithium reagent with phen at low temperature (Scheme 53). The synthesis of symmetrical bis substituted phen **332** and **334** was performed in two steps, likely to decrease the risks of unwanted side reactions.



Scheme 53. Synthetic method to prepare halogenated phen_(2,9)sub and phen₍₂₎sub from halogenated organolithium reagents

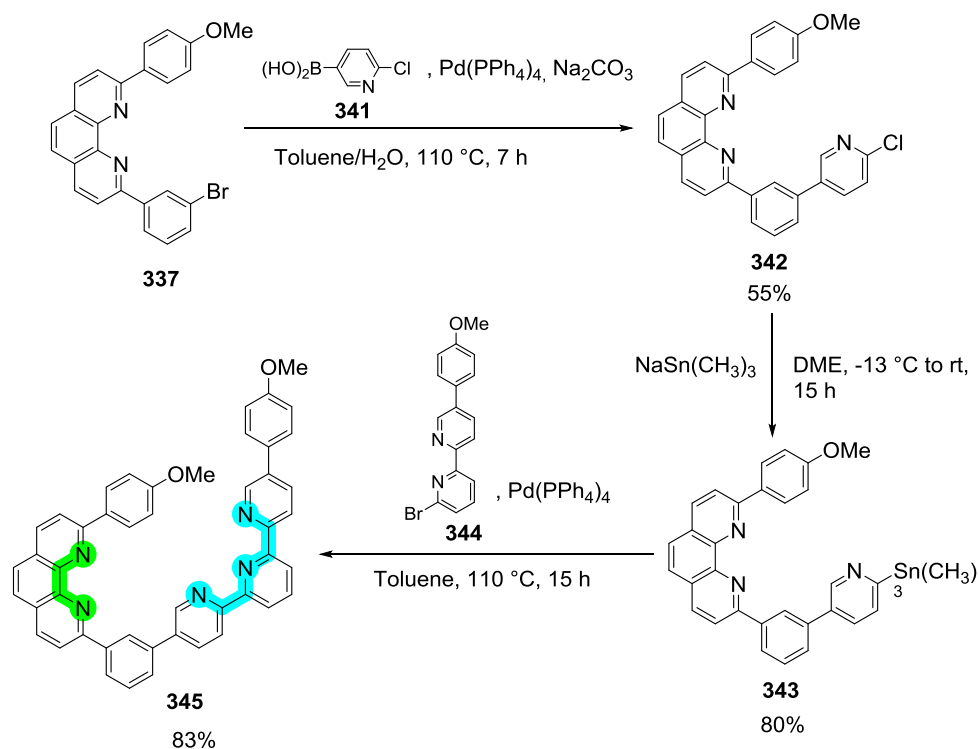
Incidentally, halogenated phen₍₂₎sub and phen_(2,9)sub **332** and **333** can be obtained *via* a different route,³⁷⁰ relying on the preparation of 4-trimethylsilyl-aryllithium (Scheme 54). The addition of the latter on phen affords **339** which can be conveniently turned into **332** in presence of Br₂ or the iodinated **340** in presence of ICl.³⁷⁰ The same protocols are operational to prepare mono-substituted compounds.



Scheme 54. Synthetic method to prepare brominated or iodinated phen_(2,9)sub from organolithium reagents bearing trimethylsilane

Phen ligands bearing aryl-halides can be further functionalized, e.g. by nucleophilic aromatic substitutions,³⁵⁶ or using well-known palladium catalyzed cross coupling reactions. Thus,

Suzuki,^{339,366,368,370-373} Sonogashira,^{367,370} Stille,³⁶⁸ Negishi³⁷⁴ cross couplings have all been explored.

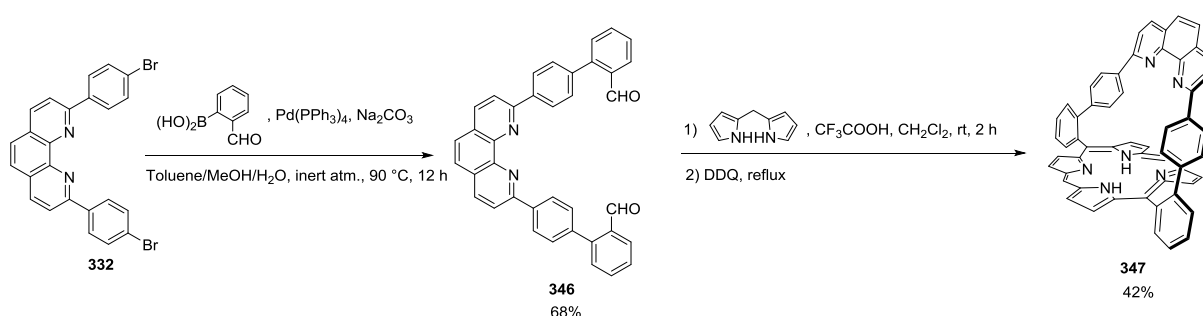


Scheme 55. Synthesis of heteroditopic phen (highlighted in green)-terpy (highlighted in blue) ligand **345**

For example, Sauvage et al. presented the multistep synthesis of an original ditopic ligand **345** using successive Suzuki (**342**, from **337** and boronic acid **341**) and Stille (from **343** and **344**) cross coupling reactions, where both phen and terpy are covalently bound.³⁶⁹ Such heteroditopic ligands have been extensively used as axles in the field of rotaxanes, to design molecular machines where the preferential affinities of phen and tpy for e.g. Cu(I) and Cu(II) respectively are used to drive a molecular ring on a chemical axle (Scheme 55).¹⁷⁶

Further functionalization can lead in many cases to highly intricate molecular systems. For example, Weiss et al. managed to combine a phen ligand strapped on top of a porphyrin macrocycle, yielding a powerful soluble chelating agent able to accommodate several ions

(Scheme 56).^{371,372} Similar work with aza crown ether instead of porphyrin has been reported too by the same authors.³⁷³

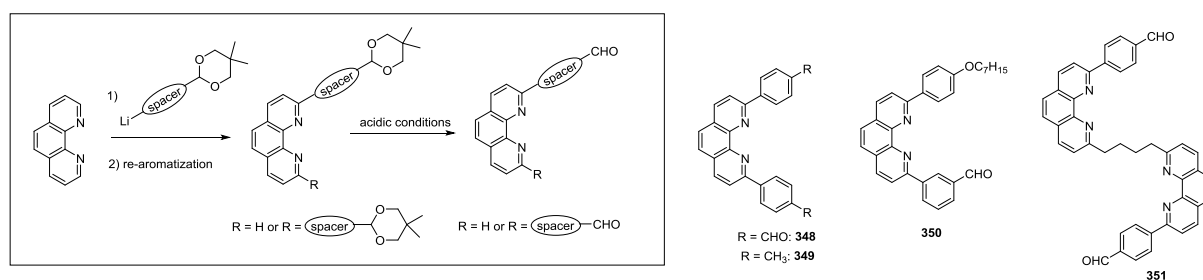


Scheme 56. Synthesis of hybrid porphyrin-phenanthroline macrocycle **347**

These selected examples demonstrate that, in those conditions, phen does not interfere in a deleterious way with the reactants and reagents involved in the cross-coupling reactions.

Organolithium reagents bearing protected aldehydes (under the shape of an acetal) can be prepared in traditional conditions and added on phen following the previously described protocol, yielding after re-aromatization and subsequent deprotection a phen bearing an aldehyde group (**348**,³⁷⁵ **350**,³⁷⁶ **351**, Scheme 57).³⁷⁷

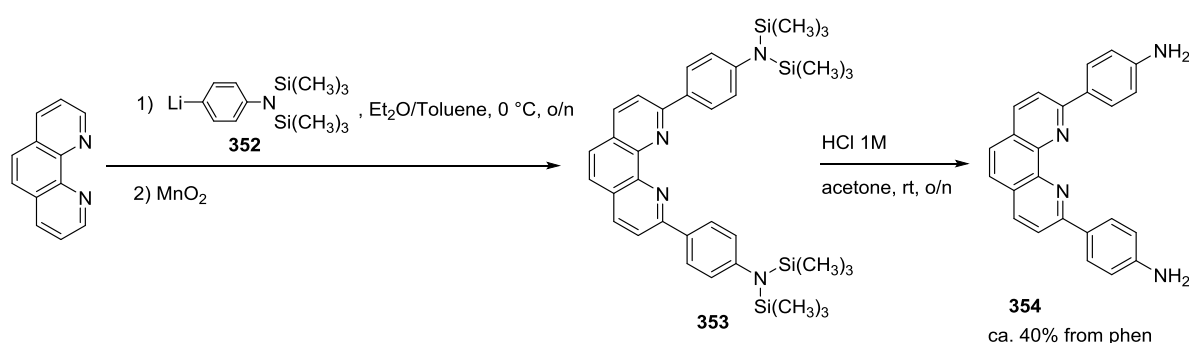
Other methods to reach **348** rely on the action of NBS of the methyl groups on **349** by NBS, followed by acidic treatment.^{378–380} This method leads to a mixture of compounds and requires therefore several purification steps which make it overall less efficient (yield below 20%) than the organolithium pathway described in Scheme 57 (45% yield from phen).



Scheme 57. Syntheses of phen_{(2,9)sub} bearing aldehyde functions through organolithium chemistry

The free aldehydes can then be used in Wittig reactions³⁵⁰ or imine formation in presence of primary amines.³⁸¹ **348** has notably been used as starting material to prepare porphyrin dimers linked by a phen spacer, *via* Adler's synthetic strategy.^{375,380} The CHO group can be reduced too in methyl alcohol,³⁸² paving the way towards multiple coupling reactions relying on the nucleophilic character of the OH group. Conversely, CHO can be oxidized in carboxylic function,^{363,383} allowing to perform all the versatile chemistry of amide and ester coupling.

Finally, amine bearing phen_{(2,9)sub} can be prepared via organolithium chemistry (Scheme 58).³⁸⁴ Reagent **352** was prepared from p-bromo-N-trimethylsilylaniline by halogen-metal interchange in presence of *n*BuLi.³⁸⁵ The addition of **352** onto phen followed by rearomatization afforded **353** which was not isolated. The silane protective groups were removed by acidic treatment to give **354** in 40% overall yield from phen. The coordinating ability and reactivity of NH₂ make such ligand a precious synthetic block for the design of hybrid materials.³⁸⁴

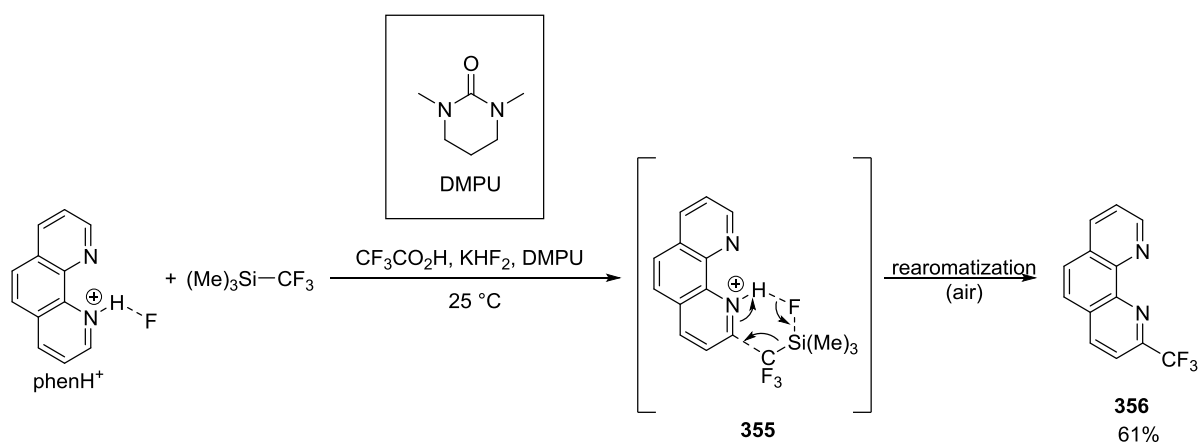


Scheme 58. Synthesis of phen_{(2,9)sub} bearing amine groups *via* organolithium chemistry

3.1.2. Functionalization in positions 2 and/or 9 by activation of phen nucleus

3.1.2.1. Activation of C₂ by protonation of phen

Protonation of one of the nitrogen atoms is an easy and convenient way to activate phen towards nucleophilic additions in positions 2 and 9. For example, Kuinobu, Kanai et al. recently demonstrated the efficient trifluoromethylation of phen in position 2 by trifluoromethyltrimethylsilane in strongly acidic medium (Scheme 59). It is inferred that a key intermediate is the formation of phenH⁺ in presence of HF and subsequent formation of a six-membered transition state **355** which ultimately leads to **356**.³⁸⁶

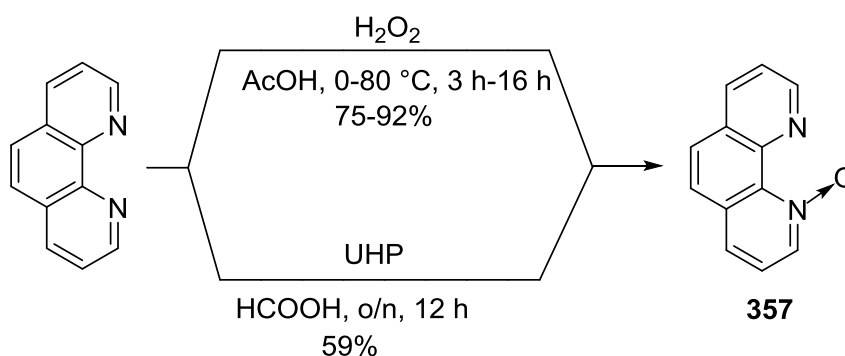


Scheme 59. HF assisted functionalization of phen in position 2 by CF₃

3.1.2.2. Activation of C₂ by formation of N₁-oxides

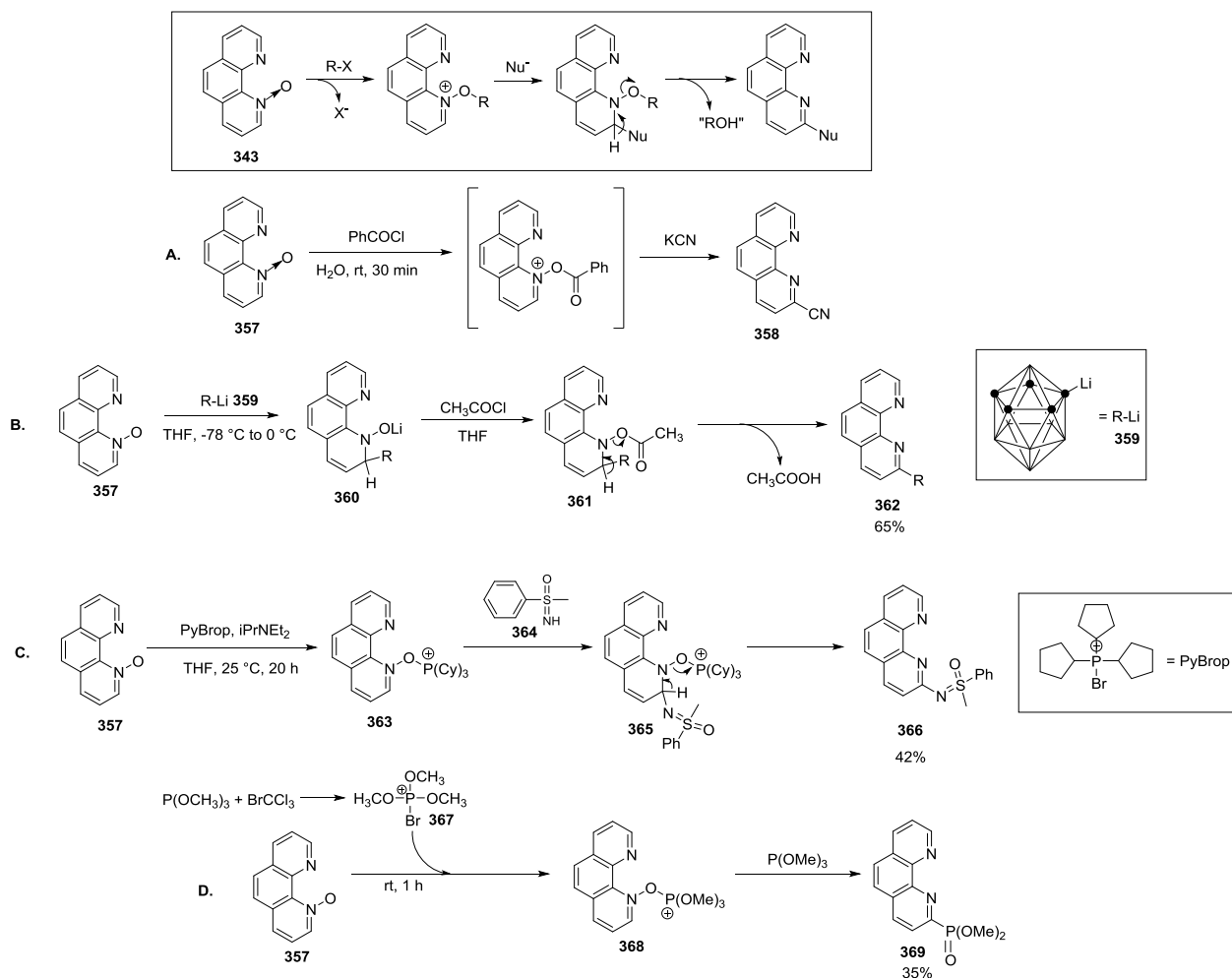
The oxidation of one nitrogen atom on phen (from phen to phen-N-oxide **357**) allows to greatly enhance the reactivity of the adjacent carbon atom.³⁸⁷ The formation of the N₁-O bond enhances the electrophilicity of C₂ and nucleophilic additions on C₂ are favored.³⁸⁸ Action of excess hydrogen peroxide on phen in hot glacial acetic acid leads to 1,10-phenanthroline-1-oxide **357** in high yields.^{389,390} The addition of H₂O₂ in three successive portions and extraction of the product with hot chloroform seem to be important experimental details to

reach higher yields (92%).³⁹¹ In addition, the synthesis of **357** must be performed with caution because of the risks of explosions inherent to the use of peroxides. An interesting alternative protocol relies on replacing H₂O₂ by the adduct formed between the latter and urea (UHP).^{392,393} The reaction of UHP with phen at room temperature in formic acid leads more safely to **357** in a respectable yield (59%).³⁹⁴ Moreover, the use of *m*CPBA instead of H₂O₂ has been reported too (Scheme 60).^{395,396}



Scheme 60. Synthesis of phen-N-oxide **357**

The most frequently used strategy to functionalize position 2 of phen-N-oxide **357** is to append a functional group R on the oxygen atom in order to generate a good leaving group on the nitrogen atom. First, the regioselective nucleophilic attack in α of the functionalized nitrogen atom is still favored, leading to a de-aromatized intermediate. Re-aromatization occurs quickly upon elimination of one “ROH” molecule. Corey demonstrated the efficacy of this strategy by synthesizing 2-cyano-1,10-phenanthroline **358** (Scheme 61A).³⁸⁹



Scheme 61. Principle of the favorable nucleophilic attack on the carbon adjacent to N-O on **357** and examples

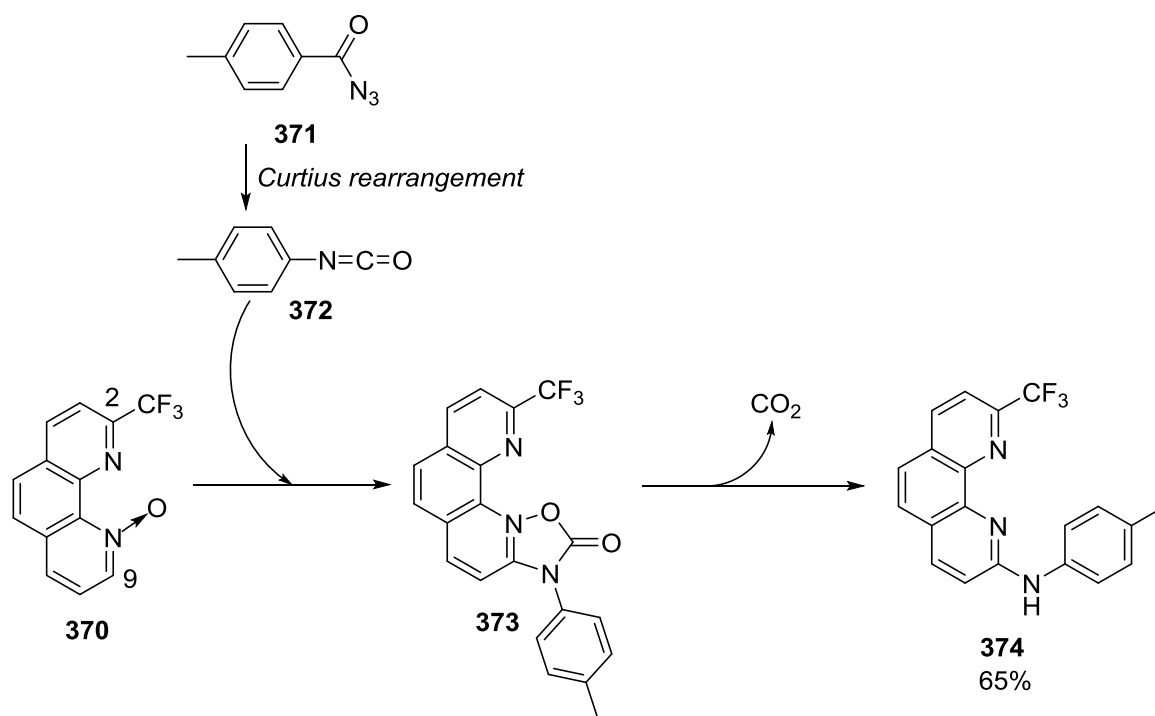
Different types of nucleophiles and leaving groups have been used since the pioneering work of Corey. For example, carboranelithium **359** was reacted with **357** to afford compound **362** in 65% yield (Scheme 61B). Regioselective addition of carborane lithium **359** on carbon C₂ of **357** yields the dearomatized compound **360**; acetyl chloride reacts readily with the latter thanks to the strong nucleophilic character of the oxygen terminus. The acetate is a good leaving group and this favors a final elimination step leading to 2-carborane substituted phen **362**, a useful molecule merging the ligand quality of phen and the many characteristics of

carboranes.³⁹⁷⁻³⁹⁹ The mechanism is thus different from the one described above for C-C bond formation with organolithium reagents (section 3.1.1), in that no oxidation step is required.⁴⁰⁰

C₂-N bonds can be formed following the same strategy: the one-step PyBrop assisted sulfoximation of **357** has been reported,³⁸⁸ leading to **366** in a moderate yield but in very mild conditions and in only two steps from phen (Scheme 61C). Other examples can be cited, where **357** is activated with CF₃-BF₂- or triflic anhydride (forming good leaving group CF₃-OBF₂- and TfO⁻ respectively).

Finally, the formation of C₂-P bond has been reported too using trimethylphosphite as an ubiquitous reagent (Scheme 61D).⁴⁰¹ In presence of bromochloroform, the phosphonium **367** is generated *in situ* and used as electrophile to tether to the oxygen atom of **357**. Then excess P(OCH₃)₃ acts as nucleophile and attacks position 2 of **368**, leading eventually to **369**.

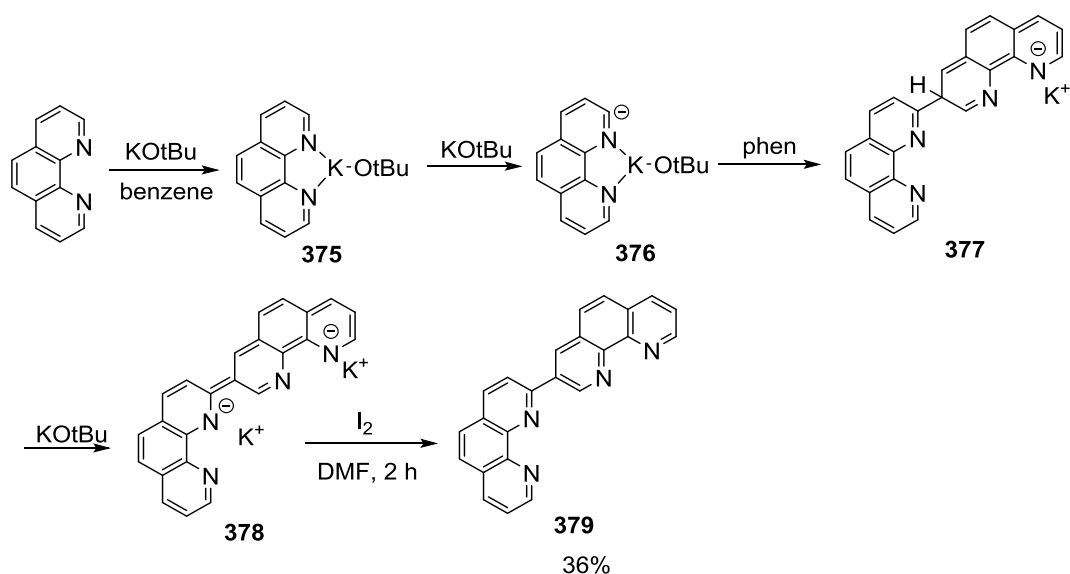
Recently, C-N bond formation from azine-N-oxides and acyl azides through 3+2 cycloadditions has been reported (Scheme 62).³⁹⁵ The strategy relies on the action of acyl azide **371**, which turns *in situ* in the corresponding isocyanate **372** by a Curtius rearrangement, on **370**. In this case, cycloaddition yields unstable **373** which affords **374** after decarboxylation.



Scheme 62. C₉-N bond formation from activated N-oxide **370**

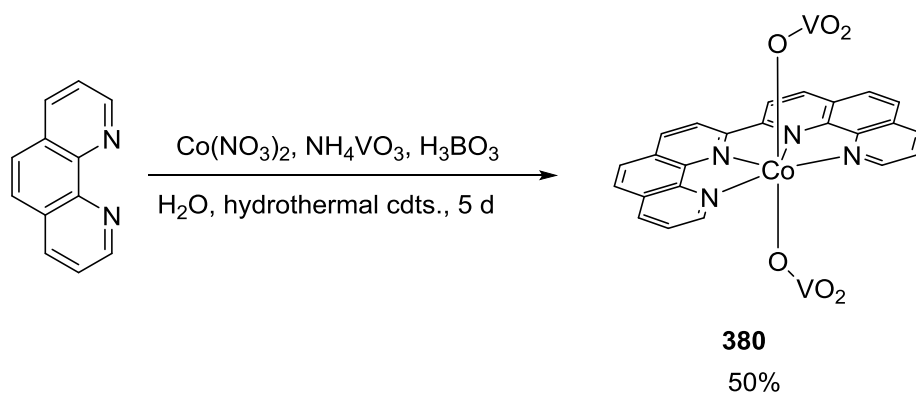
3.1.2.3. Activation of C₂ by coordination of metal ions

Phen can coordinate a great number of metal ions, from alkali to transition metals or lanthanides. The formed complexes can feature peculiar reactivities assisting in some cases functionalization reactions in position 2. For example, potassium *tert*-butoxide KOtBu has been shown to promote an interesting phen dimerization reaction, through formation of a phen-potassium complex in benzene at 130 °C in a sealed tube (Scheme 63).⁴⁰² After formation of the complex **375**, another equivalent of KOtBu can deprotonate phen in position 2, yielding the strong nucleophile **376** which can attack another phen molecule in position 3 specifically (as empirically observed and supported by calculations). After a new deprotonation step affording dianion **378**, the phen dimer **379** is formed by re-aromatization in presence of I₂ with a 36% yield from phen.



Scheme 63. Dimerization of phen assisted by KOtBu.

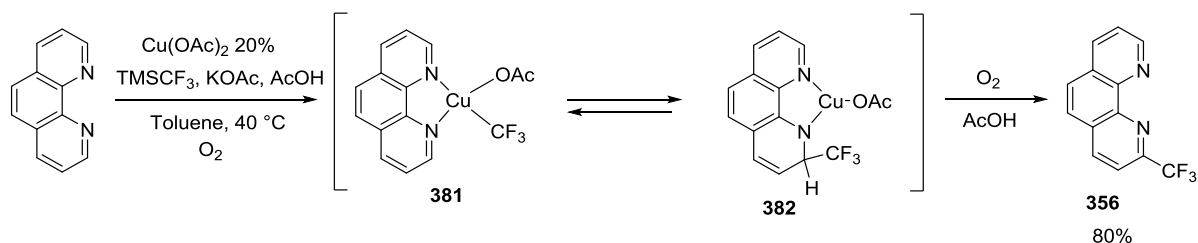
Interestingly, it is possible to change the regioselectivity of the dimerization reaction by performing the reaction in hydrothermal conditions (high pressure, high temperature) in presence of Co(II) nitrate, boric acid H₃BO₃ and ammonium vanadate (NH₄⁺)VO₃⁻. After 5 days, the cobalt complex of bis-phen **380** is obtained with 50% yield (Scheme 64).⁴⁰³



Scheme 64. Dimerization of phen assisted by Co(II) in hydrothermal conditions

Regioselective one-step trifluoromethylation of phen in position 2 is promoted in presence of TMSCF₃ and sub-stoichiometric amounts of Cu(OAc)₂ (Scheme 65).⁴⁰⁴ The copper(II)(trifluoromethylate)(phen) complex **381** is a key intermediate in this metal-assisted

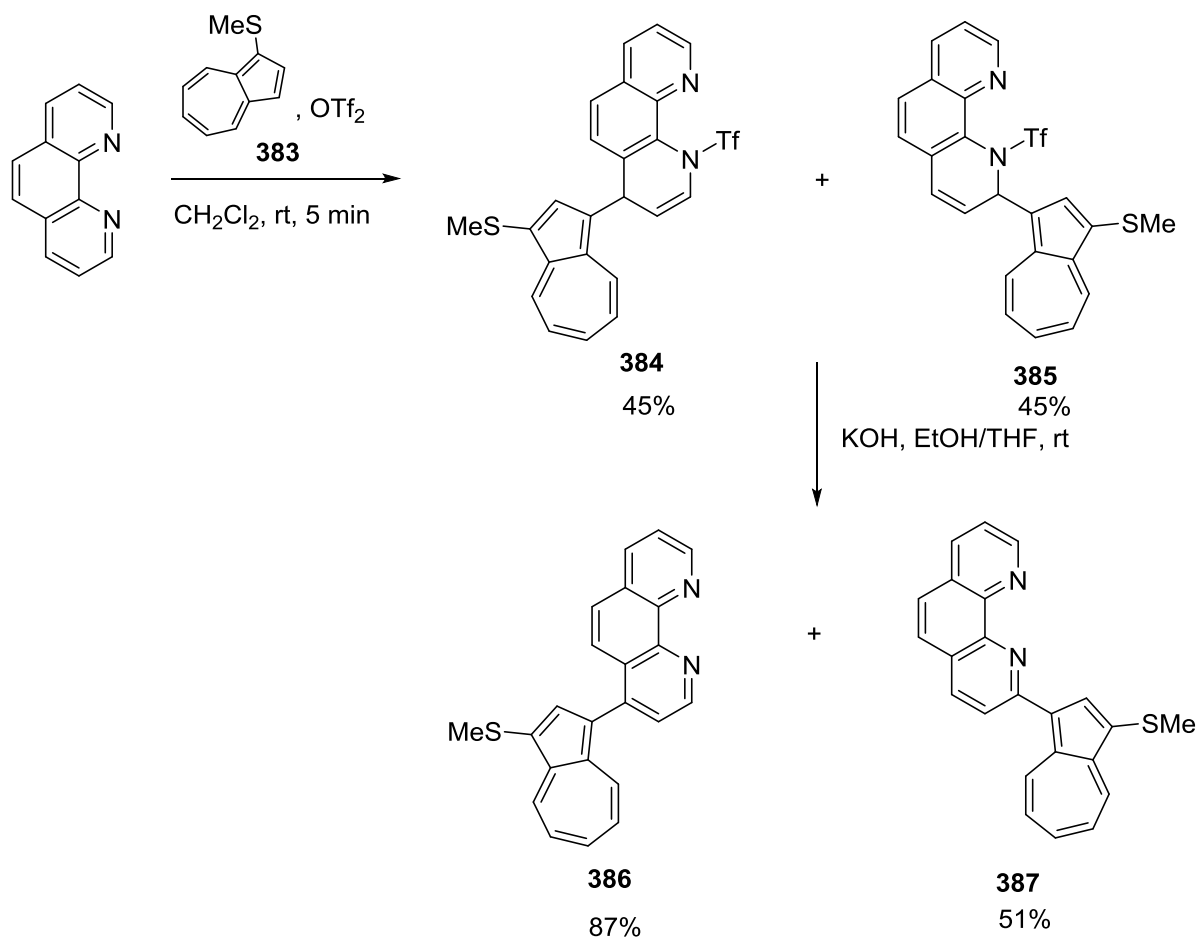
process, where oxidative addition of a CF_3 fragment takes place in position 2, affording intermediate **382**. Oxidation with O_2 eventually leads to **356** with a good yield. A similar difluoromethylation reaction of azines in presence of TMSCF_2H has been reported on several azines,⁴⁰⁵ with the complexation of silver by phen as crucial step to activate the $\text{C}_2\text{-H}$ bond.



Scheme 65. Trifluoromethylation of phen in position 2

3.1.2.4. Other activation of phen by temporary $N\text{-X}$ bond formation

Pyridine and triflic anhydride react together and form the electrophilic adduct trifluoromethanesulfonylpyridinium trifluoromethanesulfonate which can be attacked by nucleophiles like 1-Azulenyl methyl sulfide **383**.⁴⁰⁶ This was extended to phen (Scheme 66), the regioselectivity of the reaction is however poor as two regio-isomers **384** and **385** were formed in similar yields. They are nevertheless easily separated by classic chromatography, and the corresponding phen_{(3)sub} and phen_{(2)sub} derivatives **386** and **387** respectively are obtained after re-aromatization in decent yields.



Scheme 66. Functionalization of phen by 1-Azulenyl methyl sulfide using triflic anhydride

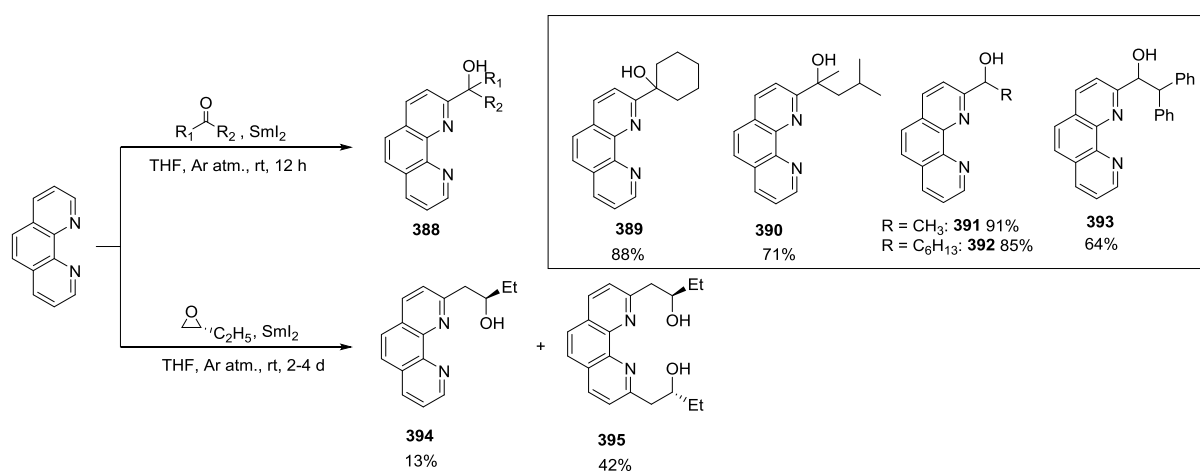
3.1.3. Functionalization of phen in positions 2 and 9 by radical chemistry

Although there are a few instances of radical alkylations of polysubstituted phen (see below), examples of direct radical functionalization of phen are rather rare.

One of the most famous example is the reductive coupling of ketones and aldehydes with phen in presence of SmI₂.⁴⁰⁷ The latter efficiently generates ketyl radicals by mono-electronic reduction of the carbonyl function. The radical readily attacks phen in position 2 of phen and affords **388** after re-aromatization (Scheme 67).^{85,146} A second addition in position 9 is feasible following the same protocol. The reaction is efficient with ketones (**389** and **390**) and aldehydes (**391-393**) provided that the synthetic protocol be rigorously respected (extra-dry THF, SmI₂ in THF added on pre-mixed phen and carbonyl substrate). The scope of the

reaction is large, but no aromatic carbonyls could be coupled in those conditions; α -enones can couple but lead to de-aromatized phen products.

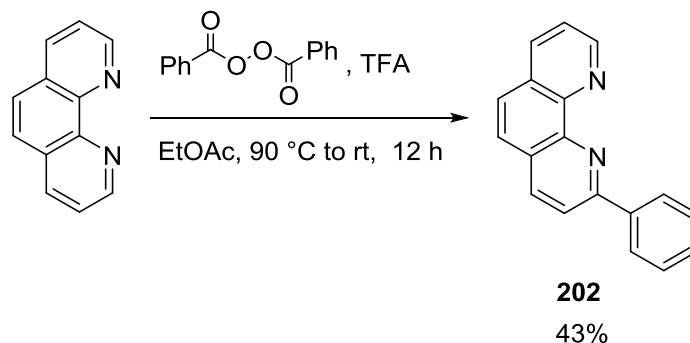
The same authors have reported coupling of chiral epoxides on phen in presence of SmI_2 , leading to diastereoisomers **394** and **395** as major products. In this case, the observed regio- and stereo-selectivities are inconsistent with a SmI_2 assisted reduction of the epoxide; instead, SmI_2 is thought to reduce phen into a reactive nucleophile radical which attacks and opens the epoxide (Scheme 67).⁴⁰⁸



Scheme 67. SmI_2 assisted radical addition of ketyl radicals or epoxides on phen

Direct functionalization of phen is easily achieved using radical nucleophiles, following the famous Minisci reaction. This reaction allows a C-C bond formation on phen and has been originally developed to functionalize quinoline regioselectively in positions alpha and gamma, using radicals generated from carboxylic acid and silver salts, in acidic medium. The method has been extensively explored and improved (using various azines and various methods and substrates to generate the radicals) and showed a great tolerance to many functional groups. The Minisci reaction has thus been successfully applied to phen, to generate C-C bonds in positions 2, 9, 4 and 7 (as will be seen later in this review). The reasons for this regioselectivity is grounded in the protonation of phen, activating positions alpha and gamma of N atoms vs. nucleophilic attacks.

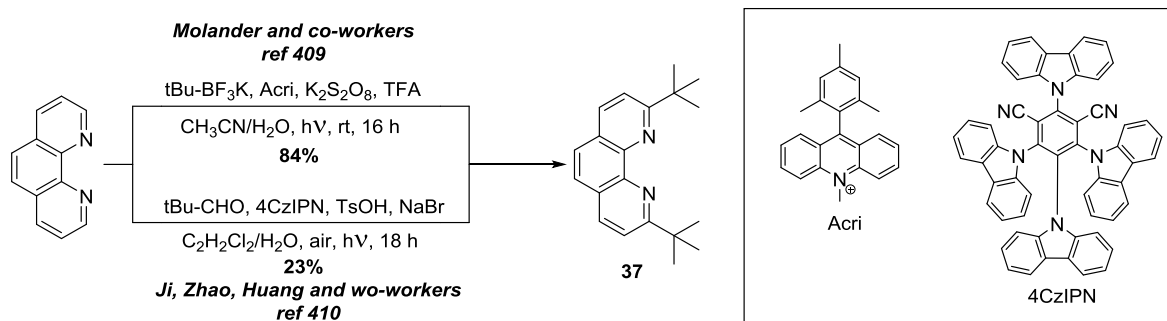
For example, Li and co-workers have recently reported that the mild thermal treatment of dibenzoyl peroxide (Ph-COO)₂ generates Ph-COO[•] radicals which lead to Ph[•] radicals after decarboxylation. The latter can then attack phen in position 2 leading to **202** (Scheme 68).



Scheme 68. Thermally activated Minisci reaction for the functionalization of phen in position 2

Photoredox Minisci type radical additions on phen have recently been proposed, presenting the advantage to be completed in rather mild conditions. Molander et al.⁴⁰⁹ have generated tertbutyl radicals tBu[•] by photo-oxidizing trifluoroborate tBu-BF₃K in presence of the strong photo-oxidant Acridinium dye (Scheme 69). The organic radical regioselectively attacks phen in positions 2 and 9 (the presence of TFA and side product BF₃ is believed to be responsible for the activation of positions 2 and 9 towards this nucleophilic attack).

Interestingly, Ji, Zhao, Huang et al.⁴¹⁰ have achieved the photoredox decarbonylative addition of aldehydes on phen (Scheme 69). This approach has the advantage to use abundant and readily available aldehydes instead of less frequent organic trifluoroborates, and only molecular oxygen (instead of S₂O₈²⁻ in the previous case) is required as oxidant to regenerate the photo-reduced dye and close the photocatalytic cycle. The same 2,9-ditertbutyl-1,10-phenanthroline **37** is obtained with however a much more modest yield than in the previous case (using organolithium chemistry). Similarly, protonation of phen is essential to activate positions 2 and 9 towards the nucleophilic addition of tBu[•] radical.



Scheme 69. Photochemically activated Minisci reaction for the functionalization of phen in positions 2 and 9

3.1.4. Key Building blocks towards functionalization of phen in positions 2 and 9

Several “pre-functionalized” phen_{(2,9)sub} and phen_{(2)sub} building blocks are readily available from several suppliers and/or easily synthesized in a few steps. Those building blocks are very useful for the functionalization of phen because they feature versatile reactivities which will be presented below. Neocuproine **1** and 2,9-dichloro-phenanthroline **396** (and the mono-substituted parent ligands **108** and **397**) are at the root of all these pivotal building blocks (Figure 23).

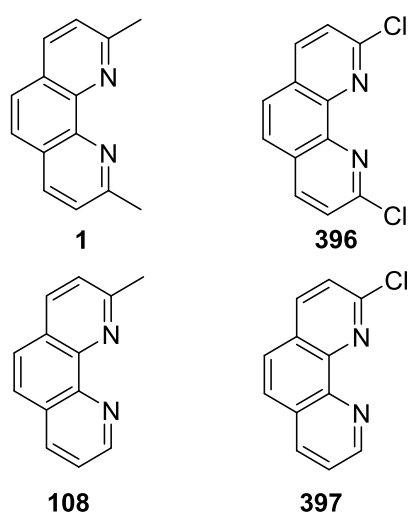


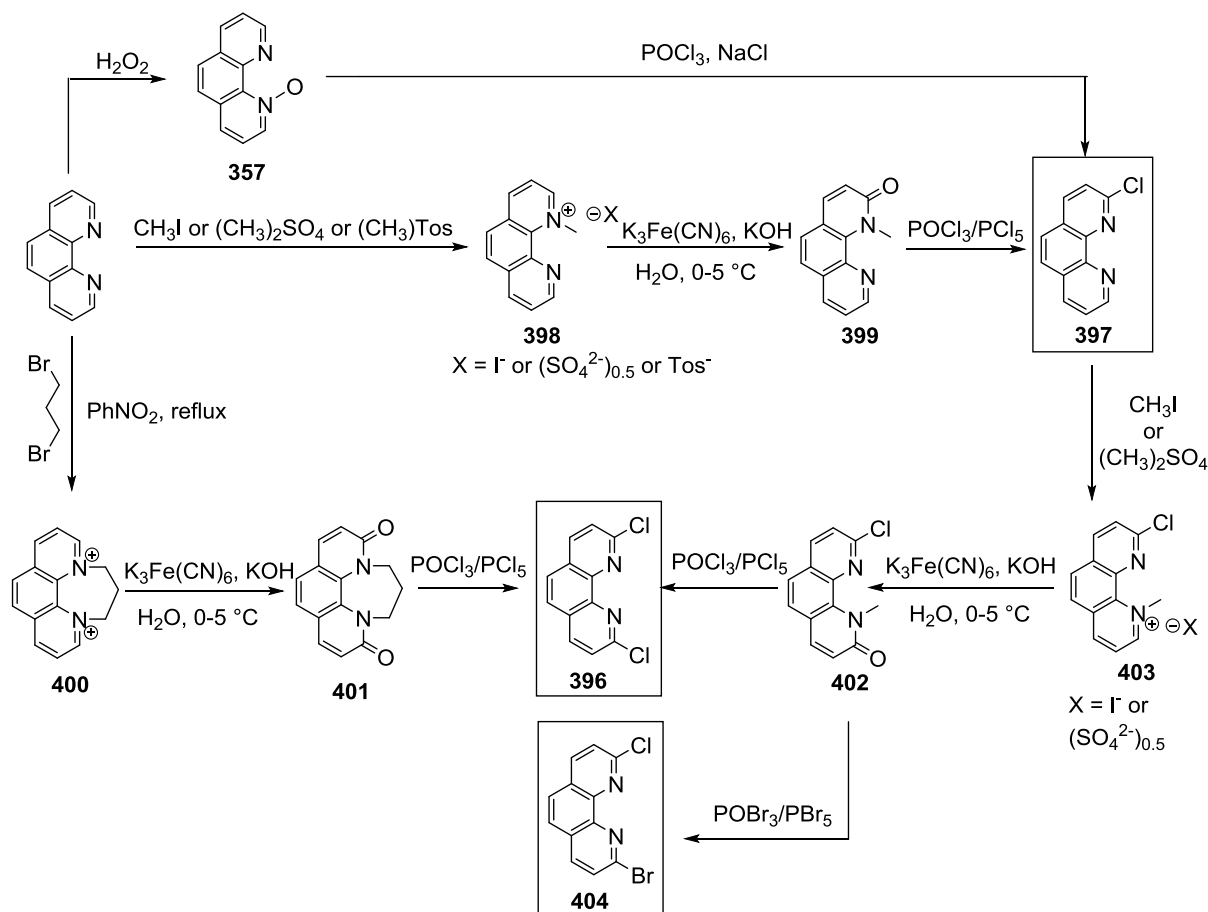
Figure 23. Pivotal phen_{(2,9)sub} and phen_{(2)sub} for the synthesis of versatile phen building blocks

3.1.4.1. Synthesis and exploitation of the reactivity of phenanthroline derivatives with halogen atoms in position 2 or in positions 2 and 9

Synthesis of 2-halogeno or 2,9-bis(halogeno) substituted phen

The first reported synthesis of 2-chloro-1,10-phenanthroline **397** was reported in 1946 by Halcrow and Kermack²⁹ and was improved in the eighties.⁴¹¹ The synthesis proceeds in 3 steps starting with methylation of one nitrogen atom of phen with CH_3I ²⁹ or Me_2SO_4 ⁴¹¹ yielding **398**, oxidation of **398** with potassium ferricyanide then leads to **399** and treatment with $\text{POCl}_3/\text{PCl}_5$ affords the final compound **397**.

The overall yield for the chlorination reaction is rather low in these initially reported conditions (less than 20% over the three steps from phen)²⁹ especially because of the low yield of the oxidation step. Several improvements have been proposed. It was first reported that the control of the temperature below 5 °C during ferricyanide addition (from **398** to **399**) is very important to get higher yields on this step.⁴¹¹ Second, the poor solubility of **398** as an iodide salt in aqueous medium was incriminated. When CH_3I was replaced by methyl tosylate as a methylation agent,⁴¹² the water soluble tosylate salt of **398** was quantitatively obtained and oxidation of the latter afforded **399** in 96% yield. Subsequent treatment with POCl_3 gave **397** with a much-improved overall yield of 67% from phen (Scheme 70).

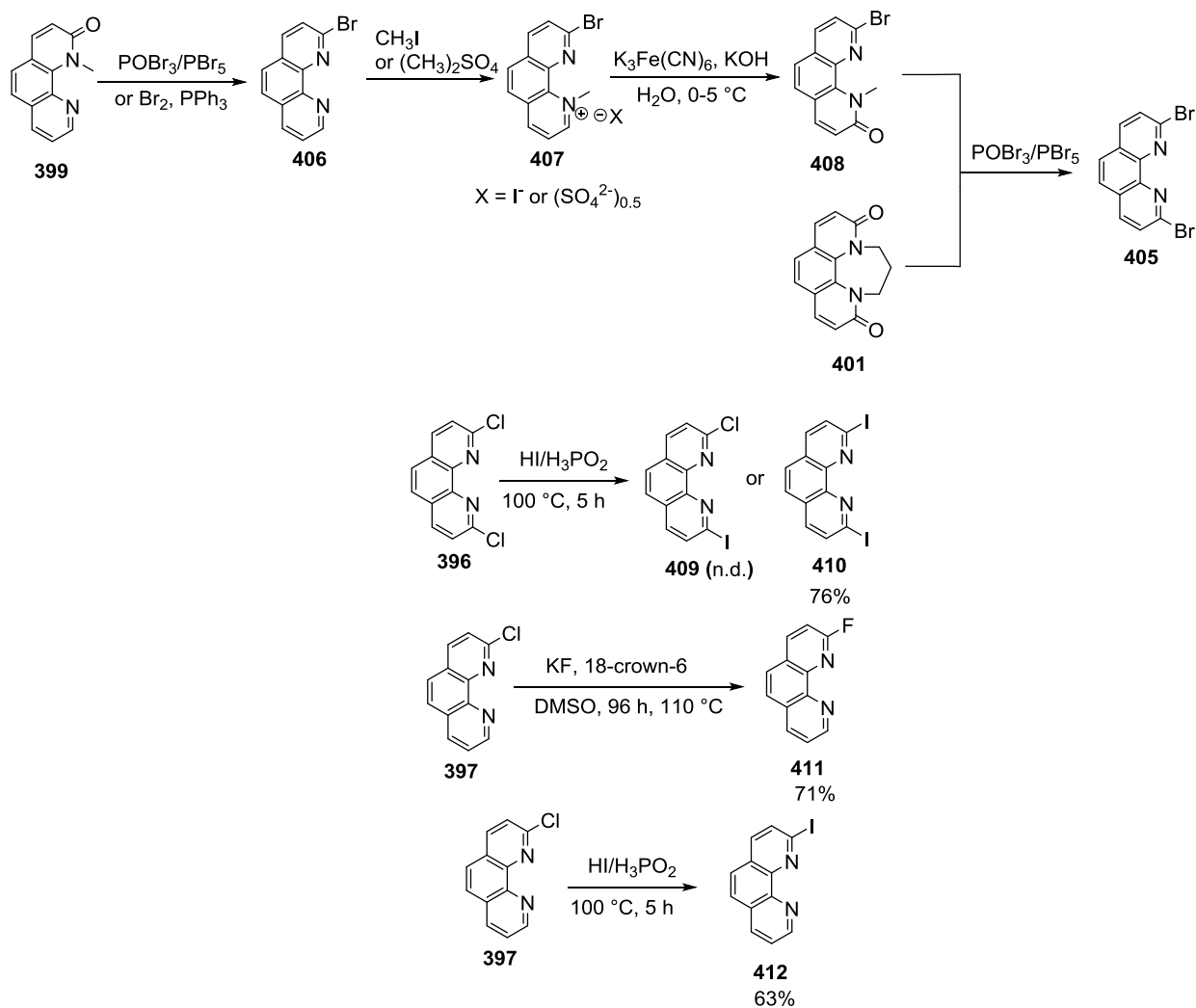


Scheme 70. Different synthetic pathways leading to **396** and **397**

Alternatively, a 2-step approach was developed by Gozin et al.⁹³ based on the oxidation of phen with H_2O_2 into **357**, which subsequently was reacted with POCl_3 and NaCl in DMF to yield **397** in 37% yield from phen. As a variation of the latter strategy, Wang et al.⁴¹³ generated a Vilsmeier reagent *in situ* with DMF and POCl_3 in presence of **357** dissolved in dichloromethane (0.1 M) and obtained **383** in yields similar to the method reported by Gozin. The syntheses of 2,9-dichloro-1,10-phenanthroline **396** and 2,9-dibromo-1,10-phenanthroline **405** was first reported by Ogawa⁴¹⁴ by merely repeating on **397** the series of steps which lead to **397** from phen (N-methylation, then oxidation and chlorination or bromination). The synthesis of **396** was then improved by Lewis⁴¹¹ and Krapcho.⁴¹² The yield of **396** from **397** is high (ca. 80%) and using the improved conditions of Krapcho, an overall yield of 43% from

phen is reported, which is satisfactory over 6 steps. Incidentally, this stepwise strategy allowed to synthesize mixed **404** with 98% yield.⁴¹⁴ Yamada improved the synthesis of **396** by activating both nitrogens with 1,3-dibromopropane, yielding the cyclic quaternized salt **400** which then undergoes oxidation on both positions 2 and 9 (**401**).⁴¹⁵ In Yamada's report, the reaction with POCl₃/PCl₅ yields **396** in 17% yield from phen which may appear low compared to the previous 6-step synthesis. The main limitation is the oxidation of **400** which shows a low yield (ca. 35%). The yield of this step was much improved (79%)⁴¹⁶ by replacing K₃Fe(CN)₆ by KOtBu in tBuOH. **396** was thus obtained in 67% and 64% yields respectively from phen over the three steps.

396 and **397** are the most abundantly used halogenated phen_{(2)sub} and phen_{(2,9)sub} but fluorine, bromine and iodine versions of **396** and **397** can be synthesized too (Scheme 71). **405** and **406** are commonly obtained following the same procedure than for **396**, reacting **399** in POBr₃/PBr₅ instead of POCl₃/PCl₅ with similar yields than **397**.^{414,417} Alternatively, **406** can be obtained by reacting bromo(triphenyl)phosphonium (generated *in situ* by action of Br₂ on PPh₃ at 0 °C in acetonitrile) on **399**^{143,418} thus avoiding the use of POBr₃ and PBr₅. Another interesting one-pot synthesis of **406** relies on the nucleophilic attack of tetra-*n*-butylammonium bromide on **357**, in presence of tosyl anhydride.³⁹⁶ The method of Wang using a Vilsmeier reagent is working too to synthesize **406** (Scheme 71).



Scheme 71. Synthesis of **405**, **406**, **410**, **411** and **412**

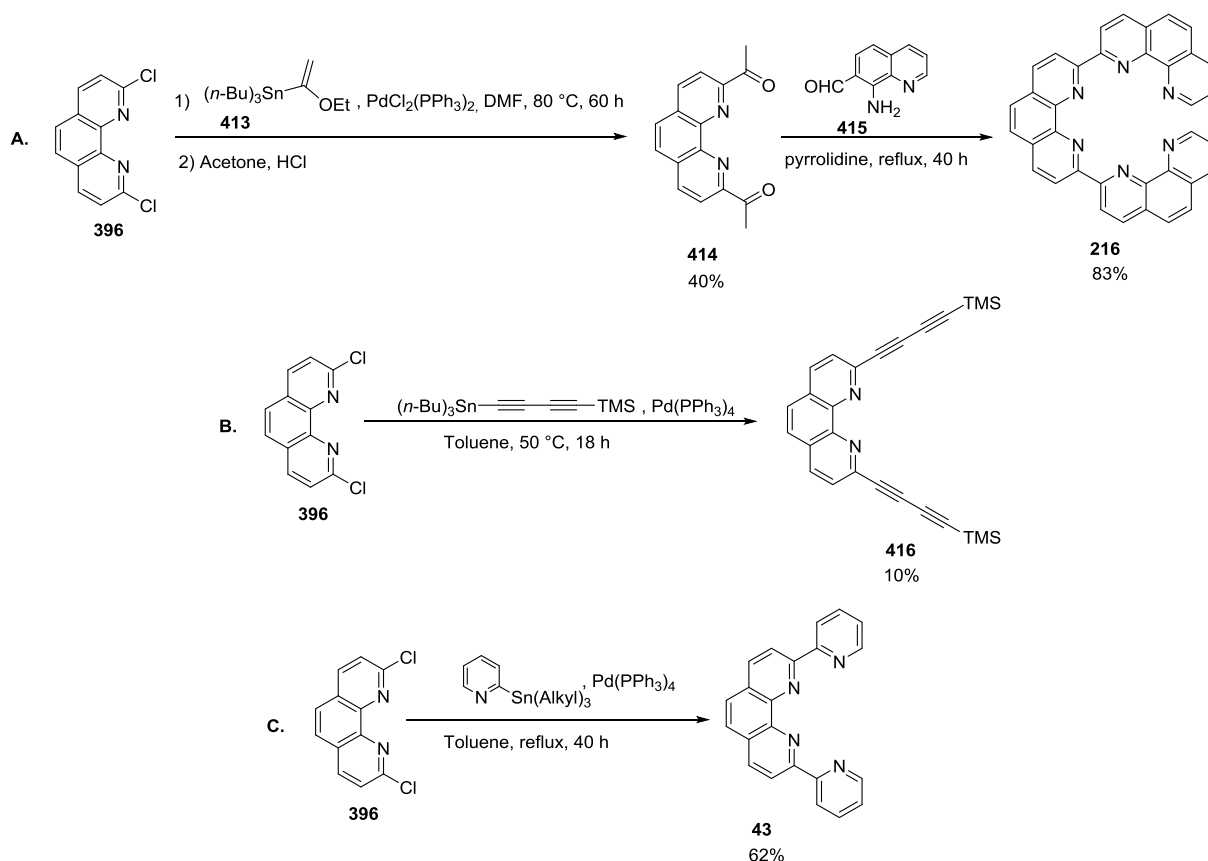
411 is obtained by heating **397** and KF in DMSO in presence of 18-crown-6 ether to enhance fluoride nucleophilicity.⁴¹⁹ This fluorinated ligand was used to prepare ¹⁸F radio-labelled Re complexes for positron emission tomography. **410** and **412** can both be obtained by reacting **396** and **397** respectively with HI in presence of H₃PO₂ as a stabilizer (reductant preventing I₂ formation).^{420,421} Interestingly, it is possible to isolate mixed **409** by controlling the reaction time and temperature (**409** is obtained on short time scales at low temperature, while **410** is obtained during overnight reflux conditions) (Scheme 71). Mixed halogen substituted phen

were envisioned as interesting building blocks allowing to take advantage of the different reactivities of C-halogen bonds.

Reactivity of the halogenated phen_{(2,9)sub} and phen_{(2)sub}: metal catalyzed C-C cross couplings

Mono and dihalogenated phen have been abundantly used as building blocks to synthesize larger phen based molecular arrays. A very obvious synthetic strategy is to use the well-known metal catalyzed cross-coupling reactions to decorate halogenated phen_{(2,9)sub} and phen_{(2)sub} ligands with (hetero)aromatic and conjugated substituents. Virtually all kinds of metal-catalyzed cross-coupling reactions have been used with halogenated phenanthrolines:

- the Stille cross-coupling consists in the reaction between **396** (or **397**) or **405** and an organostannane derivative (usually of the general formula Sn(*n*Bu)₃R) bearing the R group which will be cross-coupled to the halogenated aromatics. The coupling is catalyzed by a palladium (0) complex, usually tetrakis triphenylphosphine palladium Pd(PPh₃)₄. The reactions are often performed in refluxing toluene, under inert atmosphere, for several hours to days.^{153,422–428} Examples of phen ligands functionalized by Stille cross-coupling are given in Scheme 72. **414**⁴²² was obtained from **396** and is an interesting diketone building block which was nicely employed to prepare the terphenanthroline ligand **216** with a convergent method (Scheme 72A). **416**¹⁴³ was prepared to design Pd complexes with various steric strains and to study the influence of this steric bulk on the Pd-catalyzed nucleophilic displacement of allylic acetates (Scheme 72B). It is worth to underline that attempts to prepare a similar molecule to **416** but using Sonogashira cross-coupling conditions instead of Stille's lead only to polymerized by products. Finally, the tetradentate ligand **43** was designed to synthesize stable ruthenium complexes coordinated by four nitrogen atoms in a cis configuration (Scheme 72C).⁴²² This complex is among the best examples of water oxidation catalysts.

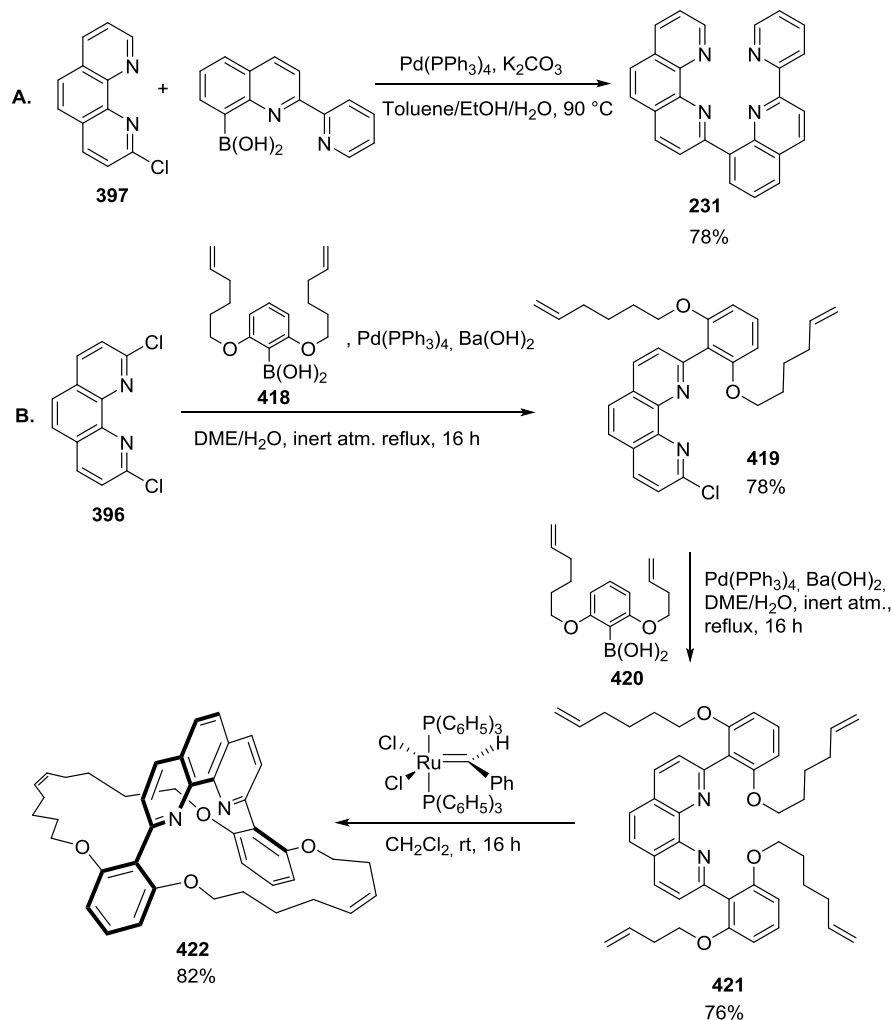


Scheme 72. Examples of Stille cross-coupling reactions involving **396**.

- The Suzuki-Miyaura cross-coupling reaction between an activated halide and a boronic acid/ester is one of the most popular reaction to generate C-C bonds, and it was abundantly applied to decorate phenanthroline cores in positions 2 and 9. In the most frequent protocols, **396** or **397** are used in presence of the appropriate boronic acid or ester, a base (often $\text{Ba}(\text{OH})_2$ or aqueous Na_2CO_3), $\text{Pd}(\text{PPh}_3)_4$ as catalyst in a solvent or mixture of solvents (toluene, dioxane or DME) sometimes with additional water.¹⁶² In a few cases, other palladium catalysts have been used, such as $\text{Pd}(\text{dppf})\text{Cl}_2$ or $\text{Pd}(\text{dppp})$ generated *in situ* instead of $\text{Pd}(\text{PPh}_3)_4$.⁴²⁹

Some examples of coupling reactions are given in Scheme 73. The tetradentate ligand **231** was formerly prepared *via* a Friedlander reaction. Suzuki conditions allowed to isolate **231** in improved yield and with less synthetic steps (Scheme 73A).⁴³⁰

Importantly, the same classical conditions can be used even in presence of very bulky aryl boronic acids or esters to afford in satisfactory yields phen ligands imposing a high steric strain around the chelating nitrogen atoms.⁴³¹



Scheme 73. Examples of Suzuki-Miyaura cross-coupling reactions on **396** and **397**

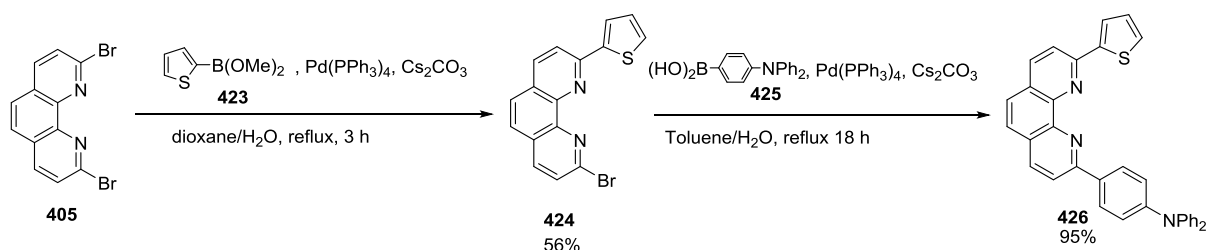
Lüning and coworkers have used such strategies to design “concave” ligands namely phen ligands with a particularly encumbered $\widehat{\text{N}}\text{N}$ cavity to mimick the anisotropic binding sites of enzymes. The synthesis of such ligands was initially performed with organolithium reagents in harsh conditions,³⁴³ not necessarily compatible with a large range of organic functionalities. Using the mild conditions of Suzuki coupling allowed to prepare several original and diverse concave phen ligands with a great synthetic flexibility and high

yields.^{162,432} In the chosen example, two different boronic acids **418** and **420** were grafted on **396** in a stepwise manner (**419** and **420**) and ring closing metathesis allowed to reach in high yield the impressive hybrid macrocycle **422** in high yield (Scheme 73B).⁴³²

The Suzuki coupling strategy is a very valuable alternative to other synthetic pathways, it proved more “user friendly” than the organo lithium protocol which requires harsh conditions and the manipulation of hazardous chemicals. This explains why molecules formerly obtained by action of R-Li on phen have been re-prepared *via* a Suzuki coupling.^{433,434}

Despite the fact that brominated and iodinated conjugated compounds are known to be more reactive than chlorinated ones,⁴¹⁸ **396** and **397** are very often sufficiently reactive to be used directly in the frame of a Suzuki coupling. This is an advantage since those reactants are easier to prepare than the corresponding brominated and iodinated derivatives. Nevertheless, brominated and iodinated phen_{(2)sub} and phen_{(2,9)sub} are sometimes preferred, though the reasons for such a choice are not systematically given.

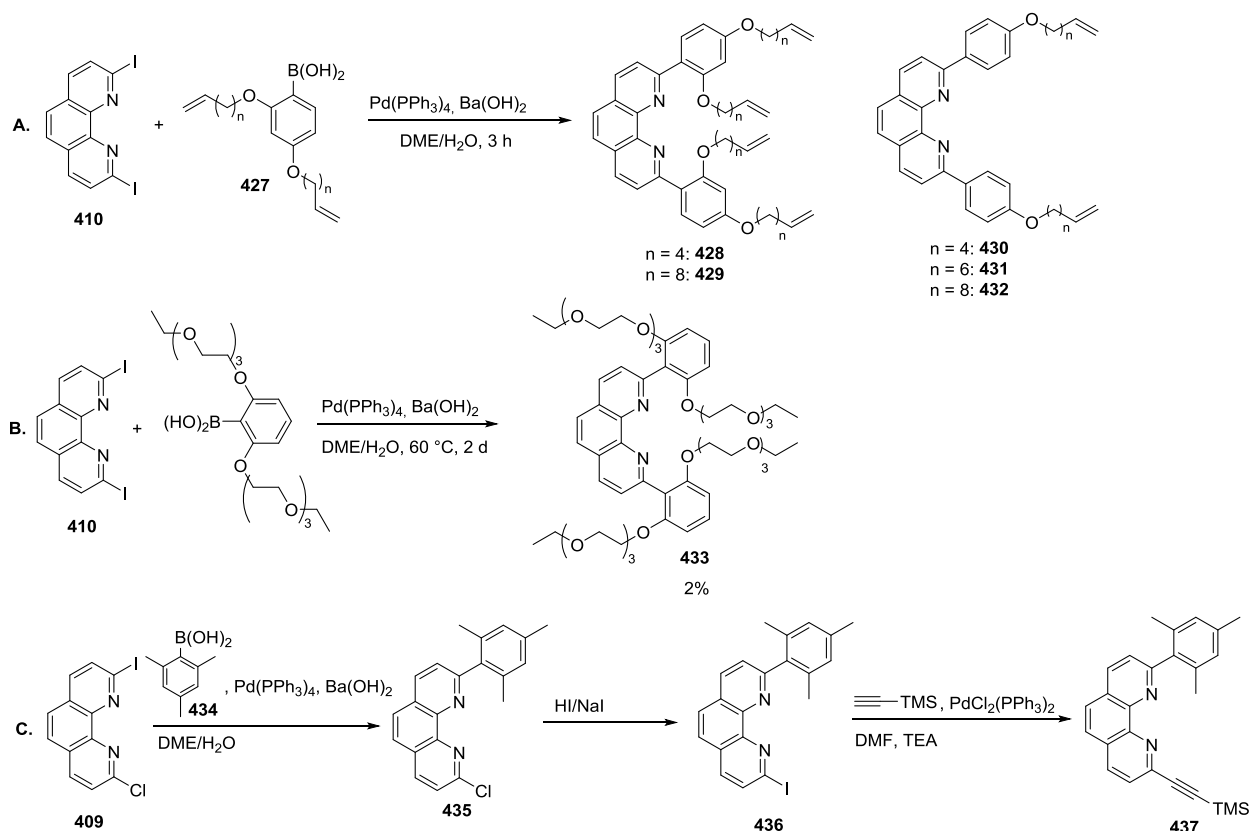
405 and **406** have been used to design several phen derivatives.⁴¹⁸ **426** has been obtained by stepwise addition of **423** then **425** on **405** (Scheme 74).⁴³⁵ The associated rhenium tricarbonyl complex was used as a chemosensor for explosives, as the electron rich thiophene and triphenylamine moieties interact with electron poor nitro-bearing unstable organic compounds.



Scheme 74. Suzuki-Miyaura cross coupling reactions with **405**.

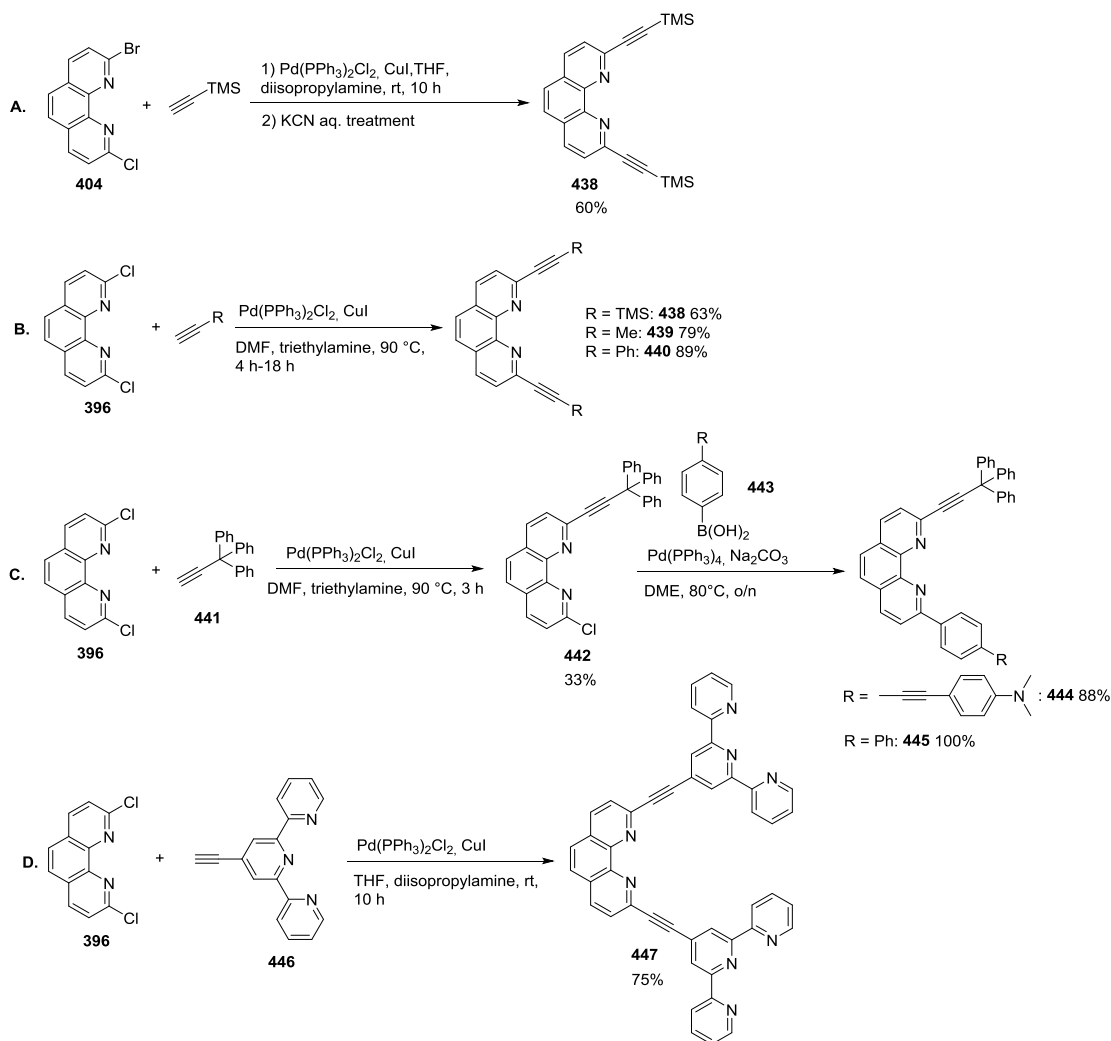
The choice of **405** (**406**) over **396** (**397**) is never justified in the above-mentioned articles.

410 was successfully used too in a few (rarer) Suzuki coupling reactions. For example, **410** has been initially used by Lüning et al. to prepare alkene bearing phen ligands **428-429** and **430-432** (Scheme 75A).¹⁶² **396** was proven sufficiently reactive by the same authors,¹⁶² affording target molecules with similar or even higher yields than when using **410**. On the other hand, when the synthesis of ligand **433** is attempted with **396**, only a mono-substituted ligand is obtained. The use of **410** allows to isolate **433**, although in very poor yield (2%) partly because of purification difficulties (Scheme 75B).⁴³⁶ The high steric bulk around the boronic acid is probably responsible for those results. **409** was utilized to prepare non symmetrical phen **437**,⁴²⁰ taking advantage of the difference of reactivities of C-I vs. C-Cl bonds (Scheme 75C). We mention however than stepwise Suzuki couplings on **396** are documented^{162,429} and that similar molecules to **437** can be obtained from **396**.⁴³⁷



Scheme 75. Suzuki-Miyaura cross coupling reactions with **409** and **410**.

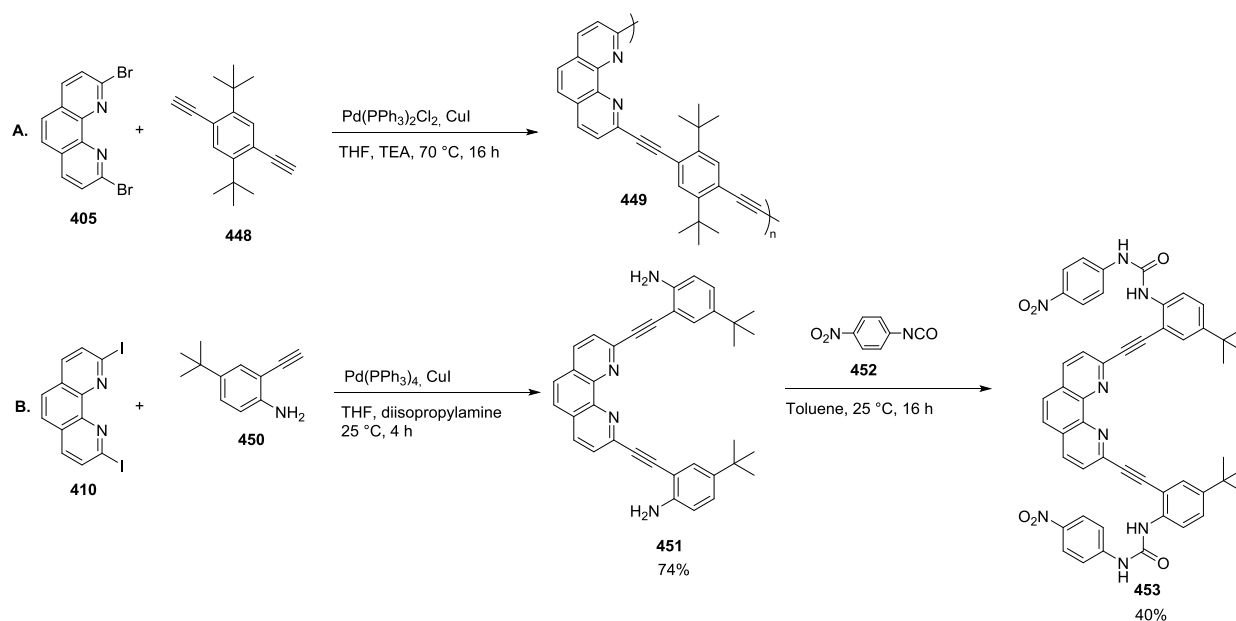
- *The Sonogashira coupling* is another popular cross-coupling reaction allowing to couple alkynes to halogenated substrates, e.g. halogenated phen_{(2,9)sub} (Scheme 76). Historically, the first example of Sonogashira coupling was performed on **404** with ethynyltrimethylsilane in presence of Pd(PPh₃)₂Cl₂ and CuI as catalysts, triisopropylamine as base in THF at room temperature (Scheme 76A).⁴³⁸ Complexation of Cu(I) by **438** during the reaction is observed and reported in a few other instances.^{438,439} In such cases, treatment of the crude reaction mixture by CN⁻ allows to break down all copper(I) complexes (by forming very stable Cu(CN)₄³⁻) and the free ligand **438** can be recovered. The same reaction proved to be just as efficient when starting from **396** in DMF and heating at 90 °C the reaction mixture, affording **438** and other similar derivatives (**439** and **440**) with very satisfactory yields (Scheme 76B).¹⁴³ In these conditions, no treatment by cyanide anions was necessary, possibly thanks to the use of more polar solvents. **444** and **445** are good examples of intricate structures obtained easily in the mild conditions of Sonogashira coupling (Scheme 76C).^{440,441} Again, one observes that non-symmetrical structures are easily obtained by a simple control of the number of equivalents of boronic acid (**443**) or alkyne reagents (**441**). Those bulky molecules were used to prepare axles with triphenylmethane stoppers in the field of copper-templated rotaxane synthesis. **447** merges the coordinating ability of phen and terpy and was obtained in good yields from **396** (Scheme 76D).



Scheme 76. Examples of Sonogashira cross-coupling reactions with **396** and **404**.

Brominated and iodinated phen_{(2,9)sub} **405** and **410** were seldom used in the frame of the Sonogashira cross-coupling probably because the C-Cl bonds are sufficiently activated towards Pd insertion to ensure the efficiency of the catalytic cycle. For example, polymeric phen ligand **449** was prepared from **405** and bis-alkynyl compound **448** (Scheme 77A). The resulting polymer could accommodate silver(I) ions (75% occupancy estimated by ICP-MS) and was used as material for the selective uptake of ethylene.⁴⁴² **410** was used only once to design urea-based anion receptor **453** (Scheme 77B). The coupling reaction is performed at room temperature in presence of alkyne **450** and affords **451** in a satisfactory yield of 74%.

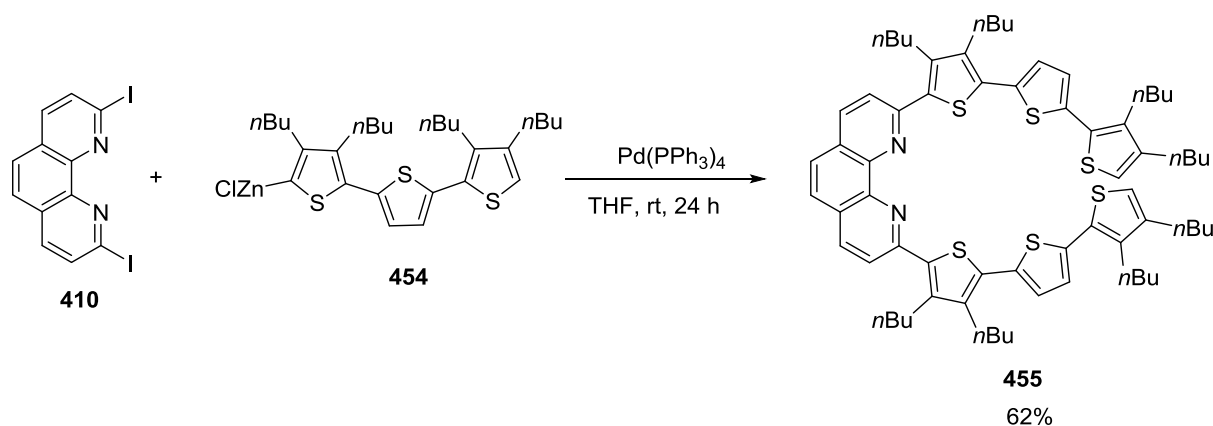
The following reaction of **451** with isocyanate **452** leads to the formation of the urea motif which is the key component of the sensor **453**.



Scheme 77. Examples of Sonogashira cross-coupling reactions with **405** and **410**

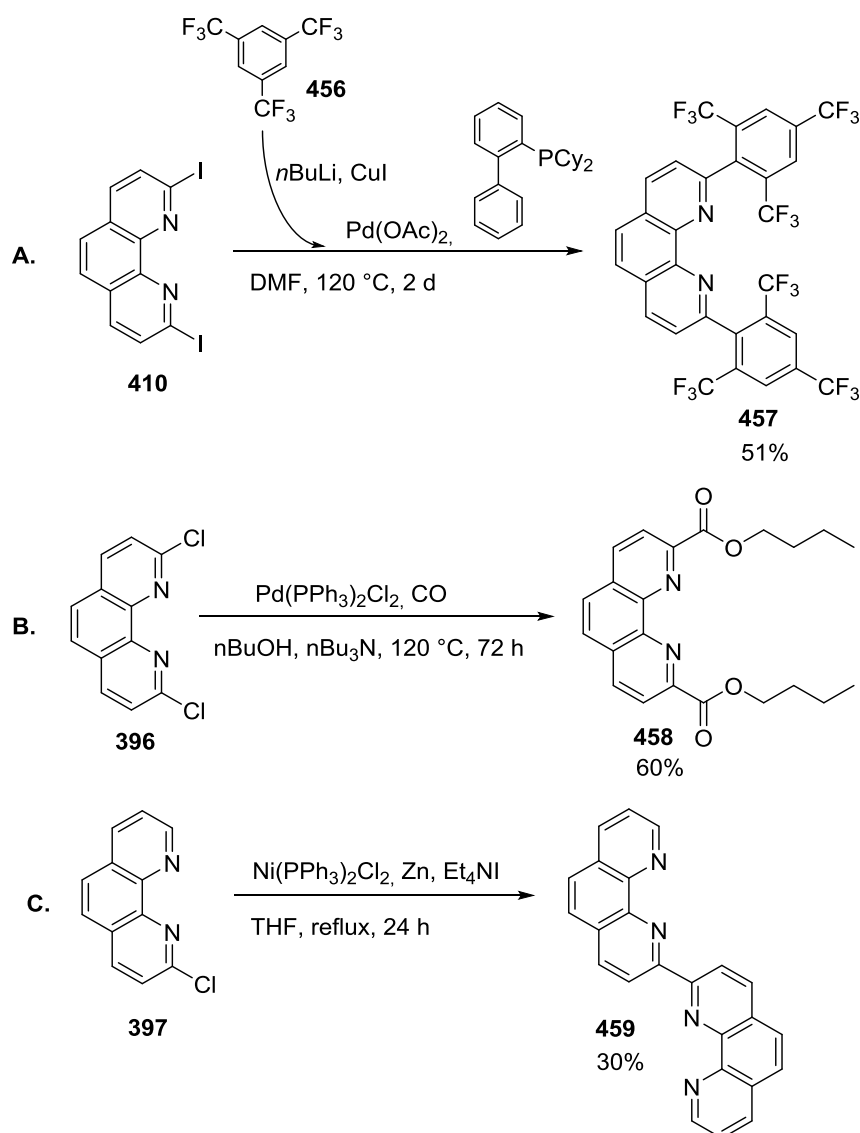
- The Negishi cross-coupling reaction takes place between an organozinc reagent (usually generated *in situ*) and a halogenated aromatic molecule in presence of a palladium catalyst. Conversely to the previously presented coupling reactions, iodinated **410** is the most frequently used reactant (there are very few examples of Negishi couplings with **396**).⁴⁴³ The coupling reaction is traditionally catalyzed by Pd(PPh₃)₄ in THF either at room temperature or at reflux. A typical example is given in Scheme 78 with the synthesis of **455** from **410** and organo-zinc compound **454**. Interestingly, this synthesis has been explored *via* Negishi coupling and *via* the organolithium pathway, allowing to compare both strategies. While reaction of trithiophene lithium on phen afforded **455** in less than 10% yield (over two successive sequences RLi/MnO₂), the reaction of **454** on **410** leads to **455** in 62% yield. The same authors thus applied the Negishi strategy to synthesize an impressive collection of

oligothiophene substituted phen ligands, which were successfully used to design catenanes via Cu(I) coordination to template the assembly.⁴⁴⁴



Scheme 78. Examples of Negishi cross-coupling reactions with **410**

- Other metal catalyzed coupling reactions involving halogenated phen₍₂₎sub and phen_(2,9)sub can be found in the literature to generate C-C or C-heteroatom bonds. As regards C-C bonds, very bulky 2,4,6-tris(trifluoromethyl)aryl groups can be tethered to **410** by action of the corresponding organo cuprate (generated *in situ* by lithiation of **456** in presence of CuI). **457** is thus obtained in 51% yield, in presence of Pd(OAc)₂ and 2-(dicyclohexylphosphino)biphenyl in DMF (Scheme 79A).⁴⁴³ One-step functionalization of **396** by ester groups is performed by palladium assisted carbonylation in presence of *n*-butanol (**458**, Scheme 79B).⁴⁴⁵ Direct coupling of two **397** to afford dimer **459** is realized in THF with stoichiometric amount of NiCl₂(PPh₃)₂ in presence of Zn (Scheme 79C). The latter reduces Ni(II) into active Ni(0). Washings with KCN are necessary at the end of the reaction to remove the coordinated nickel ions and retrieve pure **459**.⁴⁴⁶

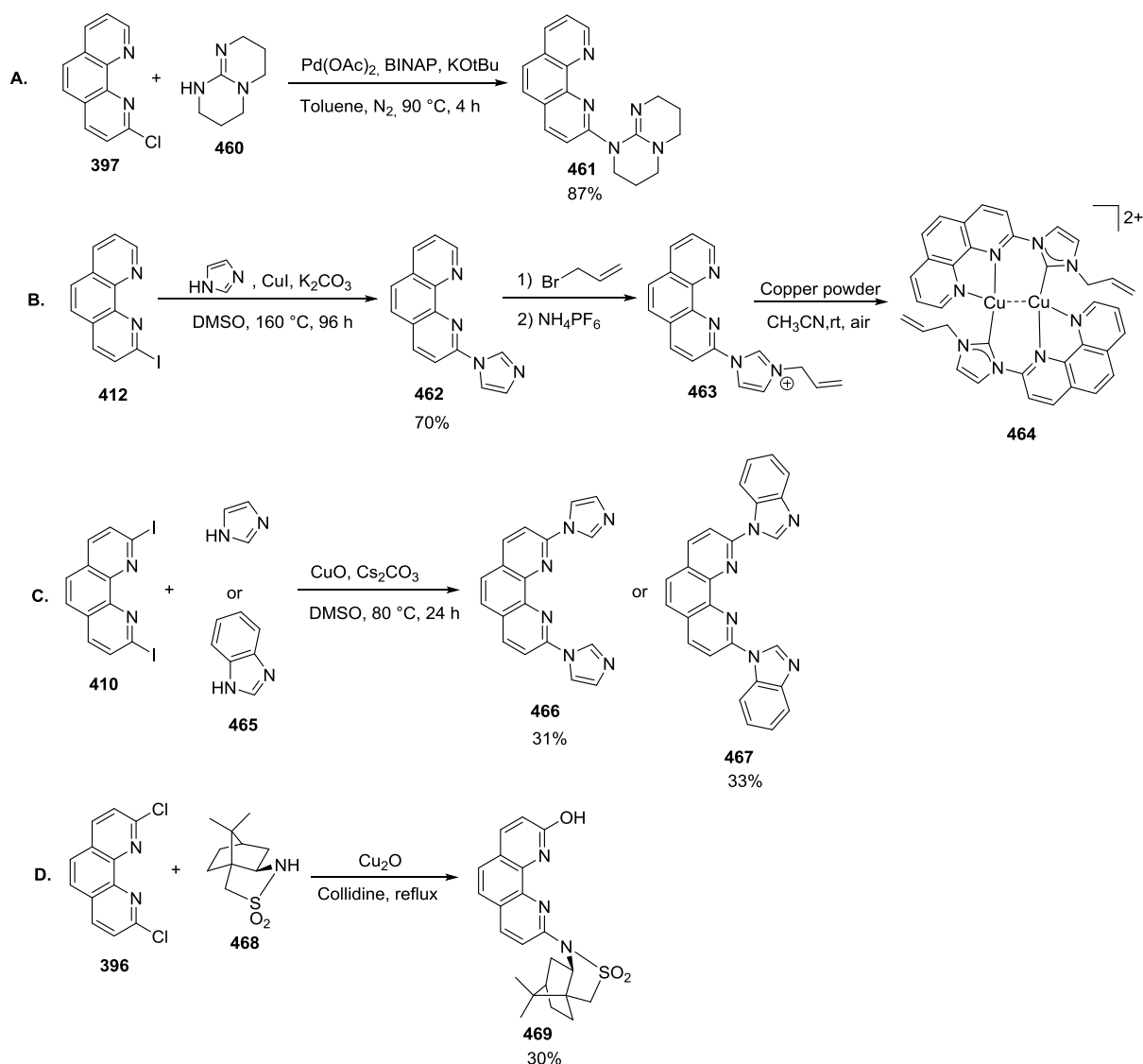


Scheme 79. Examples of other C-C cross-coupling reactions with **396**, **397** and **410**

A few examples of C-N metal-assisted coupling reactions involving halogenated phen_(2,9)sub and phen_(2,9)sub are reported too. For instance, tridentate ligand **461** is synthesized from **397** and **460** in presence of Pd(OAc)₂ and racemic BINAP, in the Buchwald-Hartwig conditions (Scheme 80A).^{447,448} The ruthenium complex obtained with **461** features a higher photoluminescence quantum yield than the terpy analogue, thanks to the more favorable bite angle imposed by **461**.⁴⁴⁹ Other C-N couplings involve copper-based catalysts. For instance, Chen et al. have published several articles on phen-carbene ligands coordinating copper(I)

ions. All ligands were formed *in situ* from phen-imidazolium⁴⁵⁰ (or phen pyrazolium and triazolium) precursors.⁴⁵¹⁻⁴⁵⁶ Those could be obtained as pictured in Scheme 80B, by first tethering secondary cyclic amines (e.g. imidazole or 2-methylimidazole for **462** and **465** respectively) to **412** in hot DMSO for several days, and in presence of CuI and K₂CO₃.⁴⁵⁰ The obtained neutral decorated phen were then reacted in presence of an adequate electrophile (e.g. allyl bromide) to give desired cationic precursors. Reaction with copper powder afforded a dinuclear copper(I) mixed phen-carbene complex such as **464** used for the copper catalyzed Huisgen click reaction.⁴⁵⁰ **410** was used too in similar conditions (Scheme 80C).^{452,457} Symmetric ligands **466** and **467** were obtained in modest yields, possibly because of the milder conditions used (lower temperature, shorter reaction time). The replacement of CuI by CuO is not rationalized in the articles, but CuO-assisted C-N bond formation is known to be efficient and easy to implement. In addition, undesired complexation of phen cavity by Cu⁺ (from CuI) is less likely with CuO as catalyst.⁴⁵⁸

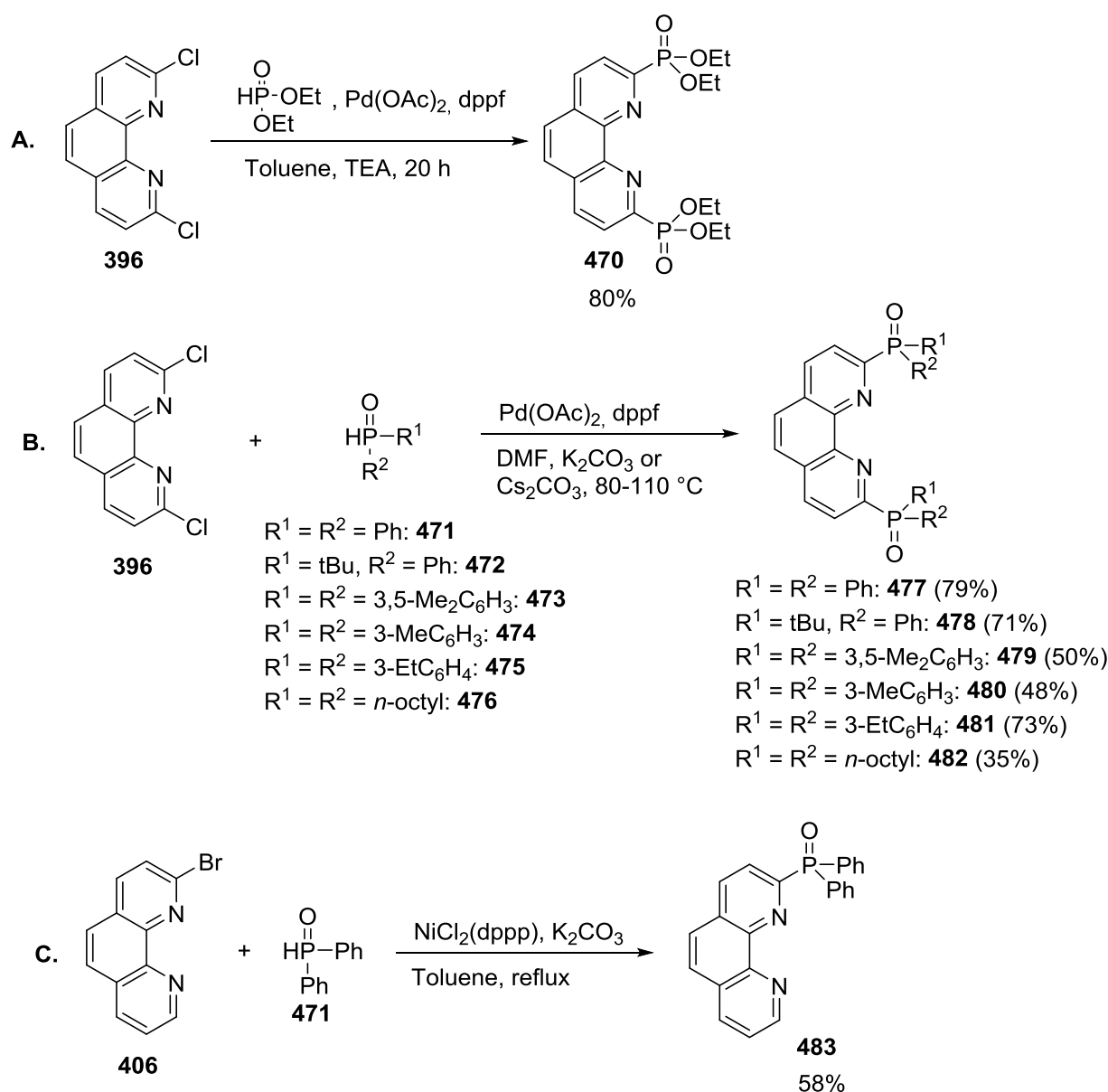
A last example of copper based C-N cross coupling reaction makes use of stoichiometric amounts of cuprous oxide Cu₂O to synthesize the chiral ligand **469** from **396** and camphor sultam **468**⁴⁵⁹ in refluxing collidine for 24 h (Scheme 80D). Despite these rather harsh conditions, the yield is modest and only one camphor group could be tethered to phen in position 2 while position 9 is occupied by an OH group (probably resulting from prolonged heating at high temperature in presence Cu₂O). The strength of the C-Cl bond (compared to other, more polarizable C-Br and C-I bonds) and the steric constraints are invoked to justify those experimental observations. Despite the promising structure of **469**, no study of enantio- or diastereo-selective catalytic reaction using a M^{x+}-**469** complex was implemented.



Scheme 80. Examples of C-N cross-coupling reactions with **396**, **397**, **410** and **412**

Metal catalyzed C-P cross coupling are reported as well. Phen is easily functionalized by phosphonic esters in position 2 or in positions 2 and 9 by reacting **396** (or **397**) with hydrogen phosphonate $\text{HP}(\text{O})(\text{OEt})_2$ in toluene presence of triethylamine, $\text{Pd}(\text{OAc})_2$ and dppf (Scheme 81A).⁴⁶⁰ Trials with PPh_3 as ligand were not satisfactory because of a competition with phen to coordinate Pd, lowering the efficiency of the catalytic system (such issue has not been mentioned in the other Pd-catalyzed reactions). The use of bidentate dppf, making more stable complexes with Pd, solved this issue and allowed to isolate **470** in 80% yield.

A similar route was undertaken to graft P(O)Ph₂ moieties on **396**. In this work, different metal catalysts (Pd vs. Ni), bases (K₂CO₃ vs. *t*BuOK) and solvents (DMF, THF and toluene) were explored.⁴⁶¹ The best optimized conditions (Pd(OAc)₂, dppf, highly polar DMF and K₂CO₃) afforded several phosphine bearing phen_(2,9)sub (**477-482**, Scheme 81B). Interestingly, it is possible to avoid the use of costly palladium catalysts as demonstrated by Wei, Liu et al. using **406** and HP(O)Ph₂ (**471**) in presence of NiCl₂(dppp) to reach **483** in a very satisfactory yield (Scheme 81C).⁴⁶²



Scheme 81. Examples of C-P cross-coupling reactions with **396** and **406**

Reactivity of the halogenated phen_{(2,9)sub} and phen_{(2)sub}: nucleophilic substitutions

The C₂ and C₉ positions of halogenated phen_{(2)sub} and phen_{(2,9)sub} are electrophilic and several aromatic nucleophilic substitutions have been published, leading in simple conditions to well-designed large molecular structures.

Many classical nucleophiles have been used. Aromatic^{463,464} or aliphatic alcohols are usually generated *in situ* from corresponding alcohol in presence of sodium^{417,421,465} or NaH^{187,466–469} and reacted with **396** or **397** in DMSO or DMF. Tethering alkoxy chains in positions 2 or 2 and 9 of phen allows to study the impact of both the steric and electron donating effects of those groups on the overall properties of the ligand itself and/or the corresponding complexes. This has noticeable fallouts in the fields of catalysis, biochemistry and supramolecular chemistry. For example, chiral alcohols have been grafted on phen (**484–486**, Figure 24), the resulting chiral ligands can be used for asymmetric catalysis.⁴⁶⁸ Interestingly, **485** and **486** were obtained from **405** and **406** respectively instead of **396** or **397** showing that the C-Br bond of **405** and **406** can be substituted too. Nevertheless, the doubly substituted ligand could not be synthesized in the described conditions. **487** was developed to bind to DNA strands⁴⁶⁶ and ditopic ligands **488** and **489** were prepared for the design of self-assembled trimetallic helicates in the presence of zinc(II) ions.⁴⁶⁹

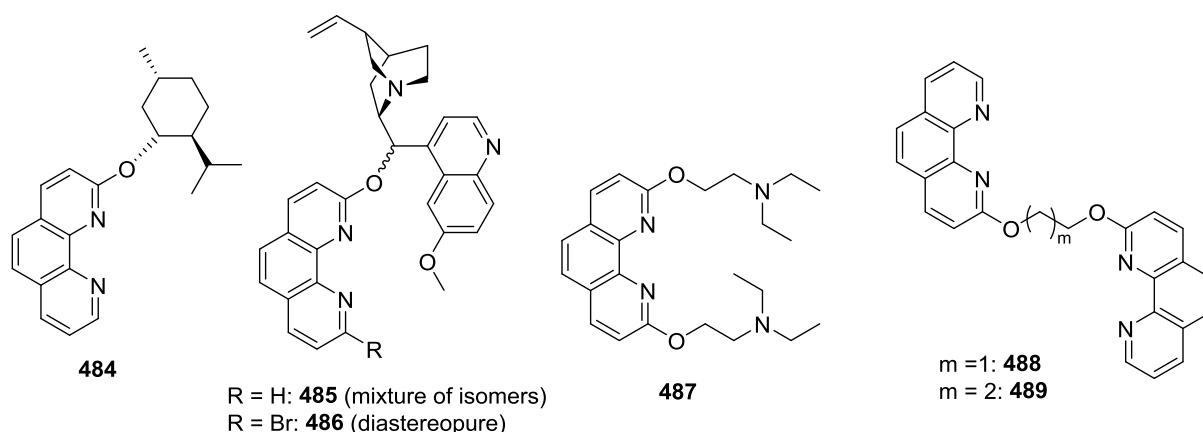
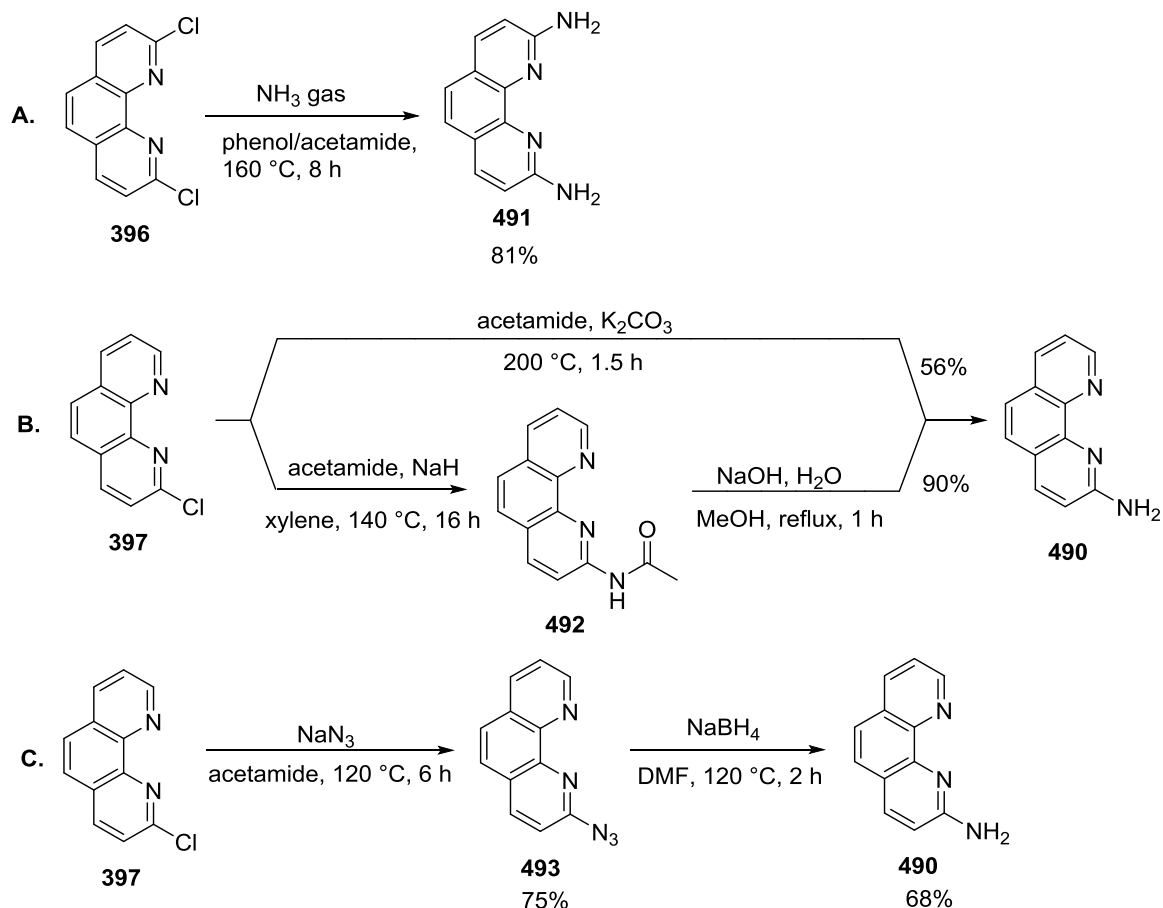


Figure 24. Examples of phenanthrolines functionalized in position 2 or 2 and 9 by alkoxy groups.

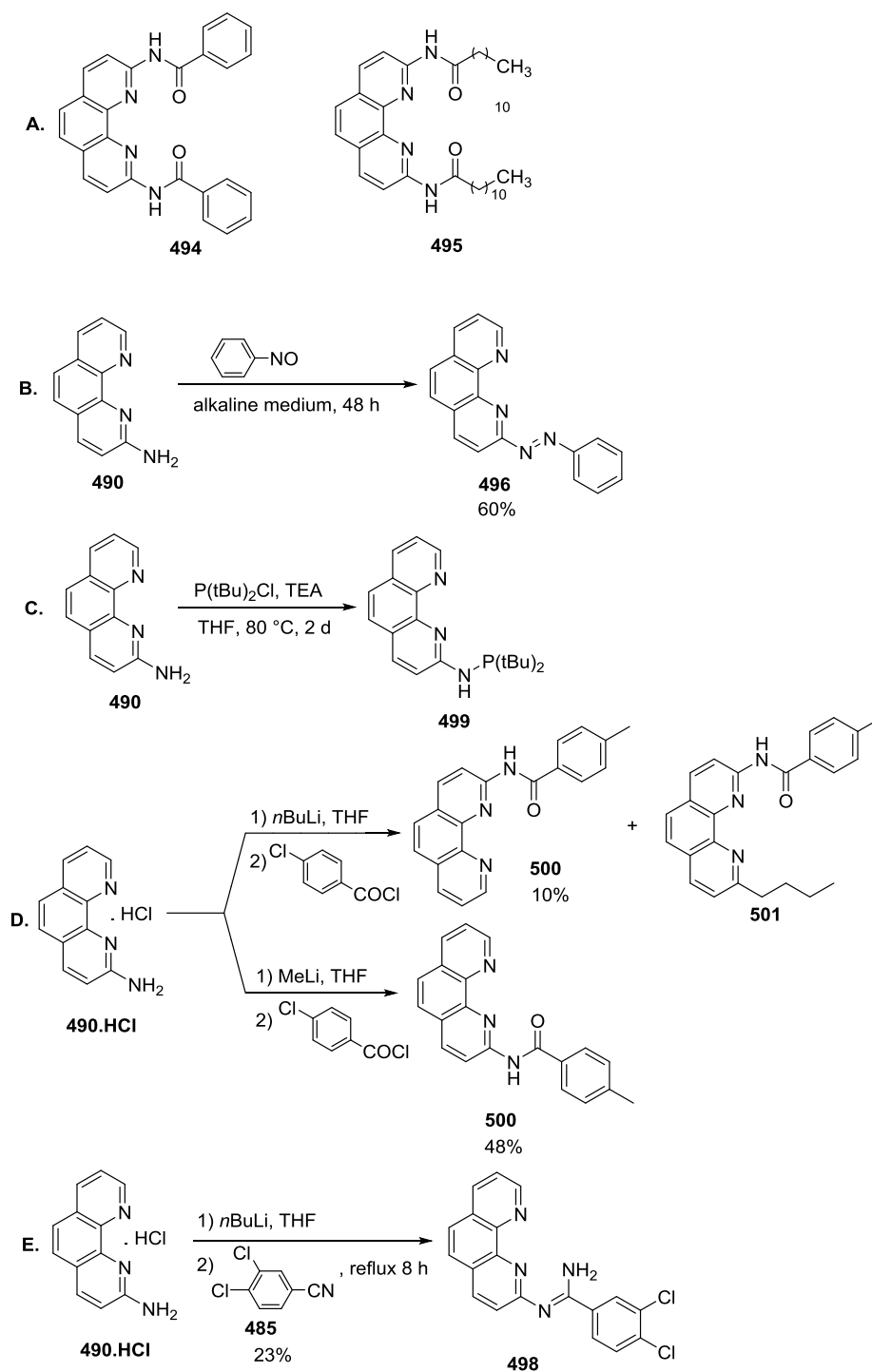
Amines have been abundantly used to generate C₂-N and C₉-N bonds from **396** and **397**. The mixture of ammonia and acetamide has been used too to generate **490** and **491**¹⁶⁰ from **396** and **397** by aromatic nucleophilic substitution and ammonolysis (Schemes 82A and 82B). In the first reported synthesis of **490**,⁴¹⁷ NH₃ was generated *in situ* from ammonium chloride at high temperature (320-340 °C) and reacted on 2-phenoxy-1,10-phenanthroline (the phenolate substituent being the leaving group in this case).⁴¹⁷ Ogawa and co-workers demonstrated that the use of gaseous NH₃ on **396** in a mixture of phenol and acetamide at high temperature was working equally well.⁴¹⁴ The use of gaseous NH₃ can nevertheless prove challenging and requires specific equipments. Satisfyingly **490** can be obtained following simpler protocols in milder conditions (Scheme 82B). Recent works report the synthesis of **490** in 2 steps, starting with heating **397** in presence of K₂CO₃⁴⁷⁰ or NaH⁹³ and acetamide. The intermediate **480** was identified and resulted from the aromatic nucleophilic substitution of Cl by acetamide, assisted by the base. Hydrolysis in basic conditions of **493** affords **490** in ca. 60% yield from **397**. Alternatively, nucleophilic attack of **397** by sodium azide yields **493** which is then reduced into **490** by NaBH₄ (Scheme 82C).⁴⁷¹ The overall yield (51%) is however lower than with above strategies. Nevertheless, the interesting azide functionalized phen **493** is easily obtained with a satisfactory yield.



Scheme 82. Nucleophilic substitution on **396** and **397**

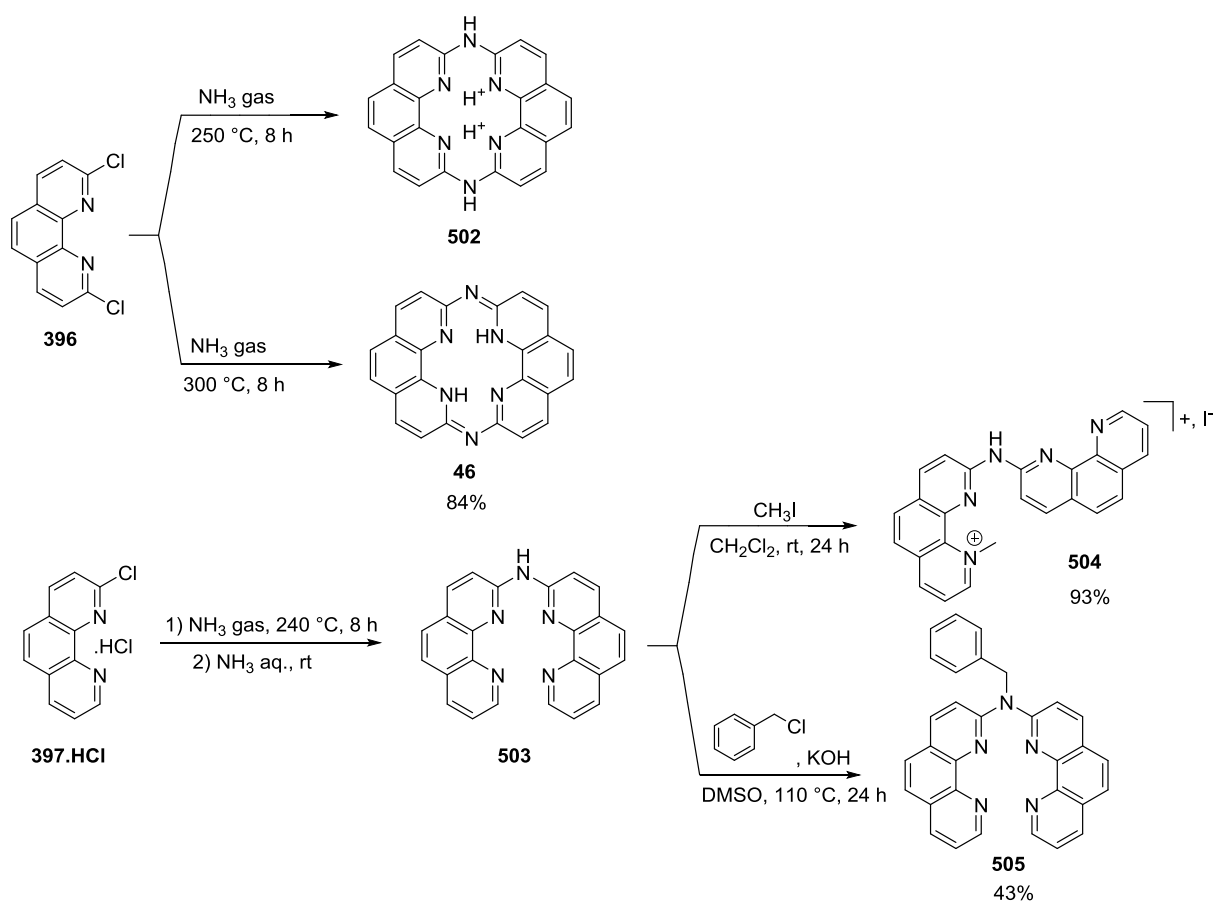
490 and **491** are easily decorated with classic amine chemistry (Scheme 83): amide bond formation with acyl chlorides (e.g. **494**¹³ and **495**,⁴⁷² designed for their potential antimycoplasmal activity and as Li^+ selective chelator, respectively, Scheme 83A), synthesis of amidine derivatives,¹³ diazo compounds⁴⁷³ (for instance, **496** was used to prepare iron complex which catalyzes C-N cross-coupling reactions, Scheme 83B),⁴⁷⁴ and phosphorylation⁴⁷⁵ (**499** is a valuable polydentate ligand used to design Ru complexes for the catalytic hydrogenation of aromatic compounds, Scheme 83C). Interestingly, Timmermann et al. used strong organolithium bases to deprotonate **490** and enhance the nucleophilicity of the latter towards acyl chlorides (Scheme 83D).¹³ When *n*BuLi was used, side products such as **501** were identified, resulting from the facile nucleophilic addition of *n*BuLi on the free position 9 of phen. This issue was solved using less nucleophile methyllithium MeLi,

avoiding parasitic nucleophilic additions in α of the chelating nitrogen atoms. A similar strategy was used to prepare **498** from **490** using nitrile **485** as reagent (Scheme 83E).



Scheme 83. Reactivity of synthons **490** and **491**

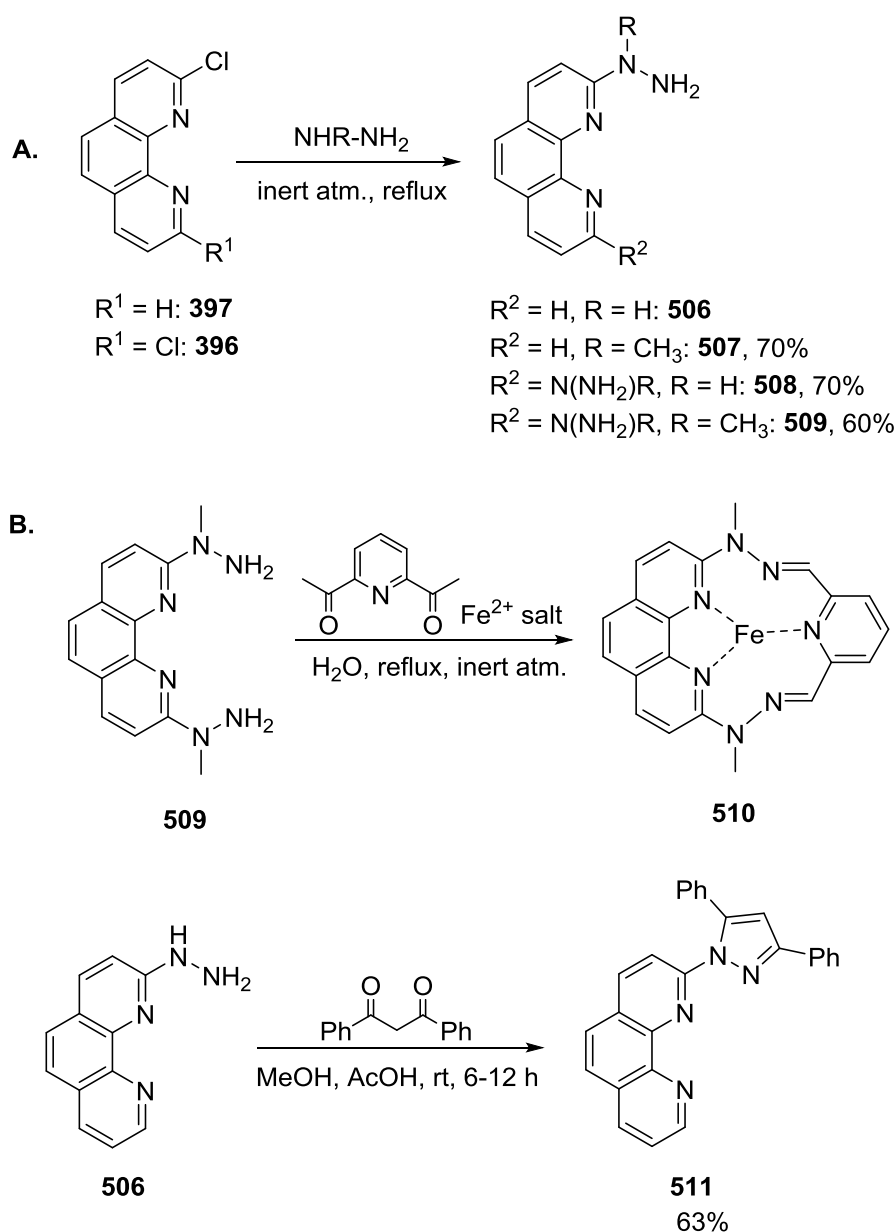
Finally, nucleophilic **491** reacts on electrophilic **396** to afford macrocycle **502**.⁴¹⁴ Metal ion templated syntheses (Cu, Ni and Co) of this molecule have been proposed.⁴⁷⁶ But the same molecule can be prepared by reacting **396** with gaseous ammonia at high temperature (Scheme 84). In similar conditions, when **396** was used as electrophile, open cycle **503** was obtained as a planar tetradentate ligand⁴⁷⁷ which has been used for example to coordinate Pt⁴⁷⁸ or Ru⁴⁷⁹ for the design of cytotoxic drugs or molecular catalysts respectively. **503** could be easily alkylated either on the nitrogen atoms of phen (yielding **504**) or on the bridging nitrogen atom (yielding **505**),⁴⁷⁷ depending on the experimental conditions (CH₂Cl₂ at room temperature vs. DMSO at 110 °C respectively).



Scheme 84. Design of macrocycles from **396** and **397**

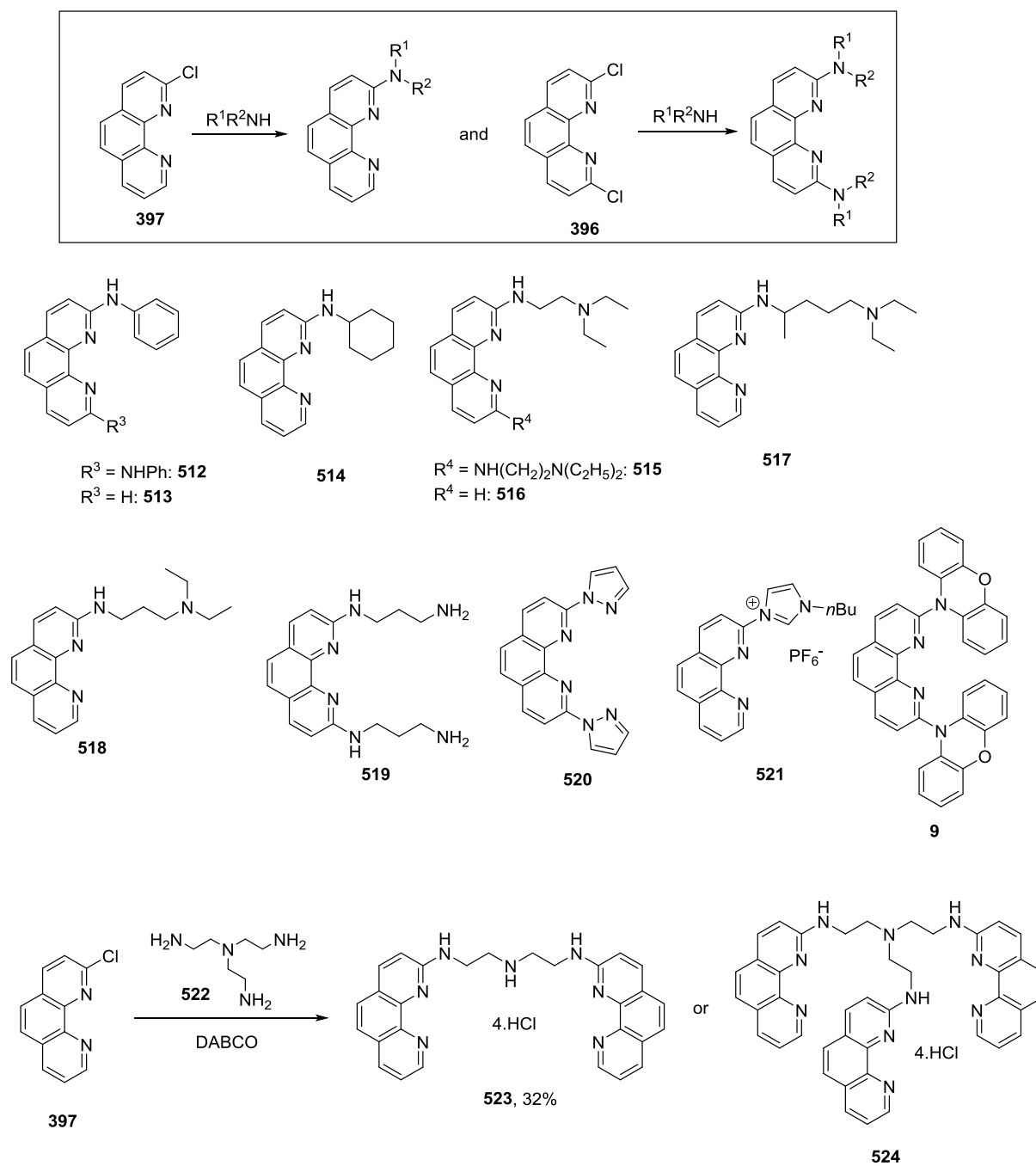
Hydrazine and derivatives are strong nucleophiles which can react efficiently with **396** or **397** (Scheme 85A). The resulting molecules **506-510** can be used directly as potent chelators (for

Zn^{2+} , Ni^{2+} , Cd^{2+} ...⁴¹¹ Alternatively, the reactivity of the amine towards aldehyde or ketones can be used to reach more extended coordinating arrays, such as **510** (Scheme 85B). The latter were synthesized by reacting **509** with 2,6-diacetylpyridine in presence of an Fe^{2+} salt acting as a template¹⁶¹ (similar template effect is possible with cobalt).⁴⁸⁰ The reactivity of **506** with a collection of 1,3-diketones has been explored too, affording phen ligands functionalized with a diazole, such as **511** (Scheme 85).⁴⁸¹



Scheme 85. Action of hydrazine nucleophiles on **396** and **397**; reactivity of the obtained synthons

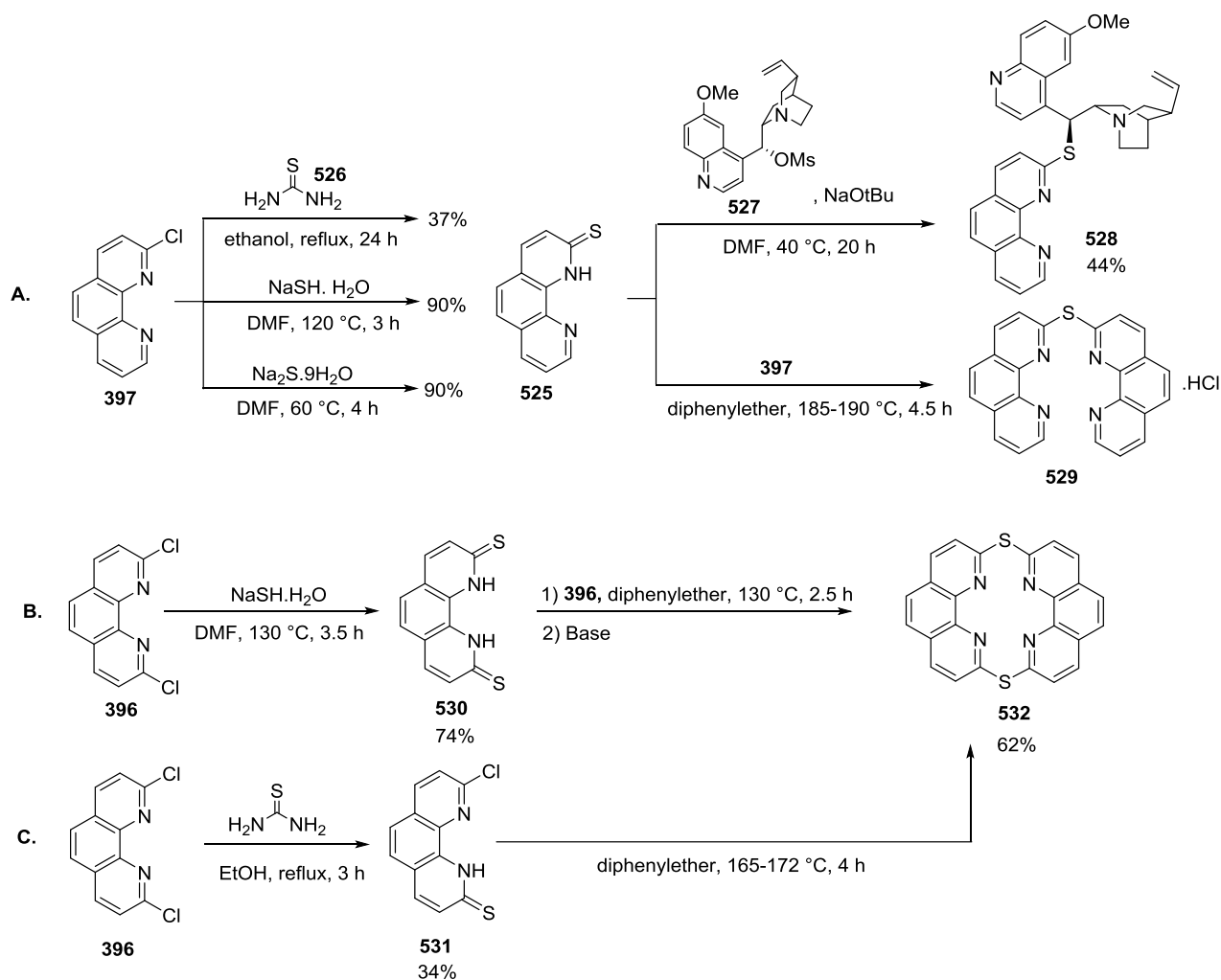
Heating at high temperatures (100-170 °C) **396** or **397** in neat primary and secondary aliphatic or aromatic amines usually leads to phen_{(2)sub} and phen_{(2,9)sub} functionalized with amine groups (Scheme 86). **512-518**^{29,482,483} were prepared as potential drugs (anti-telomerase,⁴⁸³ antimalarial)²⁹ for their propensity to bind to CUG trinucleotide.⁴⁸⁴ When amines cannot be used as solvents, like in the case of phenoxazine, refluxing the latter with **396** in THF and in presence of NaH allows to isolate the target compound **9**.⁷⁵ Likewise, strong chelator **520**^{485,486} was synthesized by heating pyrazole and **396** in DMF for 3 days in presence of potassium carbonate. When N-substituted imidazoles are reacted in presence of **412** for several days in refluxing toluene, imidazolium salts like **521**^{453,454,456} are obtained showing that sp₂ amines can be used as nucleophiles too. When polyamines such as tris(2-aminoethyl)amine **522** are used in presence of **397** in excess, phen dimer **523** or trimer **524** (used for DNA binding studies) can be easily obtained as HCl salts.



Scheme 86. Examples of amine functionalized phenanthrolines in position 2 or 2 and 9.

Many thiol and thiolate nucleophiles have been reacted on **396** and **397**. When **397** is treated with thiourea, NaSH or Na₂S, **525** is formed in mediocre to excellent yield (Scheme 87A).⁴⁸⁷ The thione tautomer is the more stable species in solution as demonstrated by NMR and FTIR. **525** is a good nucleophile which has been successfully used to prepare several 2-

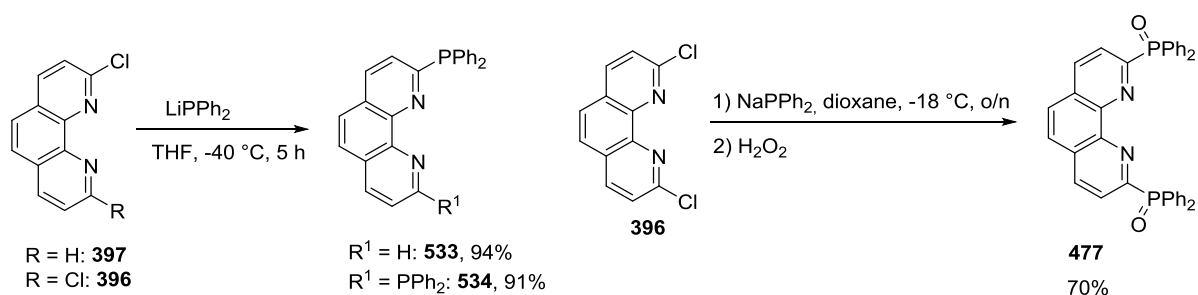
thioether-phen,⁴⁸⁷ e.g. tetradentate bis-phen ligand **529** obtained from the mixture of **397** and **525** in diphenylether at high temperature. Likewise, the reaction of **525** with 9-quinine mesylate **527** afforded chiral **528**, used for Tsuji-Trost and Henry asymmetric reactions.⁴⁸⁸ Other thiolates or pyridine/pyrimidine thiones readily react with **397** in presence of K_2CO_3 to afford phen substituted in position 2 with a thio-ether pendant group.⁴⁸⁷ **530** can be synthesized from **396** following the same protocol used for the synthesis of **525** from **397** (Scheme 87B).⁴⁸³ **525** and **530** exhibit the same reactivity towards electrophiles. For example, reacting **530** with **396** at high temperature in diphenylether leads to macrocycle **532**. This strategy leads to the highest yield for the synthesis of this S-bridged bis-phen macrocycle (ca. 70% from **396**). When **396** is heated with thiourea **526** in ethanol, a mixed 2-chloro-9(1H)-thione-1,10-phenantholine species (**531**) is obtained (Scheme 87C).⁴⁸³ The latter reacts on itself to afford macrocycle **532** when heated at high temperature in diphenylether⁴⁸³ or dimethylacetamide in presence of NaOH⁴⁸⁹ (in the latter case, the macrocycle is isolated a sodium complex). The same ligand can be obtained by heating **531** under an H_2S atmosphere at high temperature, following a similar protocol as the one utilized to prepare **46**.⁴⁹⁰ A ruthenium ion-templated synthesis of **532** is reported too.⁴⁹¹



Scheme 87. Functionalization of **396** and **397** by thiols.

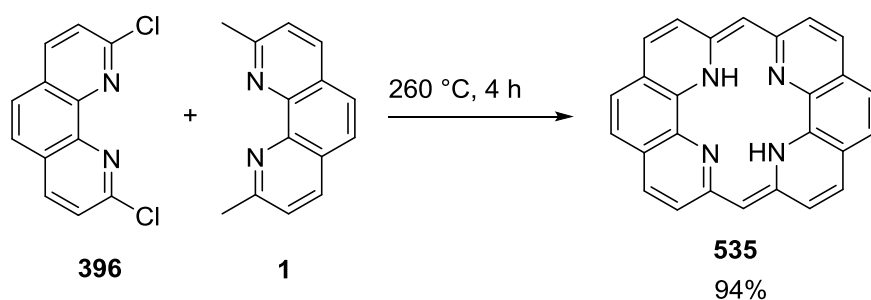
Concluding remarks

Other, rarer nucleophiles have been reacted on **396**. For example Lithium or sodium diphenylphosphide are powerful nucleophiles which can be prepared by reduction of triphenylphosphine by lithium⁴⁹² or chlorodiphenylphosphine by sodium (Scheme 88).¹⁰³ They readily react with **396** or **397** to afford **533** and **534**.⁴⁹³ Those ligands are unstable, in particular in solution phase where they quickly oxidize into the corresponding phosphine oxides. They are however stabilized when coordinated to Au, Pr, Tl or Pd ions, yielding air-stable polynuclear complexes.⁴⁹⁴ **477** has been isolated directly as the oxide, forming a ditopic tetradentate ligand for lanthanides.



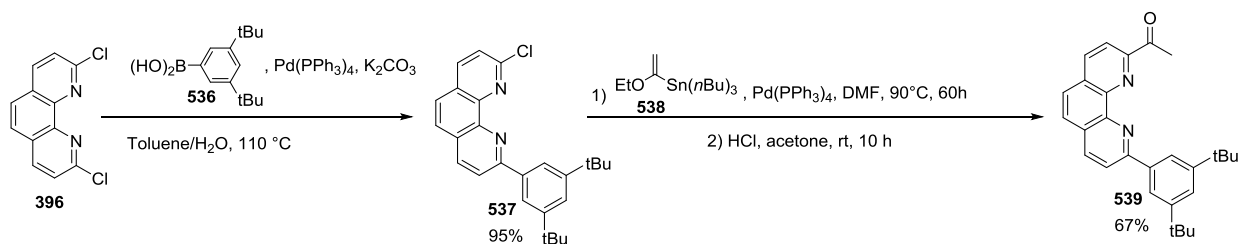
Scheme 88. Creation of C-P bonds by nucleophilic attack of **396** and **397**.

Ogawa demonstrated that neocuproine **1** could be used as nucleophile in the reaction between **1** and **396** affording the conjugated rigid tetradentate macrocycle **535** in high yield (Scheme 89).⁴⁹⁵ The Co complex formed with **535** was recently successfully used in the field of CO₂ reduction electrocatalysis.⁴⁹⁶



Scheme 89. Creation of C-C bonds and formation of a closed macrocycle by nucleophilic addition of **1** on **396**.

Finally, each C_{2,9}-X bond on the halogenated phen_(2,9)sub ligands can be solicited one by one in different ways. For instance, non symmetrical **539** was obtained from **396** in two steps, first *via* a Suzuki coupling with 1.1 equivalent of boronic ester **536**, followed by a Stille coupling with **538** (Scheme 90).⁴⁸¹



Scheme 90. Stepwise synthesis of phen_{(2,9)sub} from **396** making use of two different methods

3.1.4.2. Exploitation of the reactivity of 2,9-dimethyl-1,10-phenanthroline (neocuproine) and parent ligands

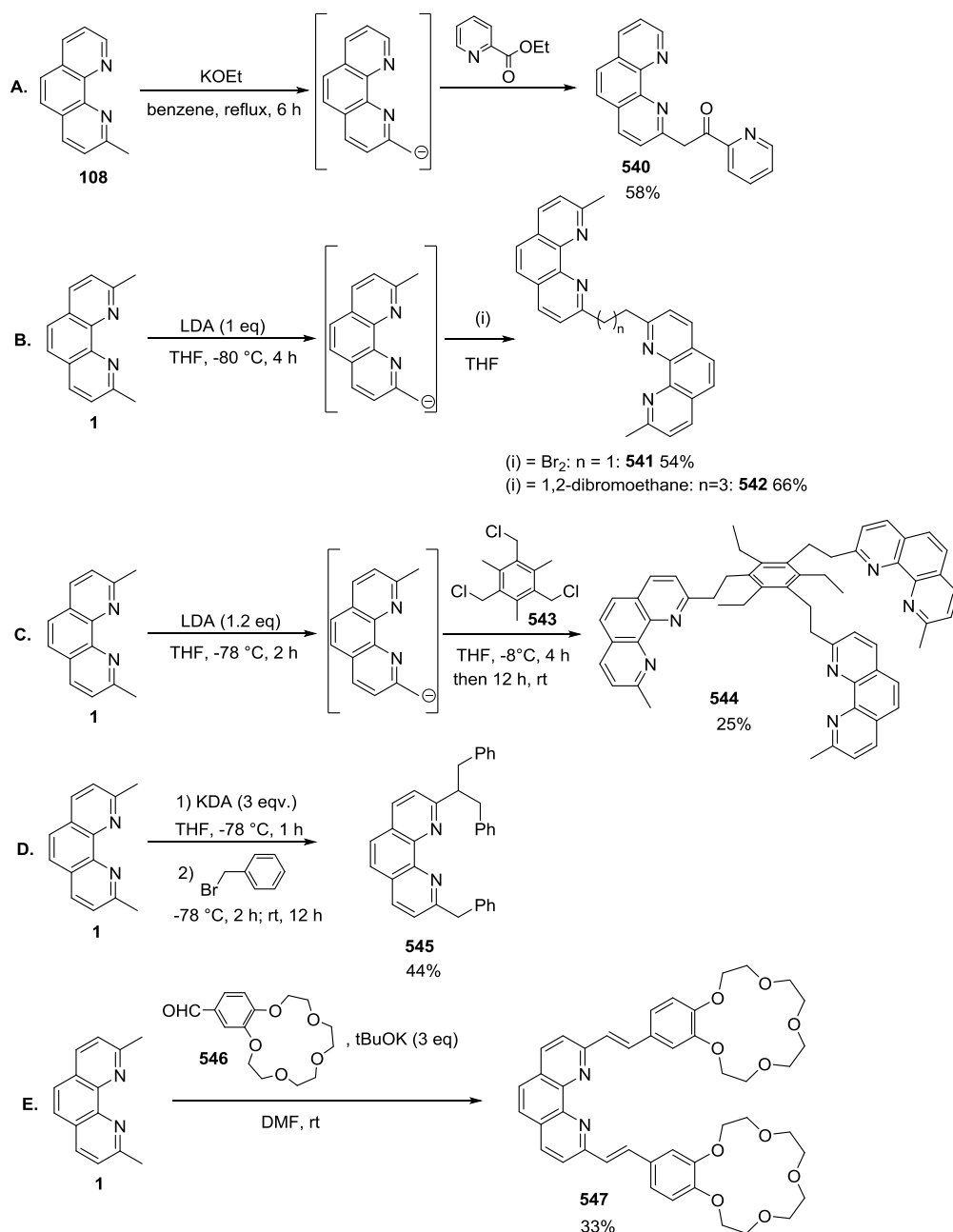
Although neocuproine **1** (and 2-methyl-1,10-phenanthroline **108**) are usually not obtained from phen by a divergent synthetic strategy, their commercial availability and synthetic versatility towards the decoration of phen in positions 2 and 9 justifies we expose the functionalization methods of **1** and parent ligands in the divergent synthetic strategies section.

Reactivity of **1** and **108**

The most straightforward way to decorate **108** and **1** relies on the acidity of the protons of the methyl group(s). Using a strong base (KOEt,⁴⁹⁷ tBuOK, MeONa^{498,499} and above all LDA⁵⁰⁰) it is possible to deprotonate **108** or **1** leading to a mono-anion or a dianion with a characteristic deep orange-red color.⁵⁰¹ Considering the literature, LDA is certainly the base which is the most frequently used to deprotonate **1** or **108**, while less basic MeONa is only marginally used.

The obtained carbanions are strong nucleophiles which can be used in a number of addition reactions on varied electrophiles. Case was the first to report the deprotonation of **108** by potassium ethanolate in benzene. The obtained anion reacts with ethyl picolinate to afford pyridyl ketone **540** in 58% yield (Scheme 91A). There are many examples where **1** is either singly or doubly deprotonated in presence of one or two equivalents of LDA, and then reacted with an electrophile. Lehn and coworkers used this strategy to generate monoanion which was

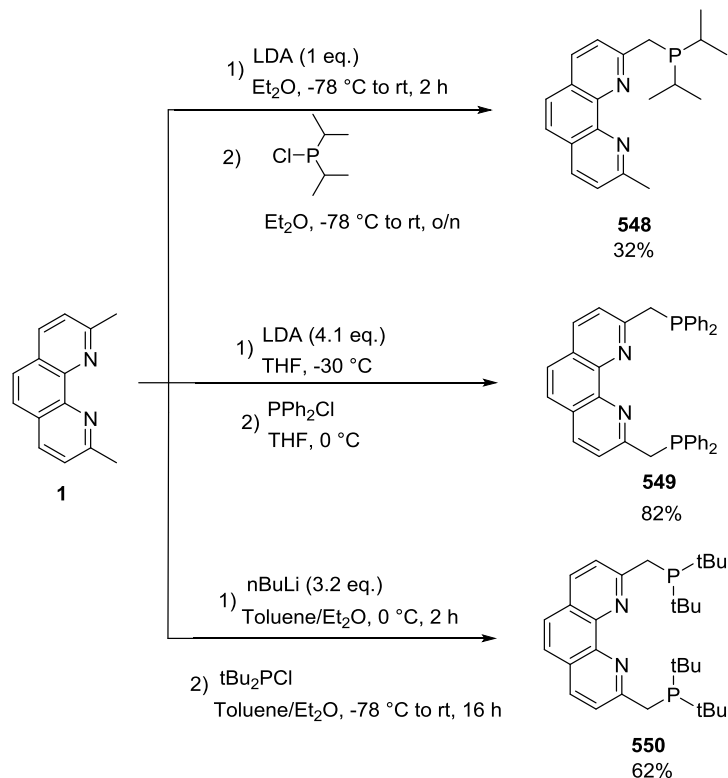
subsequently reacted with Br₂ or 1,2-dibromoethane, leading to dimers **541** or **542**, respectively (Scheme 91B).⁵⁰¹ A phen trimer was prepared in one step from the monoanion and 0.33 equivalent of **543** in 25% yield (Scheme 91C)⁵⁰² which is a significantly high yield, considering the complexity of the molecule and the fact that it was prepared in one step. In presence of excess LDA, the bis-carbanion of **1** is formed and can react with several electrophiles, like benzyl bromide and derivatives (Scheme 91D).¹⁵¹ Interestingly, adding 3 equivalents of diisopropylamide (potassium salt, KDA) on **1** allows to synthesize **545** in presence of excess benzylbromide, meaning that **1** can be deprotonated three times during the whole process.⁵⁰³ Finally, nucleophilic attack of doubly deprotonated **1** onto aldehydes leads to diol intermediates which quickly turn into fully conjugated styryl derivatives after a favorable elimination step. For example, the reaction of **1**, tBuOK and aldehyde **546** in DMF at room temperature leads to heterotopic ligand **547** (the low yield is due to the presence of significant amounts of mono-substituted compound) (Scheme 91E). Only the more stable trans isomers are obtained in each case. Sodium methanolate MeONa was reported to be far less reactive than tBuOK,⁴⁹⁹ but one successful example is reported where iron thiocyanate is added in the reaction medium and act as template to favor the reaction.⁴⁹⁸



Scheme 91. Deprotonation of **108** and **1** and exploitation of the formed carbanions to decorate phen in positions 2 or 2 and 9 through the generation of C-C bonds.

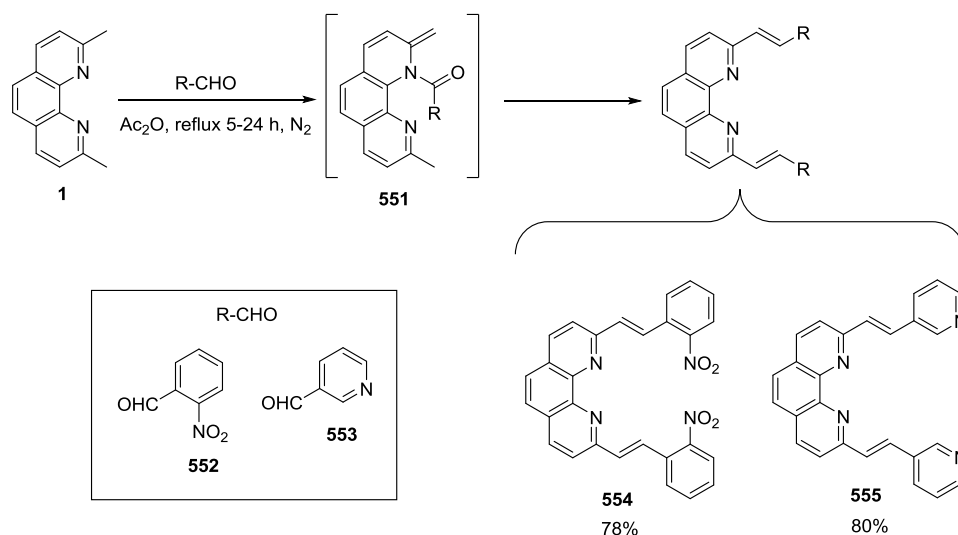
When chlorodiphenylphosphine or chlorodialkylphosphine are used as electrophiles in presence of deprotonated **1**, C-P bonds are formed leading to interesting mixed N,P chelates (Scheme 92). For example, cobalt complexes obtained with the tris-coordinating ligand **548** are catalysts for C-H borylation of heteroaromatics,¹²⁴ and planar “pincer” ligands **549** and

550 were used to design Fe⁵⁰⁴ and Ru⁵⁰⁵ complexes able to form metal-hydrides, used as catalysts for reduction reactions. It is interesting to notice that in the case of **550**, *n*BuLi was used as a base instead of LDA to deprotonate **1**.



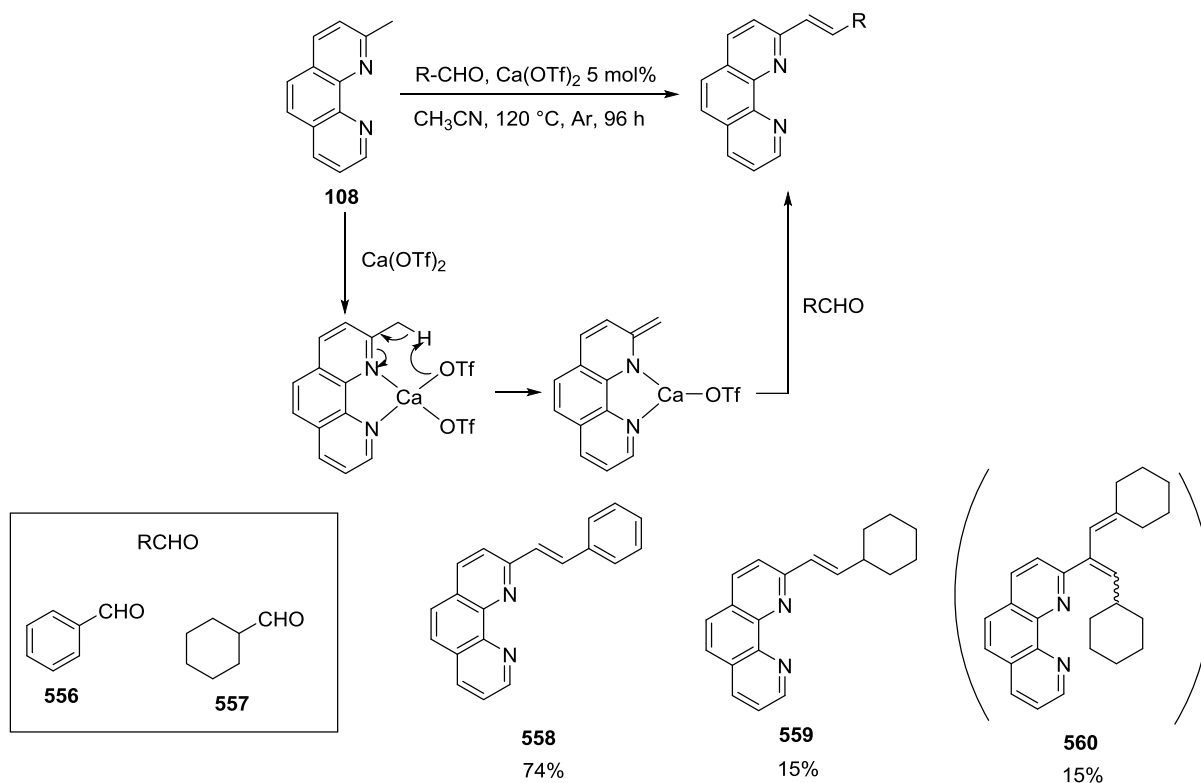
Scheme 92. Deprotonation of **1** and exploitation of the formed carbanions to decorate phen in positions 2 or 2 and 9 through the generation of C-P bonds.

Deprotonation of the methyl group(s) is not the sole way to functionalize **1** or **108**. For example, there is a milder method (i.e. not necessitating the use of a strong base) to react **1** and aldehydes towards the formation of styryl derivatives. Refluxing **1** and aldehydes **552** or **553** in acetic anhydride Ac₂O leads to the formation of styryl derivatives such as **554**⁵⁰⁶ or **555**⁵⁰⁷. Ac₂O acts as an activating agent, enhancing the acidity of the methyl group in the family of 2-methyl pyridine compounds (Scheme 93).⁵⁰⁸



Scheme 93. Action of aldehydes on **1** in acetic anhydride

The conjugation of aldehydes onto **1** is promoted when the latter is protonated⁵⁰⁹ and more particularly when complexing **108** with calcium ions.^{144,510} Indeed, in presence of catalytic amounts of calcium triflate $\text{Ca}(\text{OTf})_2$, benzaldehyde or cyclohexanecarboxaldehyde can condense on 2-methyl pyridine derivatives and on **108** in particular. This results in styryl derivatives **558** or **559** with various yields but some undesired side products such as **560** form as well (Scheme 94). This result is not further discussed in the article.

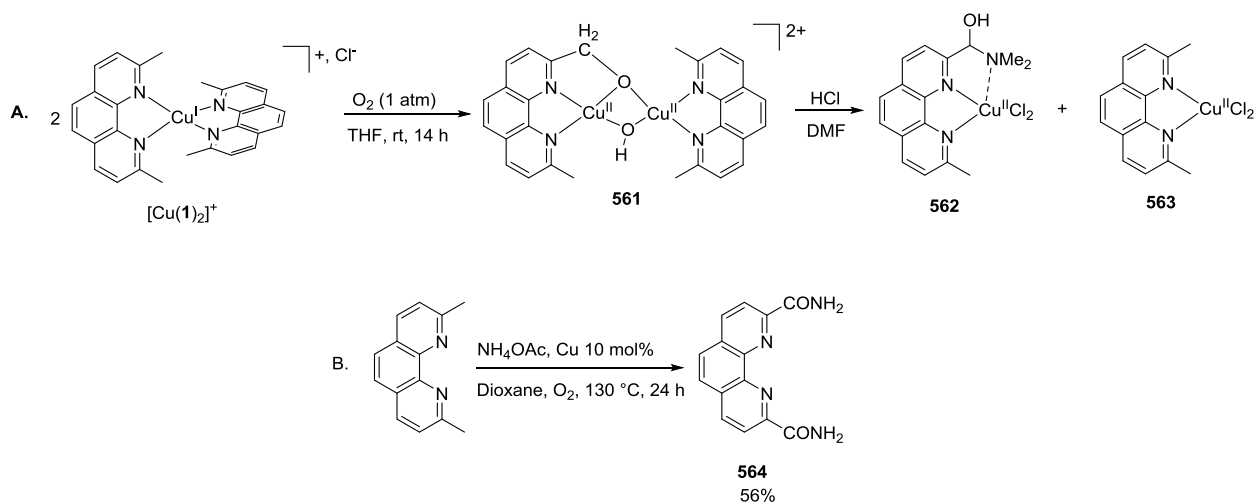


Scheme 94. Promotion of the coupling reaction between aldehydes and **117** by complexation with Ca^{2+} ions

Other ion-assisted functionalizations of **1** are reported. For example, when complex $[\text{Cu}(\mathbf{1})_2]\text{Cl}$ (forming at room temperature) is left in solution under O_2 atmosphere, an oxygen atom insertion takes place on one of the methyl groups of **1** leading to dimer **561** which, after acidic treatment, leads to complexes **562** and **563** which crystallize separately (Scheme 95A).⁵¹¹

Moreover, copper metal catalyzed direct amidation of the methyl groups of **1** has been described,⁵¹² allowing to turn **1** into **564** in only one step (Scheme 95B). The proposed mechanism relies on the copper catalyzed oxidation of the methyl group by O_2 into aldehyde functions first, followed by amine condensation and dehydration. This versatile reaction works with several 2-methyl pyridine derivatives, and is rather impressive given the usual

multistep reactions required to reach oxidized neocuproine derivatives and **564** in particular,¹² as will be demonstrated in the following.



Scheme 95. Copper ion and copper metal-assisted oxidations of **1** by O_2 .

Interesting ruthenium-assisted reactions have been proposed too,⁵¹³ but the pure functionalized ligands have not been retrieved because of the strong bonding between ruthenium and phen.

Derivatives of **1** and **108**

A number of $\text{phen}_{(2,9)\text{sub}}$ and $\text{phen}_{(2)\text{sub}}$ synthons can be synthesized from **1** or **108**. Those synthons are particularly important in the field of phen functionalization because they are very versatile and rather easily obtained from **1**. Importantly, the strategies developed to synthesize bis-functionalized $\text{phen}_{(2,9)\text{sub}}$ synthons or mono-functionalized $\text{phen}_{(2)\text{sub}}$ synthons are often quite different and will therefore be treated separately, focusing first on $\text{phen}_{(2,9)\text{sub}}$ synthons.

- Syntheses of $\text{phen}_{(2,9)\text{sub}}$ synthons.

We identified seven crucial synthons pictured in Figure 25: $\text{phen}_{(2,9)\text{sub}}$ bearing carboxaldehyde (**565**), trichloromethyl (**566**), carboxyl (**44**), nitrile (**567**), methanol (**568**), chloro- and bromomethyl (**569** and **570**) and aminomethyl (**571**) groups. Their synthesis will

be described first, then a brief survey of the possible usages of all those synthons will be given.

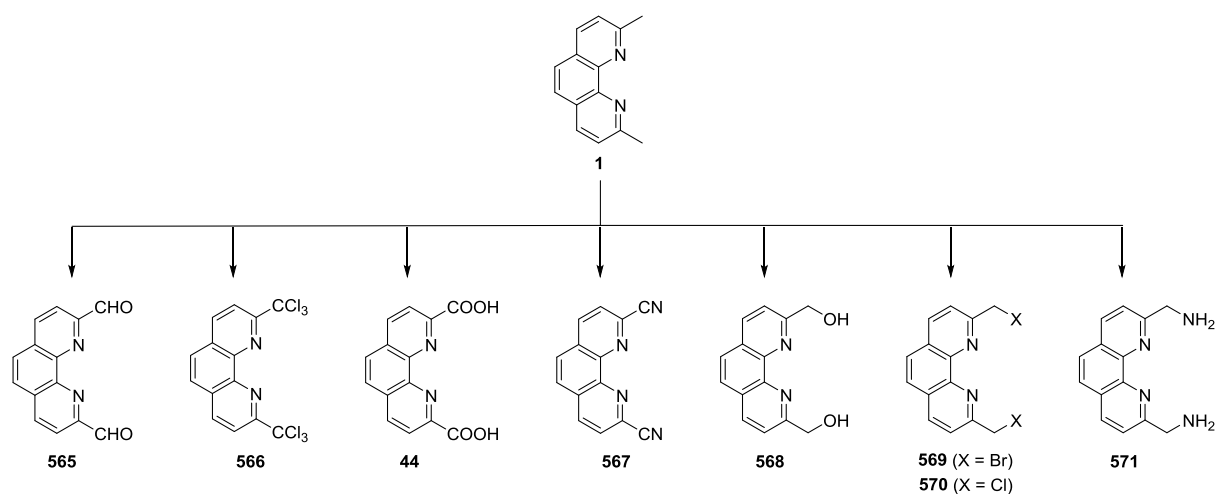
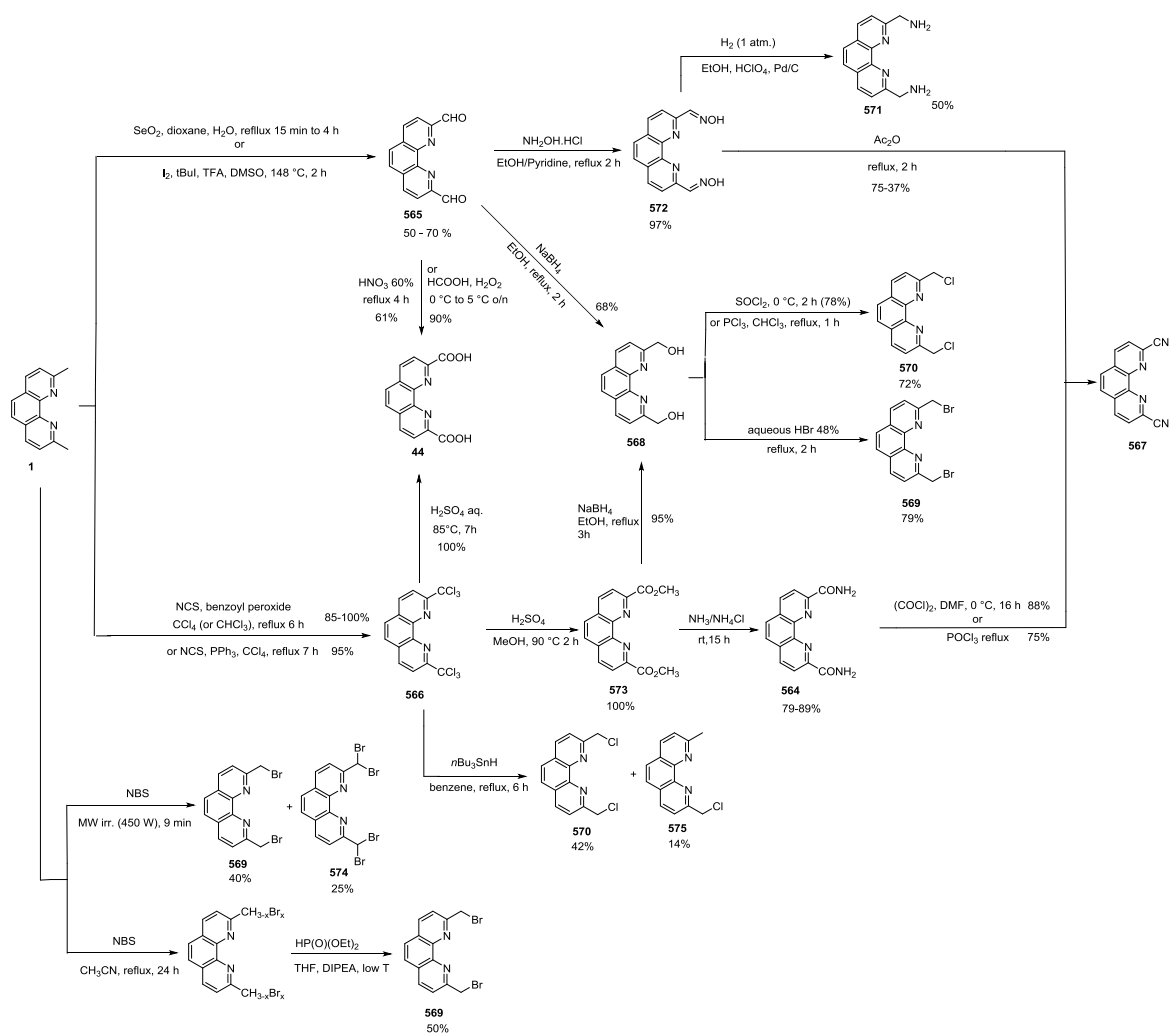


Figure 25. Pivotal synthons obtained from **1** for the decoration of phen in positions 2 and 9

Scheme 96 is summarizing all the possible strategies leading to functionalized phen in positions 2 and 9 from **1**. In all cases, those strategies are based on the oxidation of the methyl groups. Interestingly, all synthons are obtained from **565** or **566**.



Scheme 96. Summary of all synthetic strategies to reach phen_{(2,9)sub} synthons **44** and **565-571**.

The most frequently encountered synthesis of **565** relies on the oxidation of **1** by selenium oxide SeO_2 in water/dioxane mixtures. There are however many variations of this apparently simple protocol, reporting the synthesis of **565** with various yields and questionable purities. For example, Goodwin et al.⁵¹⁴ describe that they first dissolved 2 equivalents of SeO_2 in hot aqueous dioxane then add carefully **1** and quench the reaction after only 15 min of refluxing time. On the other hand, Chandler et al.⁵¹⁵ mix together almost five equivalents of SeO_2 with one equivalent of **1** in aqueous dioxane, and reflux this mixture for 2 hours. In a subsequent contribution, Hodgson et al.⁵¹⁶ underlines the importance of adding carefully **1** in dioxane solution into the SeO_2 solution at room temperature before reflux. The proportions of SeO_2

vary significantly from one protocol to another (4-5 equivalents^{241,515,516} to only 2).⁵¹⁷ Following these slightly different synthetic pathways, samples of **565** were obtained with variable yields and purities,⁵¹⁵ mainly because the following workup of the reaction is known to be tricky. The main issue is indeed to separate toxic selenium wastes from the desired bis-aldehyde which tends to precipitate prematurely during workup. This is achieved by a filtration step which must be performed on the warm mixture and with warmed-up glassware (funnels, celite bed).^{241,514-516,518} Then, the obtained crystals are likely to be analytically impure, sometimes with a pronounced red hue. Recrystallization from hot benzene, THF or CHCl₃ has been reported,^{514,517} as well as re-precipitation in a mixture of DMF and water,^{516,518} affording a white powder with ca. 70% yield. Chromatographic methods have been tried too, in order to afford a pure sample of **565** with 83% reported yield.⁵¹⁹ A micro-wave assisted version of this synthesis has been disclosed too, with a very satisfactory yield of 85%.⁵²⁰

Nevertheless, as pinpointed by Meunier et al.,⁵²¹ SeO₂ is a toxic chemical, and its complete removal from the reaction mixture is difficult. They proposed a resolutely different method to synthesize **565** from **1**, using a protocol developed by Minisci et al.,⁵²² and based on the oxidation of **1** by iodine in presence of TFA in DMSO. The yield is still satisfactory and the workup of the reaction is more straightforward.

As can be seen in Scheme 96, trichloromethyl derivative **566** is an efficient alternative to **565** for the decoration of phen in positions 2 and 9 since virtually all the key phen_{(2,9)sub} synthons obtained from **565** can be obtained from **566** too, using different methods and protocols. **566** is obtained by perchlorination of the CH₃ groups of **1** with excess N-chlorosuccinimide (NCS).^{500,515,523} Initially performed in refluxing CCl₄,^{515,523} the conditions were gradually improved by the addition of the radical initiator benzoyl peroxide⁵²³ (quantitative yield) and the replacement of highly toxic CCl₄ by CHCl₃.^{500,524,525} Addition of triphenylphosphine to

NCS in CCl_4 is reported to activate NCS and efficiently leads to the perchlorination of **1** in 95% yield.⁵²⁶

Incidentally, the brominated version of **566** could be obtained in similar conditions with Br_2 ⁵¹⁵ or N-bromosuccinimide⁵⁰⁰ as bromine sources. Nevertheless, **566** is far more utilized than its brominated alter-ego for the decoration of phen.

2,9-biscarboxyl-1,10-phenanthroline **44** is a very useful building block too because it endows phen with all the very rich chemistry of carboxylic acids (see below for a few selected examples). Like in the case of **565**, the COOH group in **44** is conjugated to the phen aromatic structure and this enhances the electrophilic character of C=O group. The COOH group allows all types of peptide and ester coupling reactions as will be shown below. In addition, the coordinating abilities of the carboxylic and carboxylates allow to use **44** as an efficient tetradentate ligand for several metal ions (Ce^{IV} , Pu^{IV} , Fe^{III}).^{158,527,528}

44 can be obtained in three different ways (Scheme 96). The most used protocol relies on the oxidation of **565**. Historically, very concentrated nitric acid (HNO_3 80%) at reflux was used as oxidant to perform this reaction providing **44** with a satisfactory yield of 61%.⁵¹⁵ Using less concentrated HNO_3 (70 or 60%) affords **44** in higher yields (97%) and with less side products.⁵²⁹ Recently, the action of a mixture of H_2O_2 and formic acid at low temperature on **565** has been reported to give **44** in 90% yield.⁵³⁰

The second method to synthesize **44** relies on the hydrolysis of **566** in aqueous H_2SO_4 at 85 °C.^{523,524} From the published data, this method seems more efficient than the oxidation of **565**, in terms of overall yield from **1**. Finally, although all attempts to directly convert **1** to **44** in a single oxidation step with SeO_2 in dioxane have failed,⁵³¹ replacing dioxane by pyridine has allowed to synthesize **44** (in low yield), isolated as its methyl ester **573**.⁵³²

567 can be obtained from both **565** and **566**. The dioxime derivative **572** is obtained from **565** and hydroxylamine in excellent yields. Then dehydration of **572** affords **567**. The yields for

this last step vary from 75%⁵¹⁵ (with probable purity issues) to 37%.¹² This protocol has been simplified by Harwood et al.¹² who have performed the hydroxylamine condensation and subsequent dehydration in one pot, meaning that **567** could be obtained from **1** with an overall yield of 44% in two steps. On the other hand, when **566** is hydrolyzed in sulfuric acid and methanol, the methyl ester derivative **573** is quantitatively isolated. The latter is subsequently converted to bis-amide **564** and finally dehydrated into **567** in neat POCl₃⁵³³ or reacted in presence of the Vilsmeier reagent.⁵³⁴

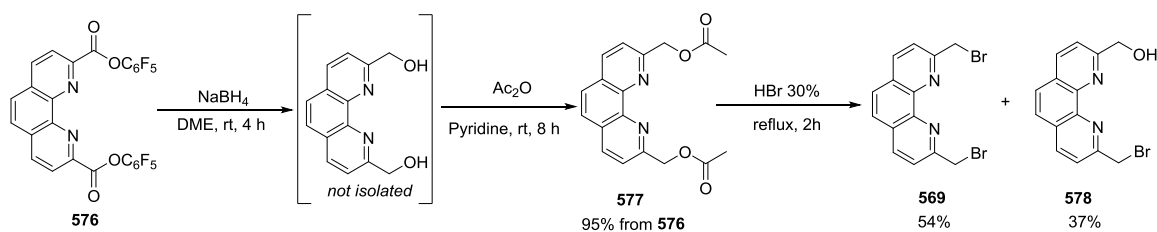
The synthetic strategy to reach **567** using **566** (4 steps from **1**) is less advantageous than the one using **565** in terms of number of steps (“**566** pathway”: 4 steps from **1**; “**565** pathway”: 3 or even 2 steps from **1**). However, the 4 steps of the “**566** pathway” are reported to work with high yields (ca. 55% yield from **1**) making this strategy more efficient than the “**565** pathway” (ca. 33% on average from **1**).

The four last pivotal phen_{(2,9)sub} synthons **568**, **569**, **570** and **571** (Figure 25) all have two common features: first the reactive groups (OH, halogen, NH₂) are not conjugated to phen and occupy a reactive benzylic-like position. Second, they can all be prepared from **565**, **566** or directly from **1** (Scheme 96).

Action of NBS on **1** in acetonitrile⁵³⁵ leads to the bromination of the methyl groups. A solvent- and radical initiator-free version of the same reaction under microwave irradiation has been reported.⁵³⁶ But in both cases, it is difficult to separate the variously brominated compounds by classic chromatography techniques. Treating a mixture of several differently brominated compounds with hydrogenophosphonate and diisopropylethylamine DIPEA allows to “cure” the mixture⁵³⁷ and affords **569** with a decent yield of 50%.⁵³⁵

570 can be obtained from **566** by reduction with *n*Bu₃SnH⁵⁰⁰ but a mixture of compounds (**570** and **575**) is again obtained and has to be chromatographed in order to retrieve the desired compound. This shows the difficulty to control the reductive dehalogenation of **566**.

Otherwise, **569** and **570** can both be obtained from **568**. The latter is synthesized either *via* reduction of **565**⁵¹⁵ or **573**⁵²³ by NaBH₄. In the latter case, there is no need to prepare the complicated **565** intermediate, and the overall yield over 3 steps (95%) is beyond satisfaction (compared to ca. 48% over two steps for the **565** pathway). It is worthwhile to mention that **568** can be difficult to separate from water soluble borate salts. To address this issue, Mayol and co-workers propose not to isolate **568** and convert it into the lipophilic acyl derivative **577** (Scheme 97) which can be more easily separated from water soluble impurities. Let us notice that **568** is obtained in this case by reduction of activated diester **576**. While the article does not mention the possibility to recover pure **568** from **576**, it seems to be a feasible and straightforward step leading to a potentially purer sample of this molecule. A subsequent addition of HBr on **577** affords a mixture of **569** and interesting mixed-functional **578**, which can be separated by chromatography column.⁵³⁸ Incidentally, the same molecule was obtained by treatment of **568** with HBr at 120 °C for 5 h (37% yield).⁵³⁹ **578** exhibits two different reactivities which can be interesting to prepare non symmetrical phen structures (see below).



Scheme 97. Alternative synthesis of **568** and **569**

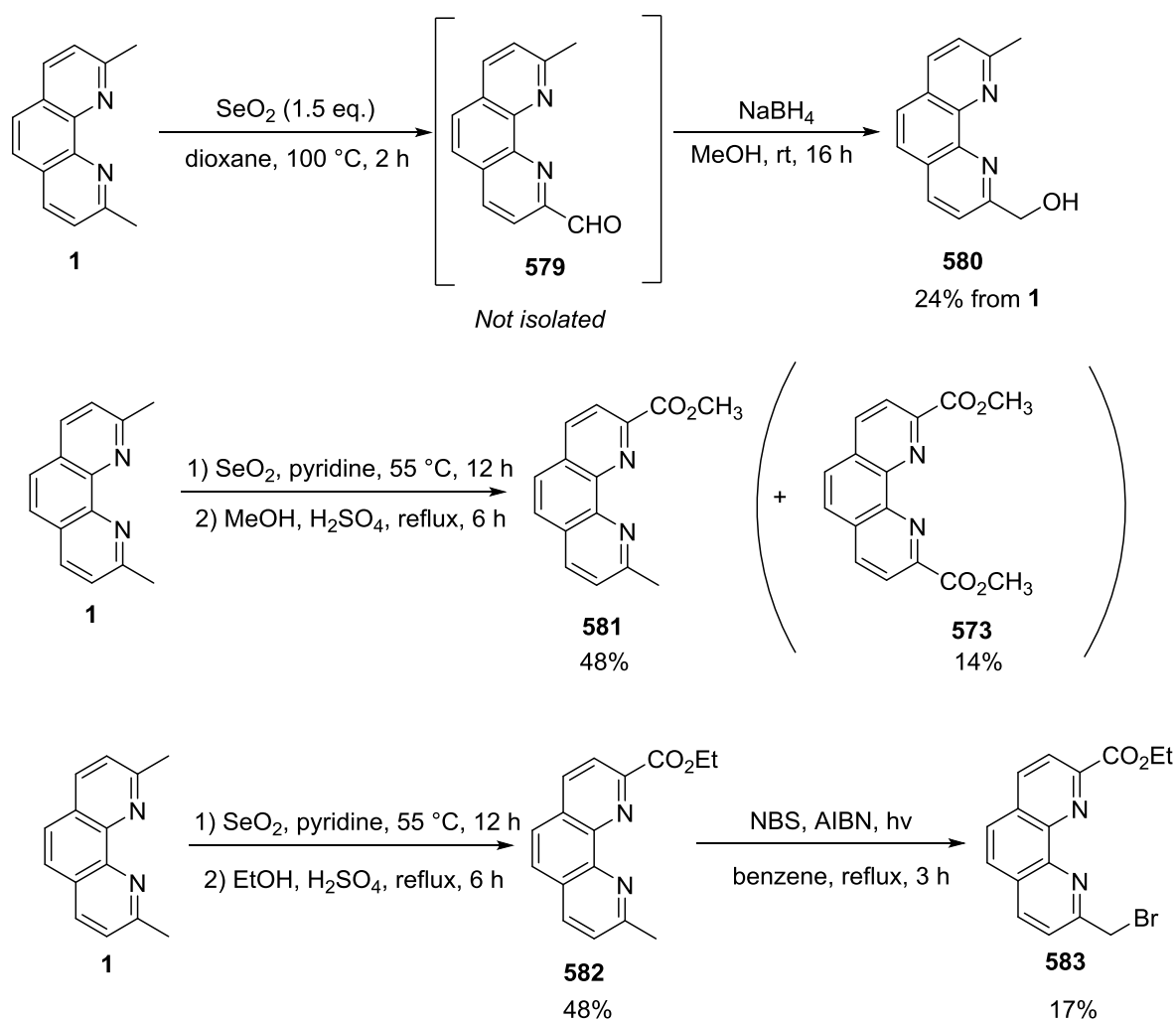
As mentioned above, chlorination of **568** by thionyl chloride⁵⁴⁰ or PCl₃⁵²³ leads to **570** in a straightforward manner. Likewise, treatment of **568** in neat refluxing HBr 48% gives **569**.⁵¹⁵ A milder protocol is reported, where HBr is diluted (1/1 v/v) in acetic acid and the mixture is heated at 45 °C for 15 h, affording the desired product with 69% yield.⁵⁴¹

It is noteworthy that in spite of the fact that all those compounds show a benzyl halide behavior, and that they are thus highly reactive, both **569** or **570** can be chromatographed on silica gel,⁵¹⁶ and show reasonable stabilities.

Finally, the more rarely used bis(benzylamine) synthon **571** is easily obtained as the HClO₄ salt by H₂ reduction of bis-oxime **572** on Pd/C.⁵¹⁵

Uncomplete reactions can lead to mono-functionalization of **1**, like in the case of **575**. As a matter of fact, a careful control of the reaction conditions allows to selectively modify only one methyl group on **1**. For example, **580** has been obtained from **1**, first by mono-oxidation of one methyl group by SeO₂ (1.5 equivalent only) in refluxing dioxane⁵⁴² leading to **579**, then reduction of the latter by NaBH₄ (Scheme 98).

Moreover, as mentioned above, a direct oxidation of **1** by SeO₂ into the mono-methylester derivative **581** can be achieved in pyridine. The mono oxidized compound is obtained in higher yield than **573**, by controlling the number of SeO₂ equivalents and lowering the temperature (55 °C).⁵³² The mono ethyl ester **582** has been prepared following the same protocol.⁵⁴³ Interestingly, the reactivity of the remaining methyl group in α of the nitrogen atom of **582** was exploited with NBS in order to form **583**, which bears therefore two different functional groups with different reactivities (Scheme 98).

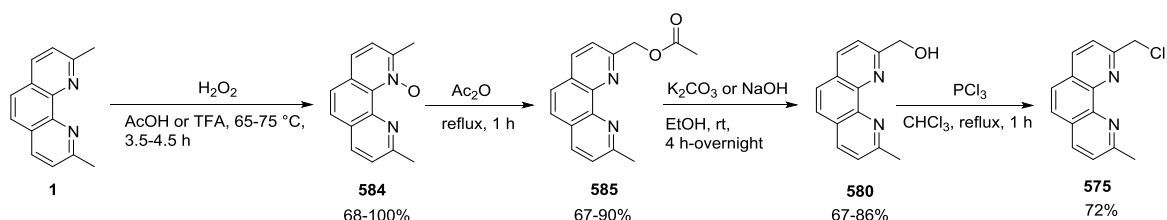


Scheme 98. Selective oxidation of one methyl group on **1**

The mono-functionalization of **1** can be achieved with higher yields and selectivity if one of the methyl group is activated by formation of the N-oxide **584** (Scheme 99). The reaction proceeds in excess H_2O_2 in glacial acetic acid. The synthesis of **584** is reported to be sensitive to a number of parameters. Newkome and co-workers mention the importance of a fine control of the temperature to reach a decent yield of **584** when reacting **1** with a large excess of H_2O_2 (11.5 equivalents).⁵⁴⁴ Replacing glacial acetic acid by trifluoroacetic acid affords a better yield, with a milder excess of H_2O_2 (3.5 equivalents).⁵⁴⁵ As a matter of fact, the quantity of H_2O_2 is a determining issue as pinpointed by Cohen and co-workers who

significantly improved the yield of the reaction (quantitative) by pre-heating the acetic acid solution of **1** before adding only 1.7 equivalents of H₂O₂.

584 is then reacted in refluxing acetic anhydride to afford **585** which is saponified in presence of K₂CO₃ or NaOH in ethanol. The resulting “benzylic” alcohol **580** is reported to be unstable and hygroscopic.⁵⁴⁴ It is then chlorinated in presence of PCl₃ in refluxing CHCl₃ to afford **575** (Scheme 99). Attempts to synthesize the brominated version of **575** lead only to the reduction of **580** into **1**; there is only one report in the literature of the brominated version of **575** and no detailed synthetic protocol is given.⁵⁴⁶



Scheme 99. Controlled mono-functionalization of **1** through formation of the N-oxide **584**

- Syntheses of phen_{(2)sub} from 2-cyano-phen 358.

Phen derivatives bearing one functional group in position 2 and featuring an unsubstituted position 9, are pivotal building blocks for a number of elaborate structures (Figure 26). A certain number of them can be obtained by oxidation of 2-methyl-phen **108** (e.g. **587** can be obtained by treatment of **586** in HNO₃⁵⁴⁷ (and apparently by direct oxidation of **108** with KMnO₄ although there is no description of the synthetic protocol)⁵⁴⁸ while SeO₂ oxidation of **108** in **586** is reported too).⁵⁴⁹

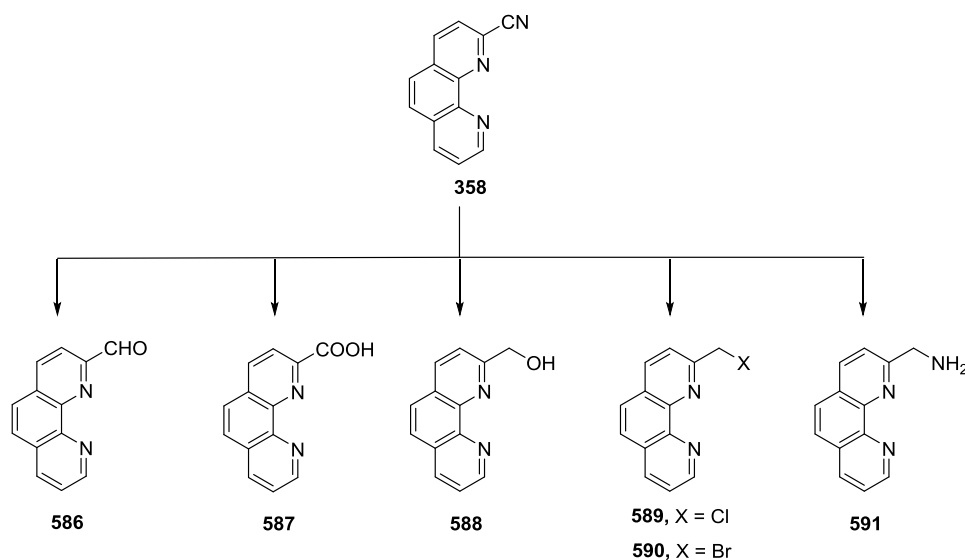
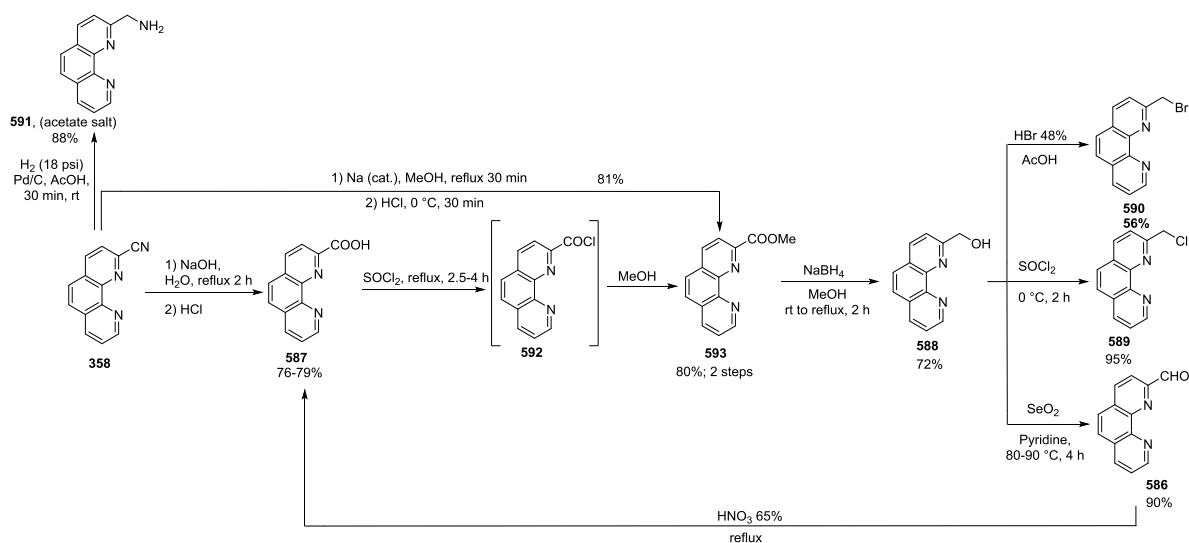


Figure 26. Pivotal phen_{(2)sub} ligands

But the great majority of them is prepared from the key synthon **358** obtained directly from phen (Scheme 61). The strategies are very similar to what has been described above to modify neocuproine **1**, and will thus be presented briefly herein. Indeed, all the synthons **586-591** (Figure 26) can be synthesized from **358** as shown in Scheme 100. First, **358** can be reduced in presence of H₂ and palladium on carbon into **591**. The latter exhibits a benzyl-amine like behavior and has a strong nucleophilic behavior. Second, hydrolysis of **358** affords useful synthon **587**, from which **586** and **588-590** can be obtained. First, esterification of **587** into its methyl ester **593** is necessary and proceeds in two steps, by treating the latter with SOCl₂ (**592**, not isolated) then MeOH. Engbersen et al. proposed to pass directly from **358** to **593** by treating **358** with catalytic amounts of Na in methanol.^{550,551} Earlier work reports on the direct conversion of **358** to the ethyl ester of **587** by refluxing **358** in ethanol in presence of H₂SO₄.⁴¹⁷ Reduction of **593** by NaBH₄ leads to the target reactive alcohol derivative **588**.⁵⁵² This step is reported with yields varying from decent to satisfactory, the slow addition of NaBH₄ at low temperature seems to favor a higher yielding reaction.⁵⁵³ Finally **588** can be either oxidized into 2-carboxaldehyde-phen **586** by SeO₂,^{552,553} or be treated with SOCl₂ to

afford 2-chloromethyl-phen **589**, or be reacted with HBr to afford **590**.⁵¹⁵ Incidentally, re-converting **586** into **587** is reported in usual conditions.⁵⁴⁷



Scheme 100. Mono-functionalization of phen using 2-cyano-phen **358** as starting synthon.

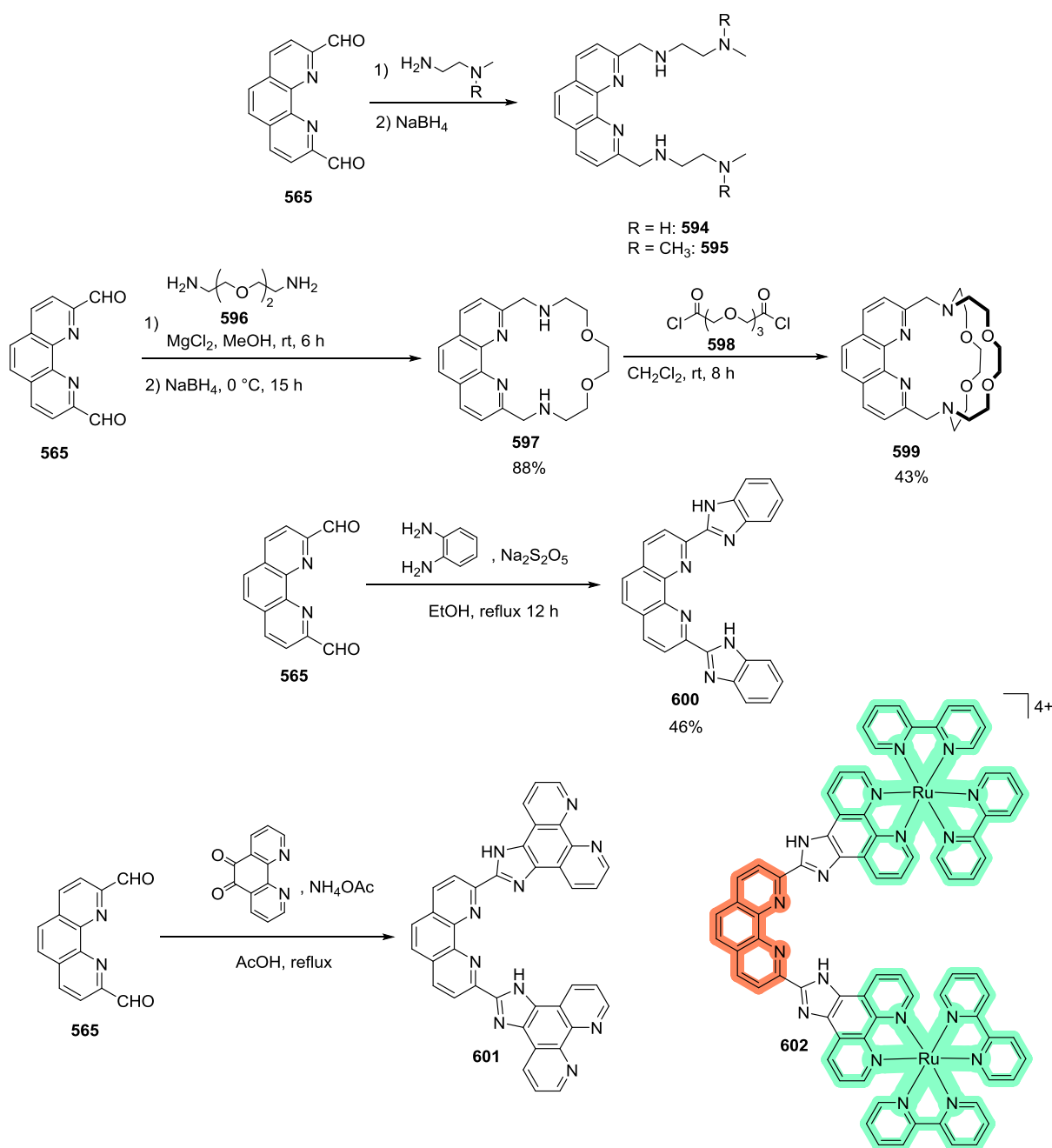
- Reactivity of the derivatives of **1** and **108**.

The reactivity of the derivatives **565** and **586**, **568** and **588**, **569-570** and **589-590**, **44** and **587**, **358** and **567**, **571** and **591** is the same than the usual reactivity of aromatic aldehydes, benzyl alcohols and halides, aromatic carboxylic acids, aromatic nitriles and benzyamines, respectively. There are many examples and it is not the aim of this review to report them all. We will therefore only show a few selected representative examples of the diversity of structures which can be reached.

565 and **586** are among the most frequently used building blocks to decorate phen in positions 2 and in positions 2 and 9. The carboxaldehyde groups are conjugated with phen, enhancing their electrophilicity and making them particularly reactive molecules *vs.* a wide range of nucleophiles, in particular amines. For example, copper(I) helicates were designed by self-assembly by simply mixing **565**, an amine R-NH₂ and either Cu(CH₃CN)₄⁺ or Cu₂O. Di- and tri-copper double helicates,^{554,555} and larger molecular wires⁵⁵⁶⁻⁵⁵⁸ showing interesting electroluminescent properties were obtained in mild conditions. The reversibility of the imine

bond formation is playing an important role in the design of the self-assembled helicates, as incidentally demonstrated in other works.³⁸¹ A similar self-assembly method was used to synthesize chiral Zn catenates in one step, a remarkable feat knowing the difficulty to prepare those supramolecular scaffolds.⁵⁵⁹

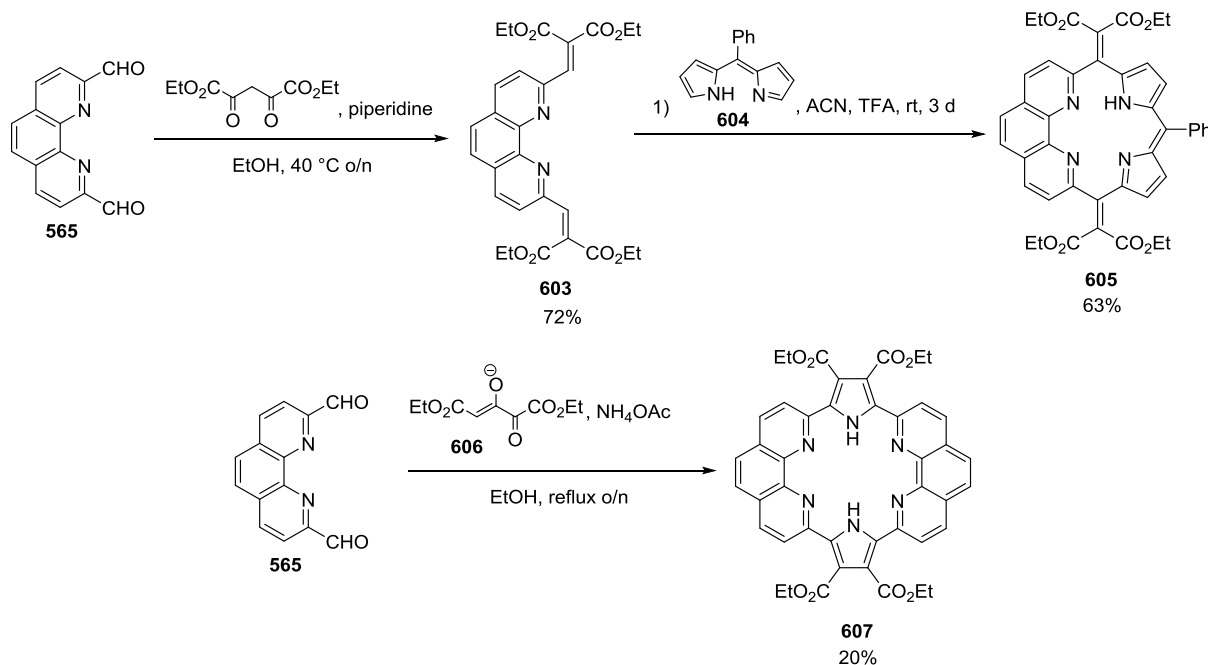
Other polydentate ligands can easily be obtained by reacting **565** with polyamines, followed by reduction of the imines by NaBH₄ (Scheme 101).



Scheme 101. Examples of condensation of amines on **565**

Mn, Fe, Co, Ni, Cu and Zn complexes of **594** were synthesized and used as cytotoxic agents towards neuroblastoma cancer cells,⁵¹⁷ while the binding of Cu and Ni complexes of **595** to DNA G-quadruplex sequences has been investigated. Using diamines allows to synthesize macrocycles in a very convenient way. For example, Lüning and coworkers⁵¹⁸ have prepared phen_{(2,9)sub} **597** (among many others) from **565** and diamine **596** with the support of Mg²⁺ (or Ca²⁺) ions acting as template agents. Interestingly, the amine could be further functionalized in presence of bis acyl chloride **598** (in high dilution conditions and with the assistance of a syring pump to control the feed of both acyl chloride **598** and **597** over seven hours) to afford the heterotopic kryptand **599** in good overall yield from **565** for such kind of reaction (Scheme 101). Condensation of aromatic diamines^{560,561} on **565** in oxidizing conditions leads to bis-benzimidazole derivatives such as **600** in conventional conditions for such reactions. Similar structures like **601** can be obtained by reacting 1,10-phenanthroline-5,6-dione on **565** in presence of ammonium acetate in refluxing acetic acid.⁵⁶²⁻⁵⁶⁴ A binuclear Ru complex **602** has been synthesized from **587**, each Ru(II) ion being coordinated in the less bulky pending phen cavities. This complex has been used as luminescent probe for DNA, able to intercalate between base pairs *via* the free rigid phen core (highlighted in red in Scheme 101). Using carbon nucleophiles on **565** allows to create C-C bond (Scheme 102).⁵⁶⁵⁻⁵⁷⁰ For example, diethylmalonate is reacted with **565** in standard Knoevenagel conditions^{568,569} and the resulting Michael acceptor **603** is then condensed with meso-phenyldipyrromethane **604** leading to the half porphyrin-half phenanthroline hybrid macrocycle **605** after DDQ treatment. **605** has been used as an efficient cation sensor.⁵⁶⁸ An interesting synthesis of a rigid conjugated macrocycle **607** has been described by Colbran and co-workers.⁵⁶⁶ The synthesis relies on the condensation of ammonia on **565** (or **586**)⁵⁶⁷ followed by the reaction of the latter imine on diethyloxalacetate **606**. Intramolecular cyclization leads to **607** in only

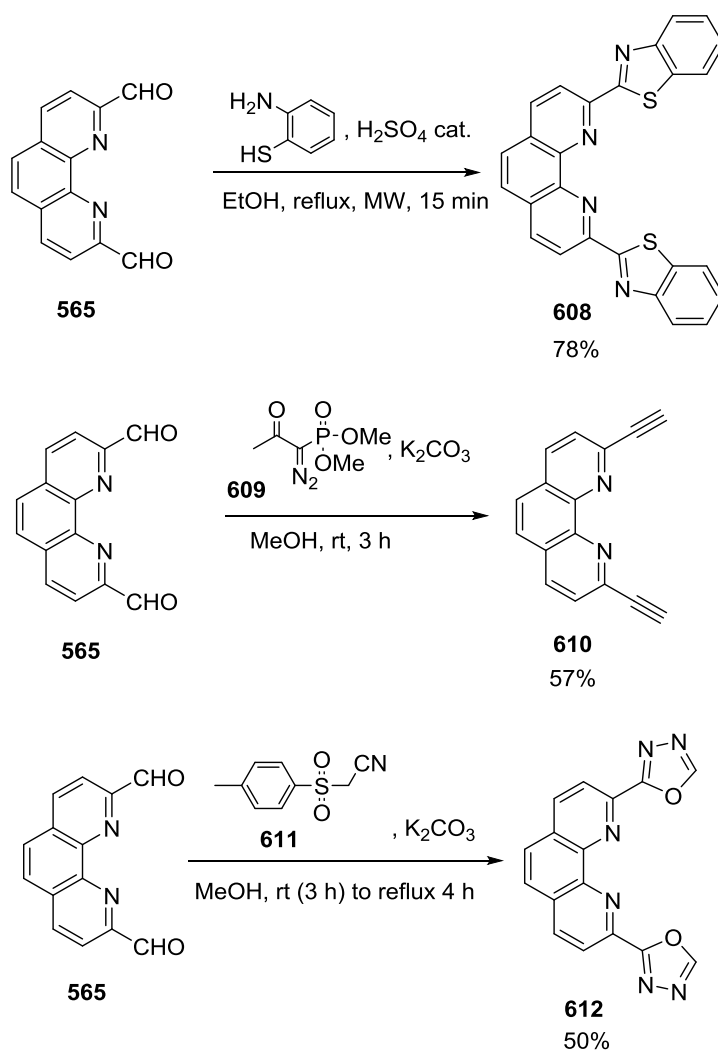
20% yield but in only one step. The obtained macrocycle shows interesting chelating properties towards lanthanides and has been demonstrated to host protic molecules through H bonding.



Scheme 102. Examples of condensation of carbon nucleophiles on **565**

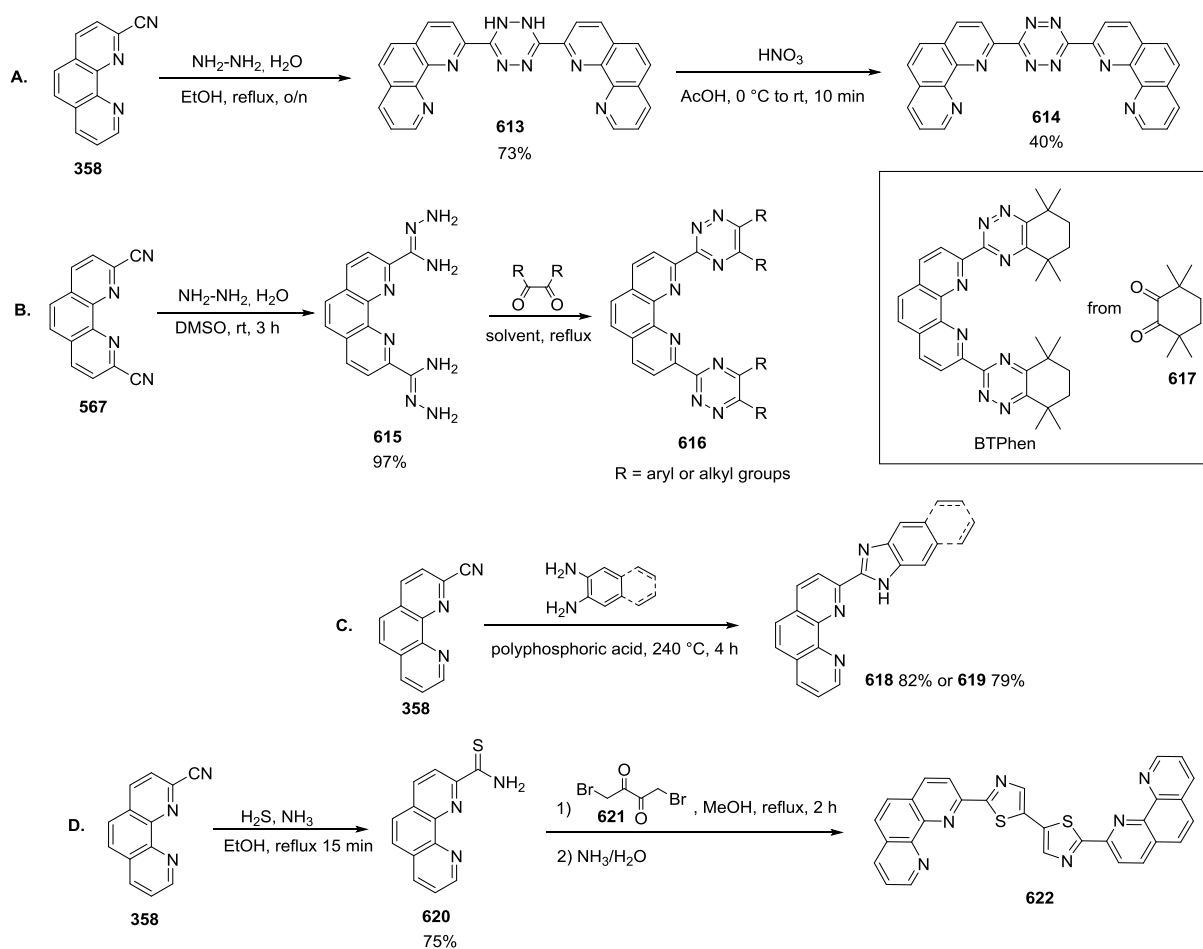
Other interesting miscellaneous reactions on **565** can be found (Scheme 103). For example, the condensation of 2-mercaptoaniline on **565** affords the bis-benzothiazole derivative **608** (the synthesis using microwave is given in Scheme 103 but a conventional reflux reaction is working too, albeit with a lower yield of 67%).⁵⁷¹ The original and convenient Ohira-Bestmann strategy^{572,573} has been used to turn **565** into **610** in presence of **609** in a satisfactory yield¹²⁷ (the same molecule was obtained with a classical Sonogashira coupling of silyl-protected acetylene with **396**, followed by silane deprotection); the yield (2 steps from **396**) was not significantly improved, making the Ohira-Bestmann strategy advantageous). Interestingly, a few articles report on difficulties to “click” azide derivatives on phen derivatives like **610** because the copper(I) ion catalyst is coordinated by phen rather than by the triple bonds.^{32,127,574,575} This issue is usually addressed by using a good copper(I) chelator

which will protect the ion from deleterious interactions.^{575–577} Ulven and co-workers used this strategy with the stable copper(II) tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl] amine (TBTA) as pre-catalyst¹²⁷: the TBTA ligand efficiently competes with phen for copper ion coordination. The authors underline the crucial importance of working in a CH₂Cl₂/water biphasic system in order to limit interactions between the water-soluble copper complex and the phen derivative in the organic phase. More information can be found in the review by Meldal and Tornøe.⁵⁷⁴ Finally, Van Leusen conditions applied to **565** in presence of *p*-toluenesulfonylmethylisocyanide **611** have been reported to afford in one step oxazole-functionalized phen **612**. This molecule has been demonstrated to show a strong binding to DNA G-quadruplex, allowing to discriminate different structures.⁵⁷⁸



Scheme 103. Other examples of condensation reactions on **565**

358 and 552 are strong electrophiles at the level of the nitrile groups, which are prone to react with many different nucleophiles. Hydrazine is one of the most frequently used nucleophiles in this context. For example, when **358** is reacted with excess hydrazine in boiling ethanol, a phen dimer linked by a tetrazine **614** (Scheme 104A) is obtained after aromatization.²⁸⁸ When similar mixtures are abandoned at room temperature for several days, acyclic hydrazones are formed (e.g. **615** from **567**, Scheme 104B). The reaction is sluggish because of the low solubility of **358** and **567** in ethanol.⁵³³ Replacing the latter by DMSO or slightly increasing the temperature to 40 °C⁵⁷⁹ greatly improved the kinetics (from 14 days to a few hours⁵³³). Condensation reactions of **615** with various symmetric 1,2-diketones (R-C(O))₂ yields 2,9-bis(1,2,4-triazin-3-yl)-phen derivatives, like BTPhen (from diketone **617**, Scheme 104B) which is an efficient chelate able to selectively complex some actinides vs. lanthanides, facilitating their extraction from radioactive waste water.¹² Many different 1,2-diketones have been used^{159,579-581}, in various refluxing solvents (THF,^{12,159,533} NMP,⁵⁷⁹ AcOH⁵⁸²).



Scheme 104. Other examples of condensation reactions on **358** and **567**

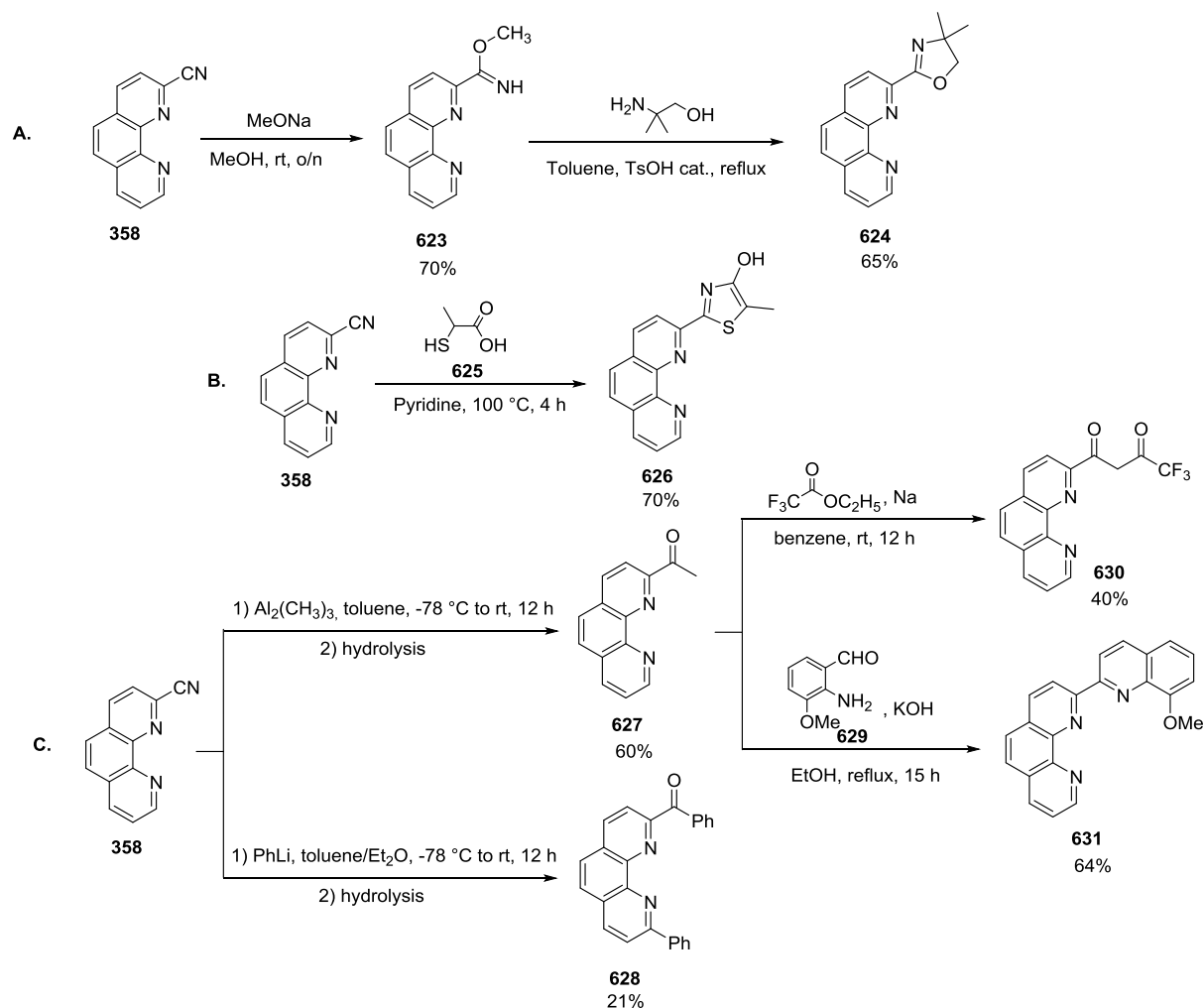
Aromatic diamines can condense on **358** in harsh conditions (high temperature, strong acidic medium) leading to conjugated benzimidazole phen derivatives⁵⁸³ used as DNA intercalators (**618** and **619**, Scheme 104C). Incidentally, similar molecules can be obtained in the same conditions from **44**.⁵⁸⁴ However, similar structures can be reached using different and milder methods (see Scheme 101). Bubbling H₂S in a NH₃-saturated ethanolic solution of **358** at reflux temperature leads to thioamide derivative **620** (Scheme 104D).⁵⁸⁵ The latter can be used as a tricoordinating ligand for Fe(II) where the sulfur atom is involved in the coordination sphere. Incidentally, the nitrogen atom of the thioamide function of **620** shows a nucleophilic character and the condensation of β -bromoketones like **621** yields **622** after a

favorable cyclization step.^{586–588} The obtained thiazole derivative is a polydentate ligand able to form helicates.

In addition to nitrogen based nucleophiles, oxygen-, sulfur- and carbon-based nucleophiles have been shown to react on the nitrile group of **358** or **567** and afford phen_{(2)sub} or phen_{(2,9)sub} with interesting functionalities. For instance, sodium methanolate attacks **358** to give **623**,⁵⁸⁹ which proves to be a valuable intermediate to synthesize the oxazole **624**⁵⁹⁰ or oxazolidine phen derivatives (Scheme 105A).¹⁴⁷ Similarly, the action of thiol **625** on **358** affords thiazole-phen derivative **626** after intramolecular cyclization (Scheme 105B).⁵⁹¹

Organoaluminium Al₂(CH₃)₆ and organolithium reagents PhLi can react on the electrophilic nitrile group of **358** (Scheme 105C). Methylation of **358** by trimethyl aluminium Al₂(CH₃)₆ followed by hydrolysis allows to synthesize the ketone **627**. The synthesis of this same molecule has been proposed by Case and Schilt in 1979 using a Claisen condensation of the methylester **593**.^{497,552} Incidentally, similar functionalization of **396** (ketone formation) by a Stille cross-coupling has been described earlier (Scheme 72, molecule **414**) with a lesser yield. Incidentally, **627** (and **414**) has proven to be an interesting building block. A variety of amines^{551,592,593} have been condensed on **627** and the resulting phen_{(2)sub}-imine adducts behave as interesting tridentate chelates, terpy analogues used to prepare Fe or Co catalysts. Besides, due to the extended conjugation of the π electrons all over the molecular skeleton of **627**, the methyl group of the acetyl moiety can be easily deprotonated. For instance, in presence of sodium at 0 °C, **627** deprotonates and the resulting carbanion adds on ethyl 2,2,2-trifluoroacetate leading to **630** after EtO⁻ elimination. Finally, Thummel and coworkers have used the peculiar reactivity of **627** (and **414**) with α,β -amino-carbaldehyde aromatic compounds such as **629** in the frame of the Friedlander reaction (see Convergent methods section). The hybrid molecule **631** featuring the coordination capacity of phen and of hydroquinoline has thus been obtained in just one step from **627** (Scheme 105C).²⁹⁵ PhLi not

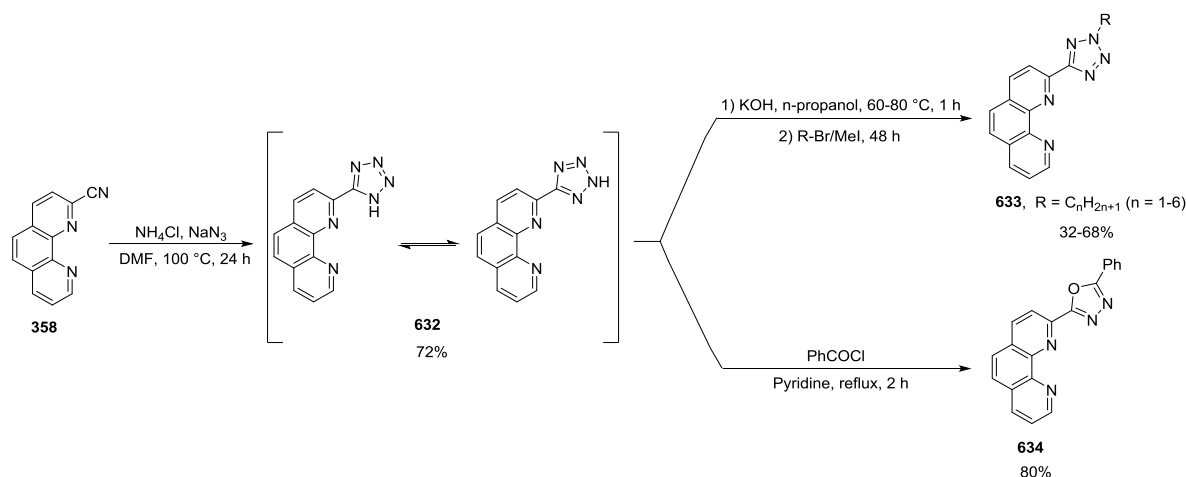
only attacks the electrophilic nitrile group, but the free C₉ position on phen too, as exposed in section 3.1.1. The net result of the reaction after hydrolysis is the formation of ketone **628** (Scheme 105C).



Scheme 105. Reaction of oxygen-, sulfur- and carbon-based nucleophiles on **358**

Other reactions than nucleophilic additions have been reported. In particular, 1,3-dipolar addition of sodium azide NaN_3 on **358** affords **632** with yields between 51%⁵⁹⁴ and 72%⁵⁹⁵ (Scheme 106). **632** can be deprotonated by a simple base (e.g. triethylamine) and used as a tridentate negatively charged ligand for lanthanides⁵⁹⁶ or Pb^{2+} .⁵⁹⁷ **632** can be further decorated with alkyl chains of various lengths in presence of the appropriate alkyl halides. Interestingly, only the 2-regioisomers **633** are obtained, probably for steric reasons.⁵⁹⁴ Fe complexes built

from neutral tridentate ligand **633** feature spin cross-over properties. Alternatively, reacting **632** with benzoyl chloride leads to **634** used as NNN tridentate ligand for lanthanide ions.^{595,596}

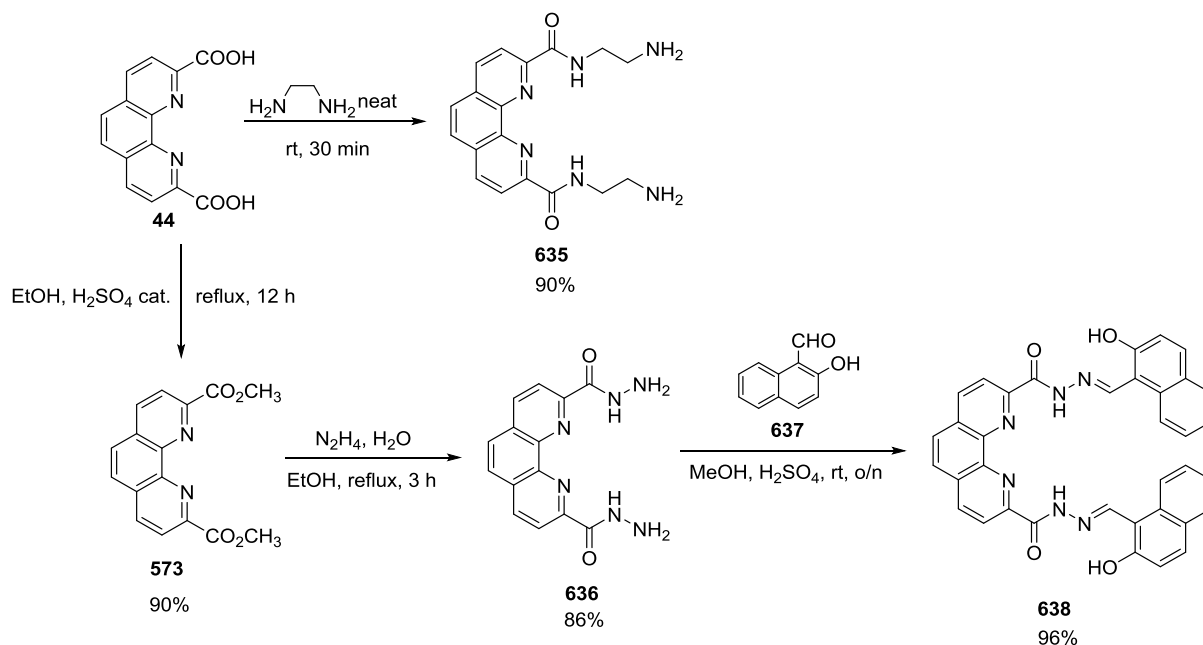


Scheme 106. 1,3-dipolar addition of NaN_3 on **358** and subsequent chemical transformations

All the reactions which have been presented in this section on **358** work *a priori* on **567**, and conversely.

Starting from 44 and 587, the most frequently used method to decorate phen in position 2 or positions 2 and 9 relies on the formation of esters, amides and hydrazides (Scheme 107). For example, stirring a mixture of **44** in neat ethylenediamine at room temperature allows to isolate diamide **635** with pendant reactive amine functions which were used to generate large supramolecular arrays.⁵⁹⁸ Nevertheless, in the most frequent situations, activation of the carboxylic functions is necessary to afford the target compounds in good yields. There are different activation methods. Simply, the methyl ester derivative **573** (obtained from **44** in boiling ethanol) reacts readily with hydrazine hydrate to give hydrazide **636**.⁵¹⁹ The latter condense on aldehyde **637** to afford hydrazone **638**, a performant chelator for the chromogenic sensing of thorium. Other hydrazones were prepared in the same fashion for

applications in anti-cancer G-quadruplex-targeting drugs⁵⁹⁹ and hydrazide **636** was used itself as potent anti-cancer agent (along with bismethylester **573**).⁶⁰⁰

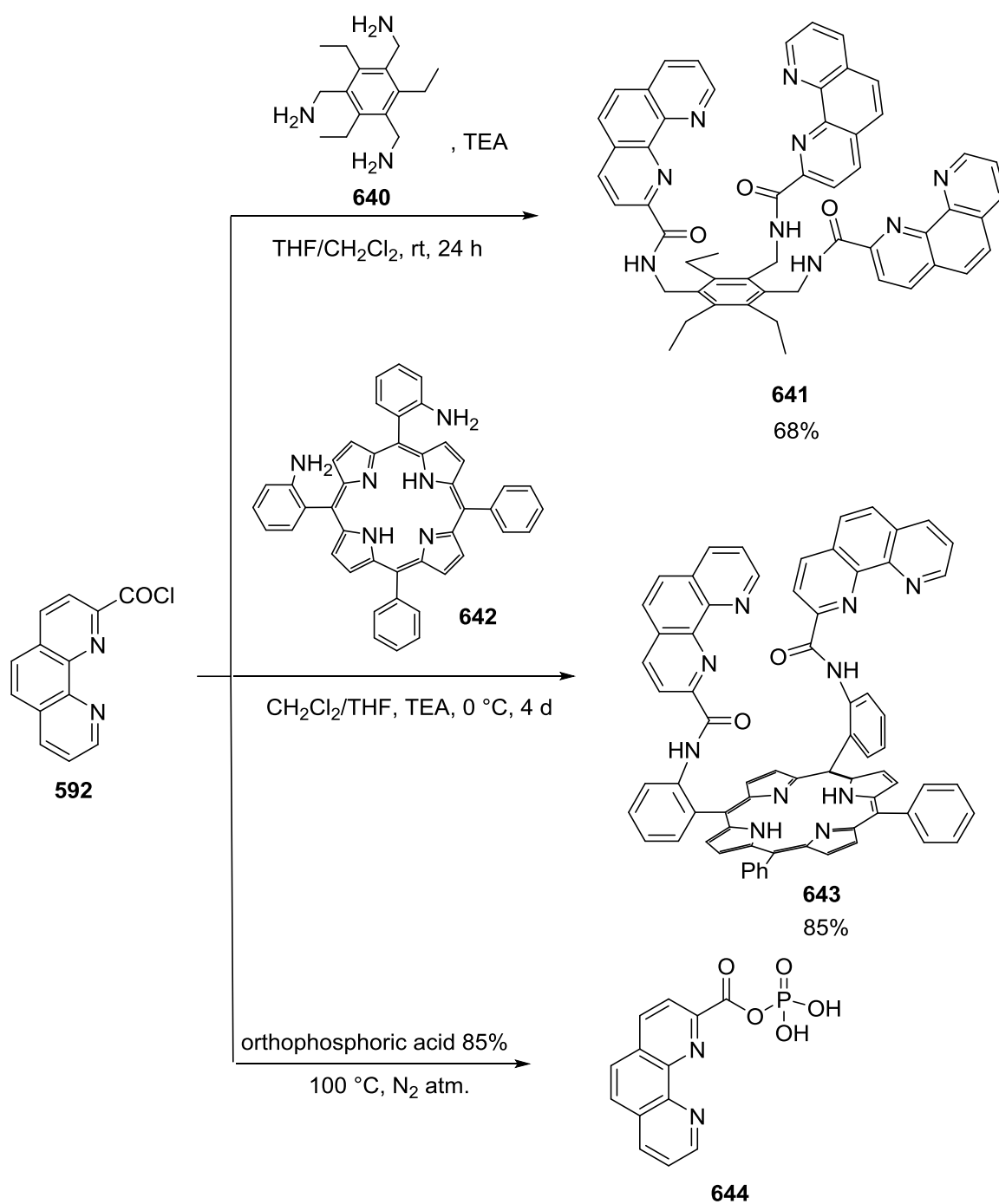


Scheme 107. Formation of amides and esters from **44**

An interesting template synthesis of dimethyl ester **573** has been published too, where refluxing **44** in methanol and in presence of iron(II) perchlorate affords complex $[\text{Fe}(\mathbf{573})_2]^{2+}$ with a yield of 74%.⁵²⁷ Incidentally, the latter features an unexpected structure, where the iron ion is octa-coordinated by two **573** ligands *via* the chelating N $\widehat{\text{N}}$ cavities and the oxygen atoms from the C=O bonds.

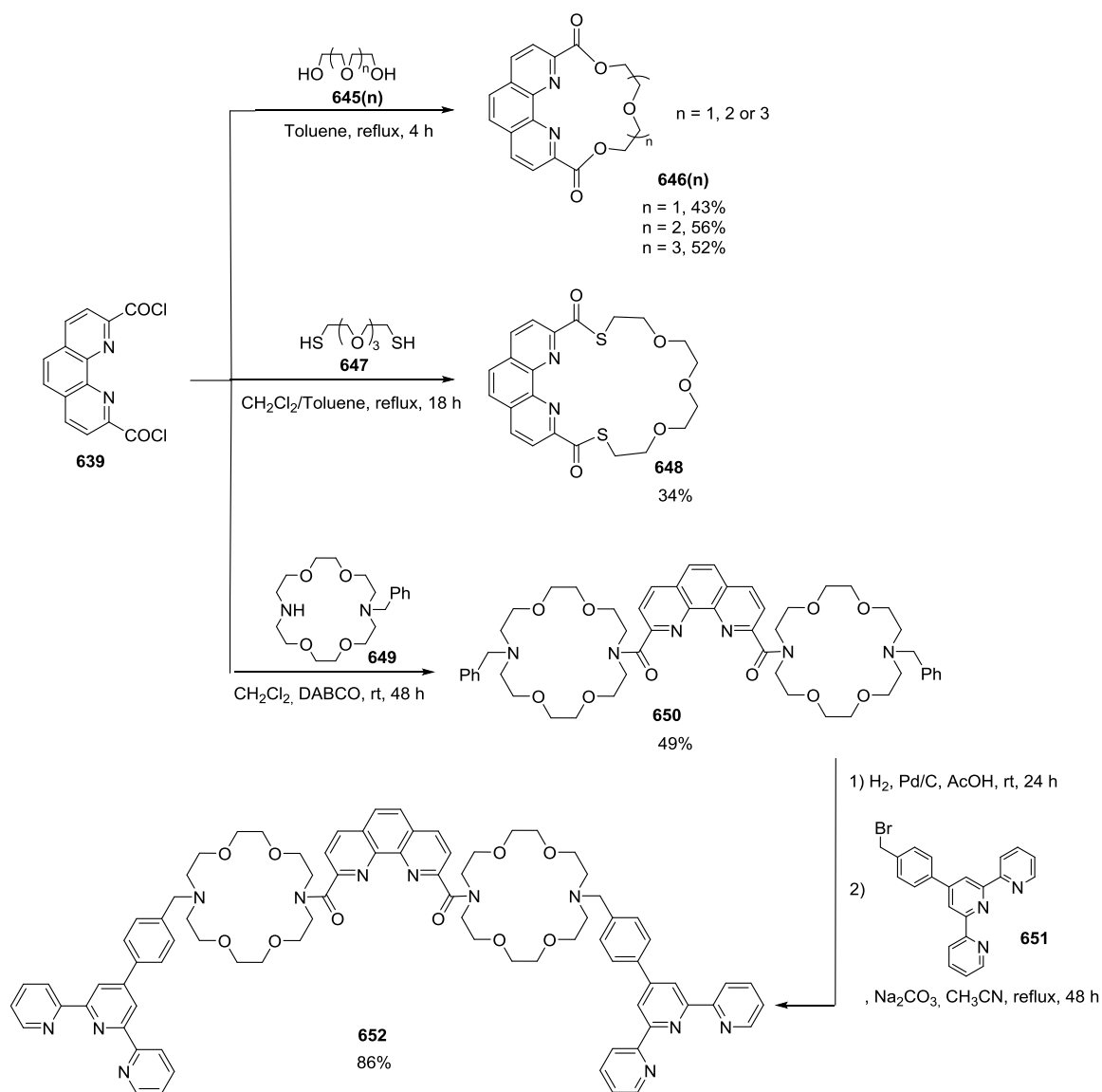
The most common activation method is the formation of the acyl chlorides **592** and **639**. These very reactive reagents are usually not isolated and prepared from **44** and **587** in refluxing SOCl_2 .^{552,601–604} Esterification and amidation reactions proceed smoothly by mixing **592** or **639** with alcohols and aliphatic or aromatic amines. Among the numerous examples that can be found in the literature, phen trimer **641** (obtained from **592** and **640**)⁶⁰⁵ or porphyrin **643** (Scheme 108) stand out because they are impressive structures rather easily

prepared. Porphyrin **643** is capped with pendant phen ligands, obtained in high yield from the pure α,α atropisomer of amino-porphyrin **642**. Complexation of **643** with Fe(II) affords an efficient catalyst for the O₂ reduction reaction, where the phen units form a pocket for the water molecules involved in the catalytic process, through a network of H bonds.⁶⁰⁶ Original esters can be synthesized too from **592**, like phosphate ester **644** obtained by heating the acyl chloride in orthophosphoric acid.⁶⁰³



Scheme 108. Formation of amides and esters from acyl chloride **592** obtained from **587**

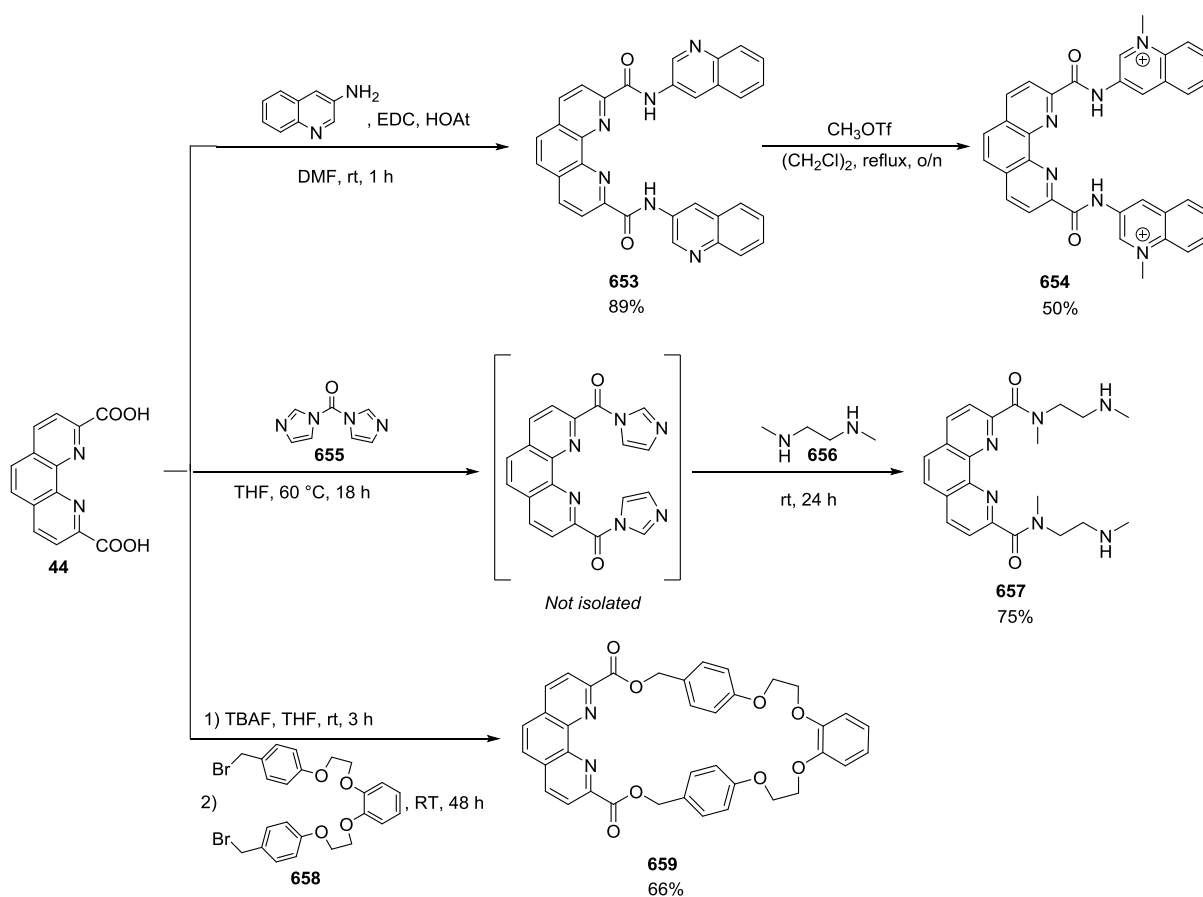
The formation of macrocycles is particularly well exemplified when reacting di-alcohols,^{602,607} dithiols⁶⁰⁸ or diamines⁶⁰¹ on **639**. A few examples are given in Scheme 109. Di-ester^{602,607,609} like **646(n)** ($n = 1-3$) or di-thioester⁶⁰⁸ **648** or amide⁶⁰¹-based macrocycles have been easily synthesized in respectable yields from **639** and α,ω -diols or dithiols or diamines, respectively (we underline the fact that those reactions are performed in high dilution conditions, as usually required to favor the intramolecular cyclization reaction vs. polymerization). The last examples illustrate well the fact that very extended phen based structures can be easily reached with simple chemical steps. An impressive hetero-tritopic ligand **652**, combining terpy, N_2O_4 crown ether and phen coordination cavities, has been synthesized in 42% yield from **639**.⁶¹⁰



Scheme 109. Formation of macrocycles from the bis-acyl chloride **639** of **44**

Peptide coupling agents are fully compatible with **44** and **587** (Scheme 110). In particular, the very practical EDC coupling (and variants) was successfully used in a number of reactions in presence of additional activators like HOAt¹²⁸ and HOBt.^{609,611,612} For example, 3-aminoquinoline is efficiently connected to **44** *via* the formation of an amide bond.¹²⁸ Incidentally, quinolines on **653** were quaternized in presence of excess methyl triflate MeOTf while the nitrogen atoms of phen are untouched, possibly because of steric issues. Alternative activation modes of **44** towards esterification and amidation reactions can be found, where

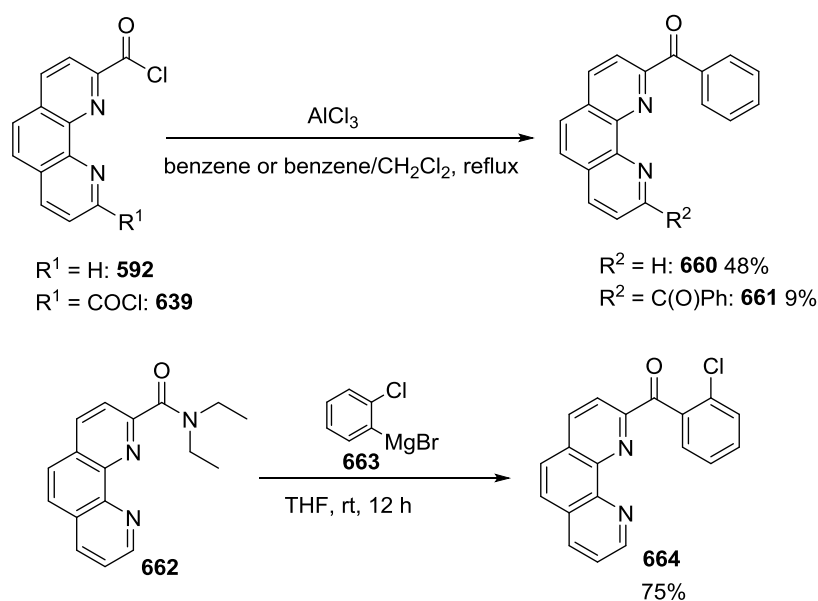
EDC is for example replaced by urea derivative 1,1'-carbonyldiimidazole **655**.⁵³¹ Fluoride anions (e.g. TBAF) are known to activate carboxylic acids by forming a very reactive carboxylate which can easily perform nucleophilic substitution on convenient organic halides.⁶¹³ This strategy was successfully applied to the case of **44** and dibromo derivative **658** leading to macrocycle **659**.⁶¹⁴



Scheme 110. Formation of macrocycles from **44**

Other types of functionalization than (thio)ester or amide bonds forming can be achieved from carboxylic acid derivatives **44**, **587** and their derivatives (Scheme 111) like Friedel and Craft acylation of benzene using **592** or **639**⁶¹⁵ leading to **660** and **661** respectively, the very different yields could be grounded in the slightly different conditions used, as well as the larger steric hindrance of **639** vs. **592**. Finally, subjecting amide-derivatized phen_{(2,9)sub} to

organolithium⁶¹⁶ or Grignard reagents⁶¹⁷ (cf. the addition of **663** on **662** leading to **664**, Scheme 111) leads unsurprisingly to ketone derivatives.

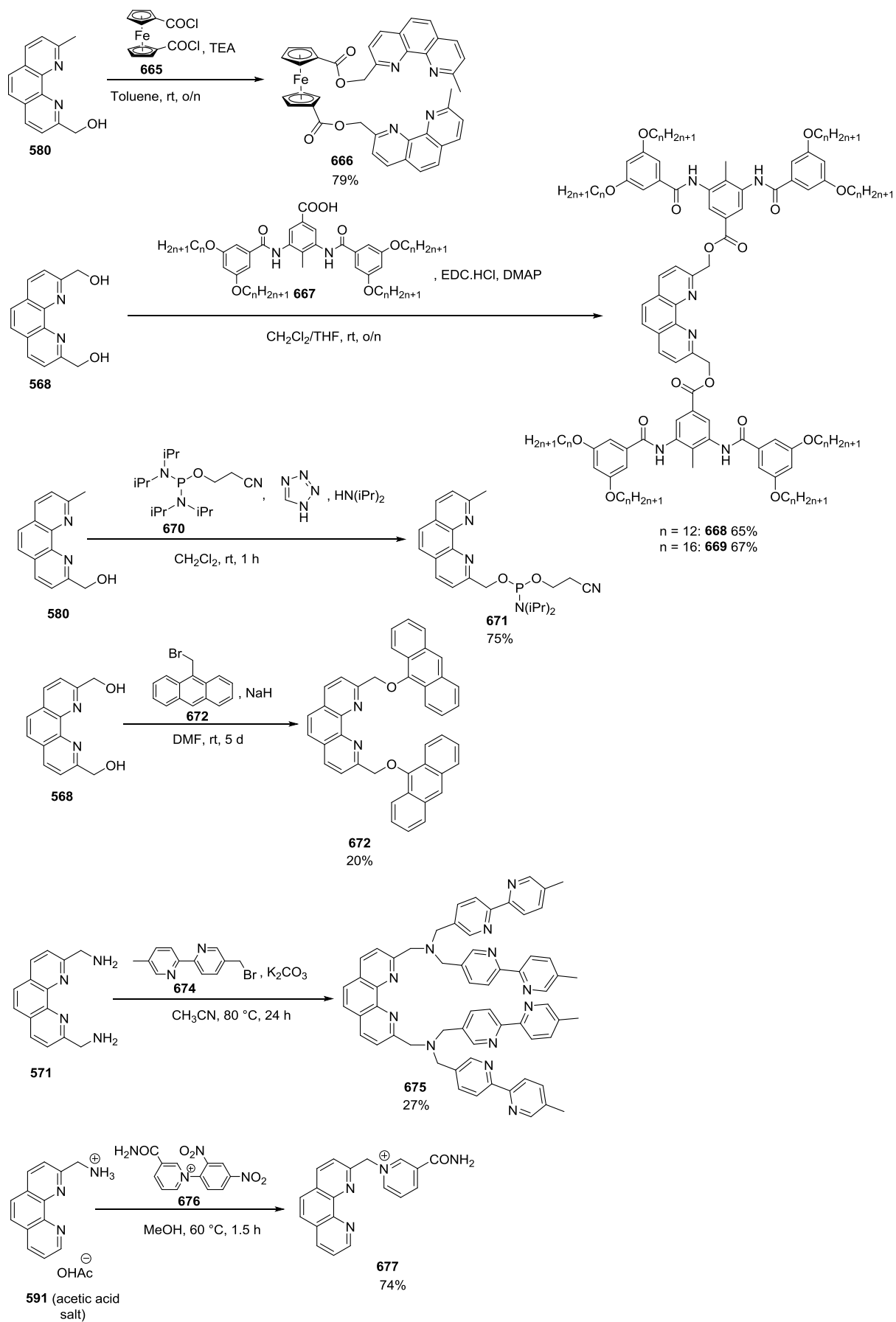


Scheme 111. Alternative methods to functionalize derivatives of **44**

Synthons 568, 588, 571, 580 and 591 behave basically like benzylic alcohols and amines, namely as powerful nucleophiles (Scheme 112). **568**, **580** and **588** have been used in esterification reactions and in nucleophilic substitution. For example the redox active face-to-face phen dimer **666** was obtained by reacting the acyl chloride derivative of 1,1'-bis(chlorocarbonyl)-ferrocene **665** with **580**.⁶¹⁸ The EDC-coupling of **568** (or **580**) with carboxylic acid **667** affords phen_{(2,9)sub} derivatives **668** and **669** with liquid-crystalline properties.⁶¹⁹ Practical phosphoramidite coupling (usually employed for the hybridization of nucleosides)⁶²⁰ has been applied to **580** giving **671** and allowing to incorporate this ligand in an oligonucleotide sequence.⁶²¹

Finally, **568** can be deprotonated (e.g. by NaH) and the alcoholate can substitute the bromine atom on anthracene-methylbromide **672** leading to the phen-anthracene adduct **673**; the corresponding copper(II) complex has been designed for DNA photo-cleavage under UV light.⁵³¹

Amines **571** and **591** have been comparatively less used than the alcohol parent molecules. The reason behind this could be that the synthesis of **571** and **591** are long multi-step procedures, and that similar structures, namely phen_{(2,9)sub} and phen_{(2)sub} where the substituents in positions 2 or 2 and 9 are -CH₂-NH-R (R = any functional group) can be reached with different, less cumbersome methods (e.g. imines reduction, see Scheme 101). Nevertheless, peptide coupling of **591** with acyl chlorides has been reported.^{622,623} Repeated nucleophilic substitution steps occur when electrophilic brominated bpy **674** is put in presence of **571** leading to an extended polypyridine ligand **675** featuring five chelating sites.⁶²⁴ Finally, an original coupling reaction of pyridinium **676** on **591** affords pyridinium **677**⁶²⁵ which, after reduction by dithionite, affords interesting phen-NADH models (Scheme 112).



Scheme 112. Examples of functionalization reactions on OH and NH₂ bearing neocuproine derivatives **568**, **580**, **571** and **591**.

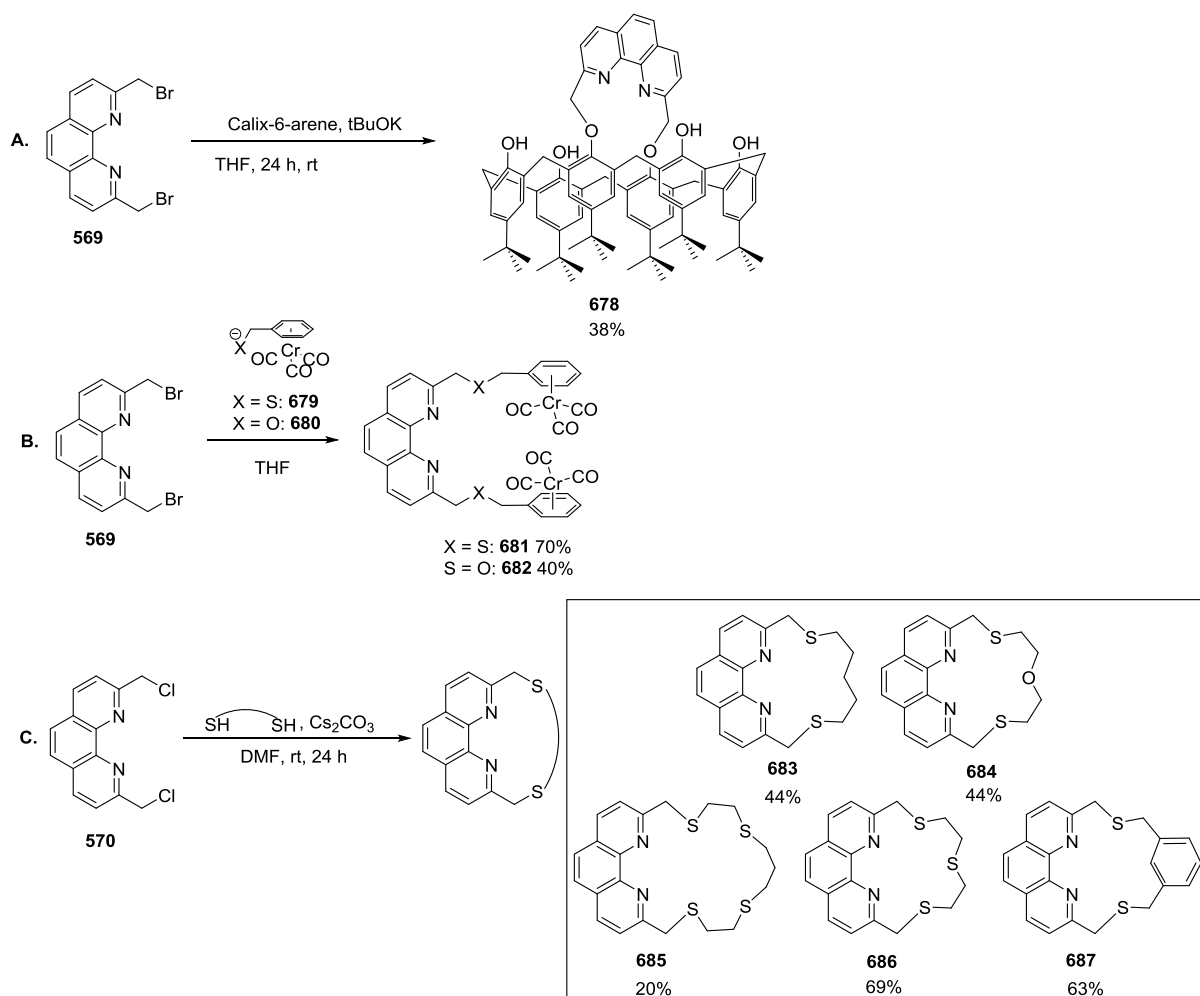
Phen_{(2,9)sub} derivatives 589-590, 569-570 bearing halogeno methyl groups in positions 2 or 2 and 9 are extensively and exclusively used as electrophiles in a great number of reactions

involving nucleophilic attacks, leading to the formation of C-O, C-S, C-P and C-C bonds.⁶²⁶⁻

⁶²⁸ A few selected examples are given in the next paragraph (Scheme 113).

When two diametrically opposed alcohol groups on a calix-6-arene⁶²⁹ and calix-8-arene⁵³⁵ are deprotonated (respectively by potassium *tert*-butanolate and CsF), substitution of both bromine atoms on **569** leads to phen-capped calixarenes (e.g. **678**) combining the abilities of calixarene and phen to respectively accommodate several molecular hosts and a great many different metal ions (Scheme 113A). Those scaffolds are used as nano-reactors for the catalytic formation of C-S bonds for example.⁶³⁰ As far as we can tell, C-O bond formation through the nucleophilic attacks of alcohols or alcoholates on **570** or **559** have never been published. The brominated molecules **569** or **590** are always used instead, probably because Br⁻ is a better leaving group than Cl⁻.

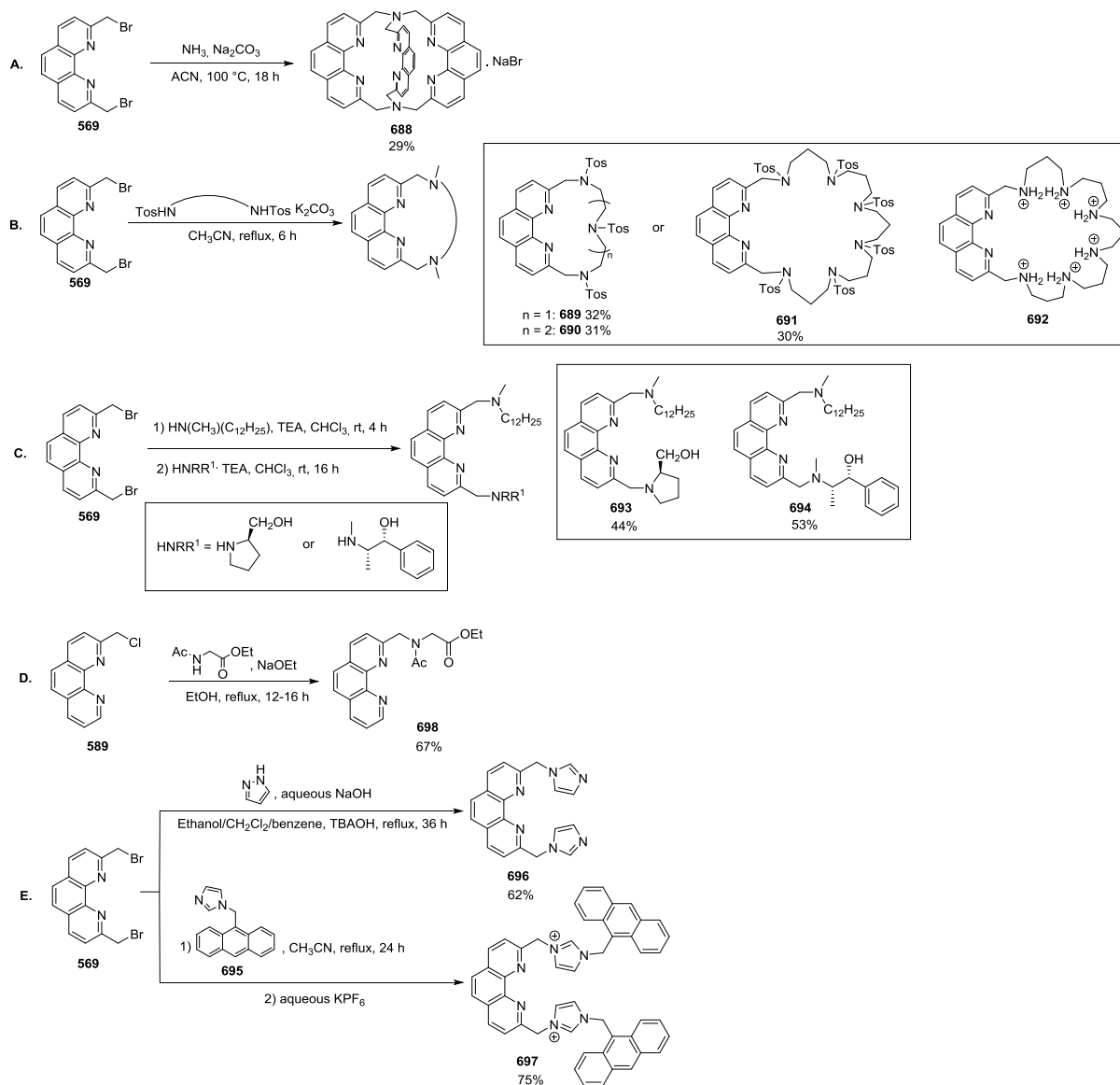
Bromine in **569** is readily substituted by thiolate **679** to give thio-ether derivative **681** (Scheme 113B).⁶²⁷ Interestingly, the same reaction with the alcoholate version of thiolate **679** affords the target etheroxide but with a significantly lesser yield. Again, this is probably due to the stronger nucleophilic character of thiolates *vs.* alcoholates. The stronger nucleophilicity of thiolates allows to use less reactive **570** as electrophile. For example, mixing **570** with dithiolates affords a family of macrocycles with various sizes **683-687**, able to accommodate distinct ions and acting as fluorimetric chemical sensors for Cu(II), Zn(II), Pb(II), Cd(II), Ag(I), and Hg(II) ions (Scheme 113C).⁶³¹⁻⁶³⁶



Scheme 113. Examples of functionalization reactions of **569** and **570** with alcohols and thiols

Aliphatic amines have been amply used as nucleophiles on **569-570** and **589-590** (Scheme 114).^{539,637-640} The reaction between ammonia and **570**⁶³⁷ affords a phen trimer kryptand **688** in simple conditions with the help of sodium ions as templating agents (Scheme 114A). Other large macrocyclic structures such as **689**, **690** or **691** have been prepared in presence of tosylated diamines (Scheme 114B). The corresponding macrocycle exhibits a strong chelating ability towards metal cations (Pb^{2+}).⁶³⁸ In addition, at pH below 6.9, the hexaprotonated macrocycle **692** features a strong affinity for phosphate anions;^{639,640} in combination with the fluorescence properties of phen, this makes **692** an interesting fluorescent probe for ATP.

It is worth mentioning that **569** can be functionalized in one pot by two different amine nucleophiles. This strategy was applied by Engbersen and co-workers¹⁴⁵ to design lipophilic phen ligands **693** and **694** bearing a fatty C₁₂H₂₅ alkyl chain and chiral copula in positions 2 and 9 respectively (Scheme 114C). Those ligands were used to prepare useful metal complexes in the field of asymmetric catalysis in micellar medium. Finally, rarer aminated nucleophiles like deprotonated glycine are worth to mention, and known to react on **589** to afford e.g. **698** (Scheme 114D). Nucleophilic attacks of **569** by sp₂ amines are reported too. For instance, **696** is obtained by refluxing **569** with pyrazole in a complex mixture of ethanol, benzene, dichloromethane and aqueous NaOH (Scheme 114E).⁵¹⁶ The reaction medium is biphasic and tetrabutylammonium hydroxide is thus used as phase transfer agent.

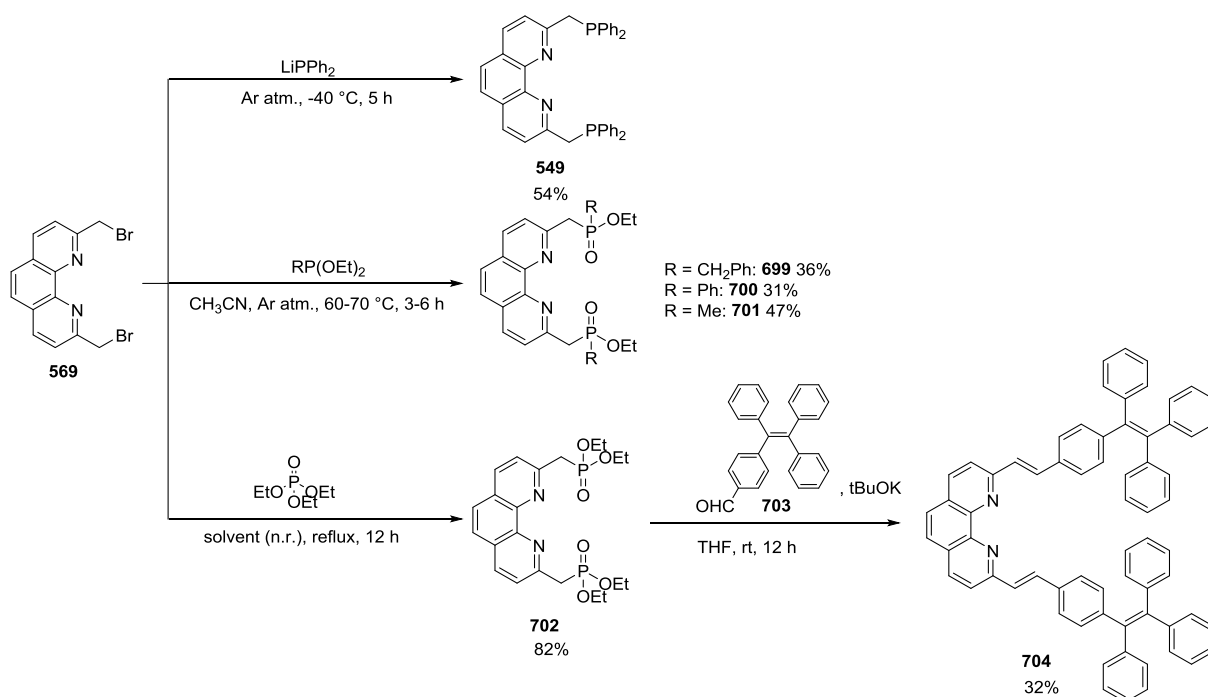


Scheme 114. Examples of functionalization reactions of **569** and **589** with amines

When anthracenyl-imidazole **695** is reacted with **569**, the fluorescent phosphate chemosensor **697**⁶⁴¹ is isolated (the presence of H_2PO_4^- anions freezes the imidazolium moieties in such a conformation that the two anthracene chromophores are brought face-to-face leading to excimer formation and quenching of the fluorescence).

C-P bonds can be formed too when phosphorus nucleophiles are reacted with **569**^{541,642} or **570**⁶⁴³ (Scheme 115). For example, addition of PPh_2Li (generated from lithium on triphenylphosphine in THF ⁴⁹²) on **569** affords N_2P_2 pincer ligand **549**,⁵⁴¹ while the simple

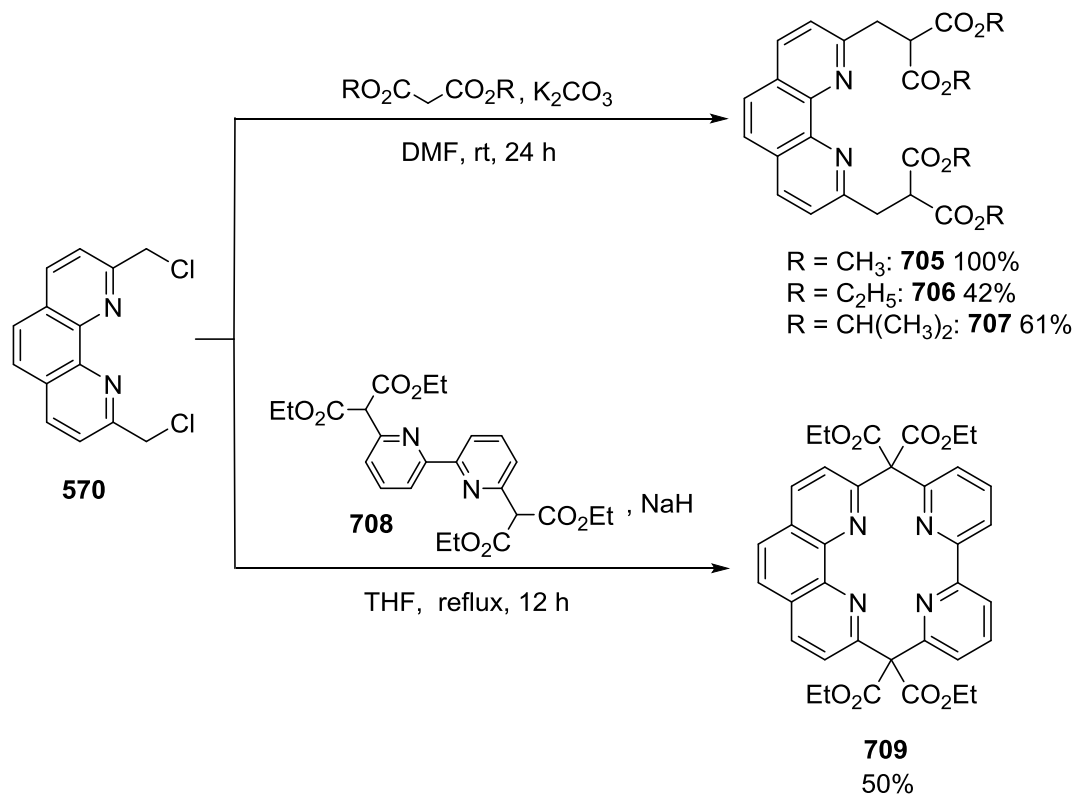
Arbuzov reaction between phosphine $\text{RP}(\text{OEt})_2$ ($\text{R} = \text{Me}, \text{Ph}, \text{or } \text{CH}_2\text{Ph}$) and **569** gives **699-701**.⁵⁴¹ In the two previous examples, the appended phosphorus moiety was used to complete the coordinating ability of phen. On the other hand, Yam and co-workers have reported the formation of **702**⁶⁴² as an intermediate for a subsequent Wittig-Horner reaction with aldehyde **703** in presence of potassium *tert*-butanolate leading to highly conjugated **704**. This method interestingly complements the one exposed above in Scheme 94.



Scheme 115. Examples of functionalization reactions of **569** with phosphorus bearing nucleophiles

The formation of C-C bonds from **570** is not very common (Scheme 116). The carbanions obtained by deprotonation of malonate esters (by NaH in THF ⁶⁴⁴ or K_2CO_3 in DMF)⁶⁴⁵ have been successfully used as nucleophiles with **570**.⁶⁴⁵ Interestingly, the nature of the substituent on the malonate impacts strongly the yields of the reactions (100% yield is reported for $\text{R} = \text{CH}_3$, and drops to 42% only for $\text{R} = \text{ethyl}$). This result is not commented but could be due to

steric effects). In addition, Using the acidity of the malonates and their derivatives like **708** has allowed to prepare the mixed phen-bpy macrocycle **709**,^{523,644} in high dilution conditions.



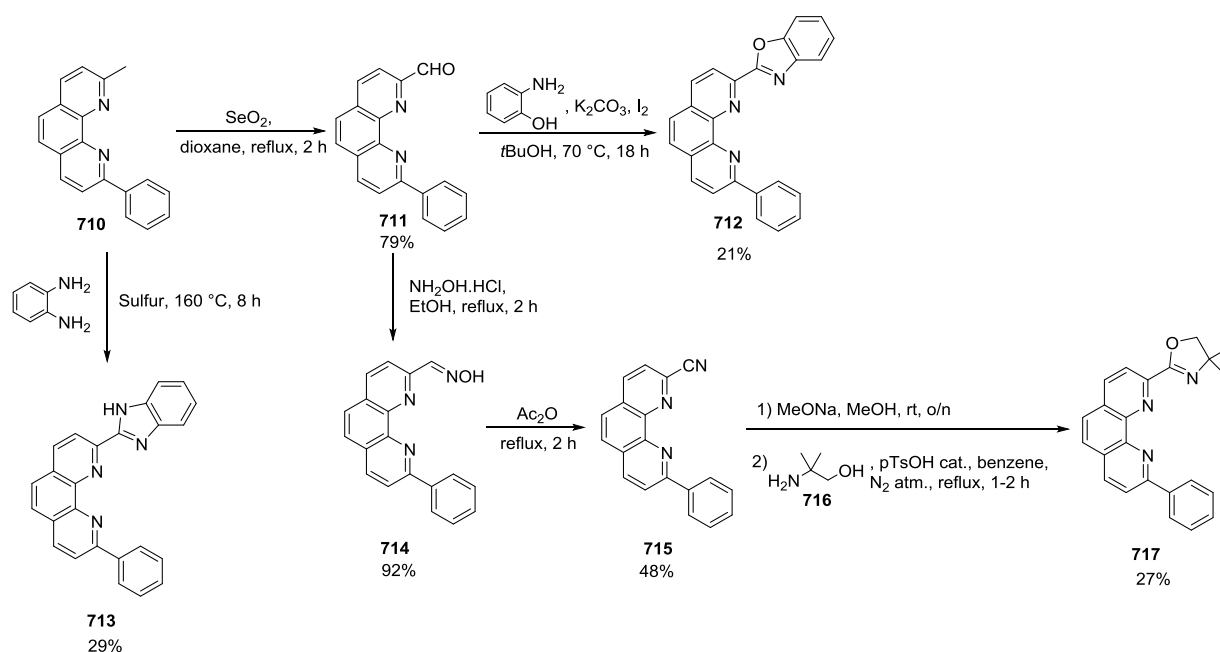
Scheme 116. Examples of functionalization reactions of **570** through Knoevenagel reactions

The brominated or chlorinated derivatives of neocuproine both feature a high reactivity. Choosing one over the other is quite empirical but will depend on the reactivity of the nucleophile. In some instances, the tosylate derivatives of **568** is preferred to **569** or **570**.^{646–648} The tosylate is an excellent leaving group, justifying the use of such intermediate.

3.1.5. Concluding remarks

In the above sections, we have described the overall strategies to reach crucial phen_{(2,9)sub} and phen_{(2)sub} molecular bricks, from phen and neocuproine. The diversity of possible phen derivatives is so large that we had to overlook a few particular examples. For instance, **710**

which synthesis is based on the successive attacks of MeLi and PhLi on phen (see section 3.1.1) features the typical reactivity of **108**. Therefore, mono-aldehyde **711** has been obtained in high yield from **710** and has been used to reach molecules **712-715** following traditional reaction conditions that we presented above for symmetrical **565** (Scheme 117).⁶⁴⁹

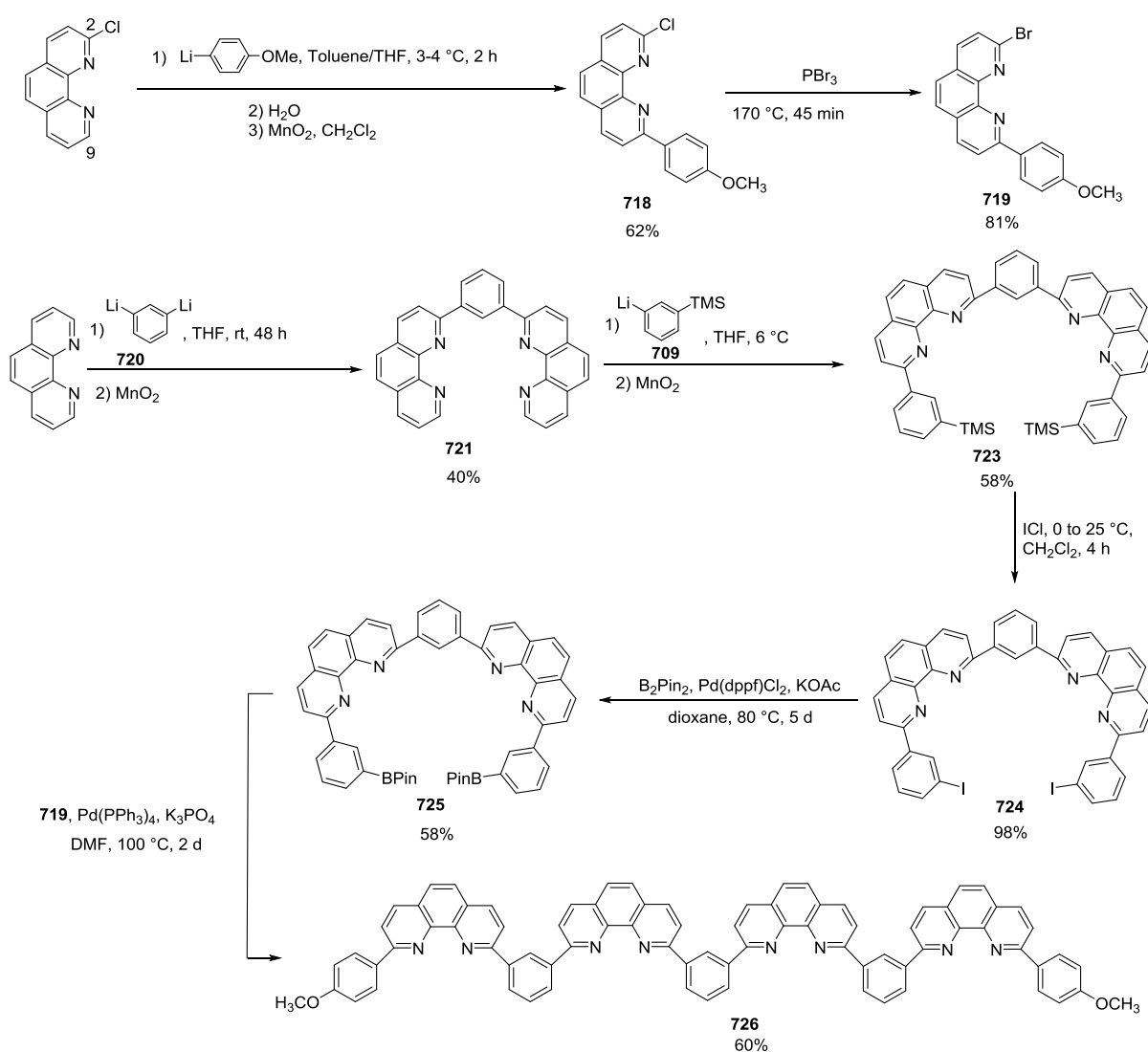


Scheme 117. Examples of functionalization reactions of phen in positions 2 and 9 using two different strategies for each position

The same starting compound **710** is used to prepare **713** in presence of aromatic orthophenylenedimaine and sulfur. Interestingly, the reaction is believed to proceed through the *in situ* oxidation of the methyl group into the carboxylic function by sulfur,⁶⁵⁰ a feat worth mentioning since the direct oxidation of the methyl groups on neocuproine and derivatives into carboxylic groups is not straightforward.

In a few cases, non-symmetrical phen have been obtained using simultaneously two different but compatible strategies. A very compelling example has been published by Sauvage and co-workers, where **397** undergoes a nucleophilic addition of anisyllithium in position 9, yielding **718** after rearomatization. Importantly, the authors underline that the C-Cl bond is unaffected

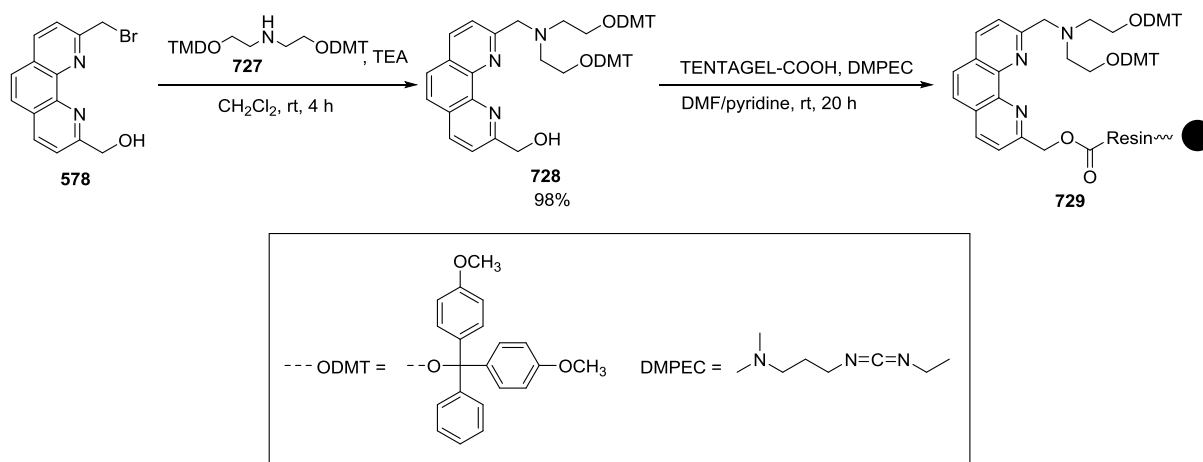
in the presence of the organolithium reagent and no Li/halogen exchange is observed,⁶⁵¹ authorizing further modification of the phen molecular skeleton, as shown in Scheme 118.



Scheme 118. Synthesis of phen tetramer **726** using multiple strategies (organolithium nucleophilic attacks and Suzuki cross-coupling strategies)

In addition, as mentioned above (Scheme 97) derivative **578** exhibits both nucleophilic and electrophilic characters through the CH_2OH and CH_2Br groups, respectively. This feature was exploited to access extended non-symmetrical structures, such as **727**, where Br was first substituted by secondary amine **729** and the remaining OH group was then involved in an

ester coupling with a COOH-functionalized resin in presence of N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (DMPEEC) (Scheme 119).⁵³⁸



Scheme 119. Examples of functionalization reactions of phen_{(2,9)sub} where each substituent bears a different reactivity

3.2. Functionalization of phen in position(s) 3 or 8 / 3 and 8

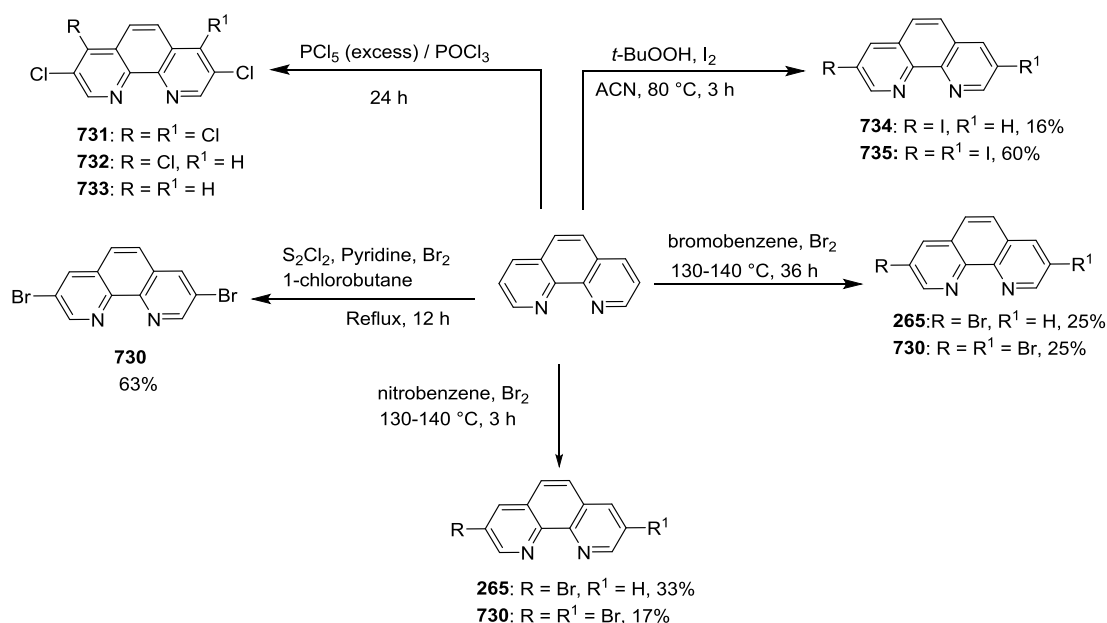
The functionalization of phen in positions 3 and 8 by divergent methods (i.e. from naked phen to phen_{(3,8)sub} or phen_{(3)sub}) is much less documented. The regio-selective halogenation in position 3 or in positions 3 and 8 of phen is the most reported method.

3.2.1. Halogenation of phenanthroline in position 3 or in positions 3 and 8

Substitution at the 3,8 positions will influence the properties of phen without interfering with its coordination ability. Among the different types of functionalization reported in the literature, halogenation of phen is the most important because halogenation on the selected position opens up various possibility of functionalization through aromatic nucleophilic substitutions and above all C-C bond forming reaction such as Suzuki, Stille and other metal catalyzed reactions.

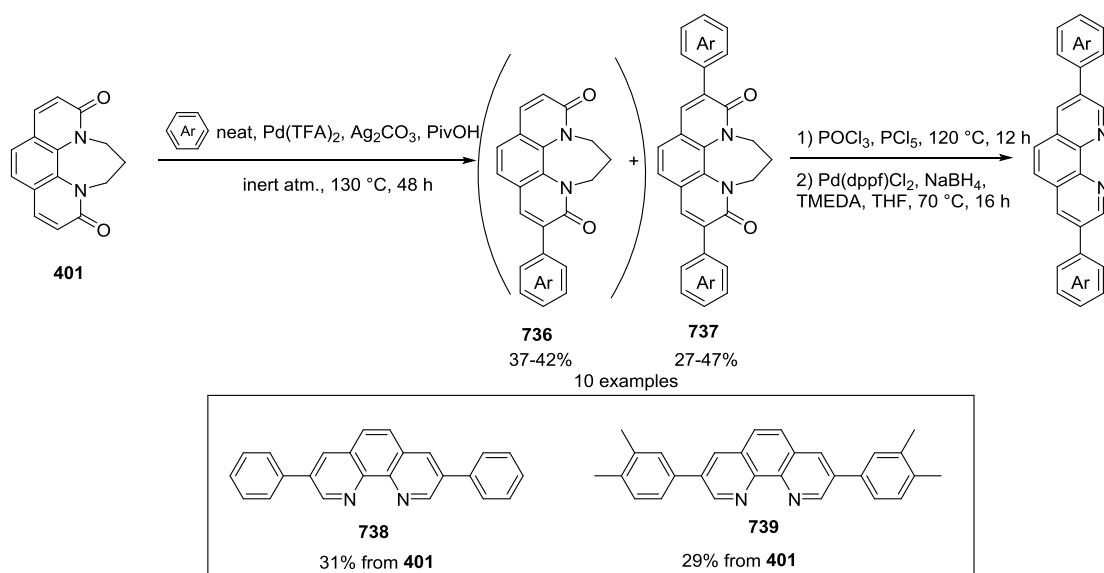
Refluxing phen with an excess of phosphorus pentachloride and phosphoryl chloride for short reaction times affords the chlorinated phen mixtures of **731-733** (Scheme 120).⁶⁵² In a typical

bromination condition, refluxing phen monohydrochloride monohydrate with bromine in nitrobenzene for 3 h gives a mixture of 3-bromo-1,10-phenanthroline (**265**) and 3,8-dibromo-1,10-phenanthroline (**730**) with 33% and 17% yield, respectively (Scheme 120).⁶⁵³ In bromobenzene as a solvent after 36 h, 3-bromo-1,10-phenanthroline (**265**) and 3,8-dibromo-1,10-phenanthroline (**730**) can be isolated, both with 25% yield.⁶⁵⁴ It is mentioned that other brominated phen (3,6-dibromo-1,10-phenanthroline and 3,5,8-tribromo-1,10-phenanthroline) were formed in those conditions but in very small amount. Zhu et al.²⁶³ refluxed the solution for 8 h and added liquid bromine gradually. They obtained 45% yield for compound **730**. Later bromination of phen in presence of S₂Cl₂, pyridine in 1-chlorobutane exclusively gave **730** with 63% conversion yield (Scheme 120).⁶⁵⁵ Iodination of phen in presence of tert-butyl hydroperoxide tBuOOH in acetonitrile medium gave a mixture of 3-iodo-1,10-phenanthroline (**734**) and 3,8-diiodo-1,10-phenanthroline (**735**) with 16% and 60% yield, respectively (Scheme 120).⁶⁵⁶



Scheme 120. Halogenation of 1,10-phenanthroline at 3,8 positions.

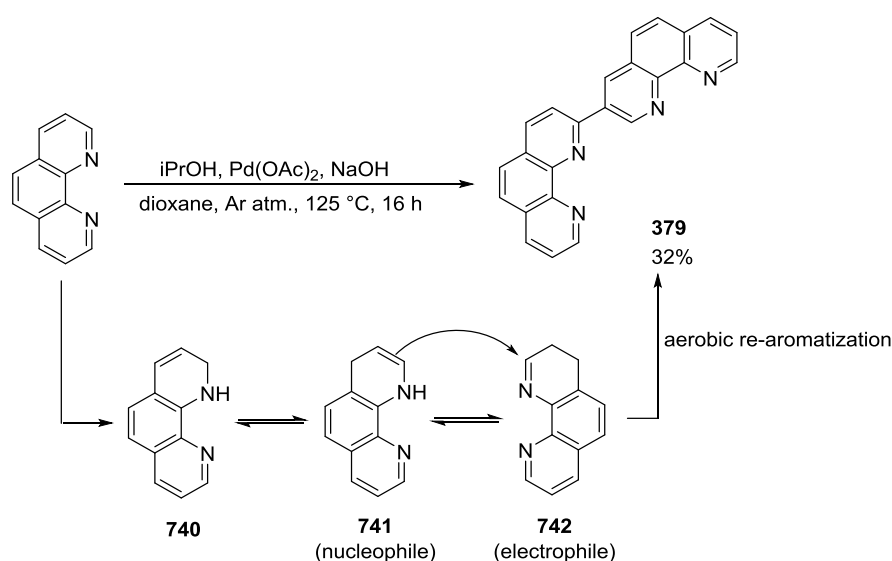
The halogenation (and the bromination in particular) reaction is indisputably the most frequent means to functionalize phen in positions 3 and 8. But an elegant direct C-H arylation of phen by unactivated arenes has been reported too (Scheme 121) by exploiting the reactivity on the N,N'-annelated diketone **401** (presented above as a crucial intermediate to synthesize **396**). Indeed, a series of several arenes has been directly tethered on **401**, in presence of a palladium catalyst and Ag⁺ as oxidants.⁶⁵⁷ Mixtures of mono- and bis-substituted compounds (**736** and **737** respectively) are obtained but can be easily separated by chromatography techniques. Unsymmetrical compounds are within reach too, by performing two subsequent C-H arylation steps. In addition, the reaction is fully operational and regioselective on **736**. Importantly, all the obtained intermediates can be *a priori* transformed into the corresponding phen_{(3,8)sub} ligand, by chlorination and reductive hydrogenation.⁶⁵⁸ The overall yield from **401** is ca. 30% (e.g. for **738** and **739**), which is reasonable given the challenge to functionalize phen in positions 3 and 8.



Scheme 121. Direct C-H arylation of **401** to afford phen_{(3,8)sub}

Finally, Dix-Neuf et al have published a phen dimerization reaction catalyzed by palladium in presence of isopropanol (Scheme 122).⁶⁵⁹ The latter serves a hydrogen donor to form

catalytically active PdH₂ which can reduce phen into amine **740**. The latter has several tautomer forms, among them forms A and B have nucleophile (on C₃) and electrophile (on C₂) characters, respectively. Thus, nucleophilic attack of **741** on **742** leads to phen dimer **379** after re-aromatization, where both positions 2 and 3 of each phen has been functionalized in a respectable yield considering the challenging structure of **379**. We remind that **379** has been presented in the previous section (Scheme 63) but was obtained with a different method, based on the activation of the reactivity of phen by potassium *tert*-butanolate.^{402,660}



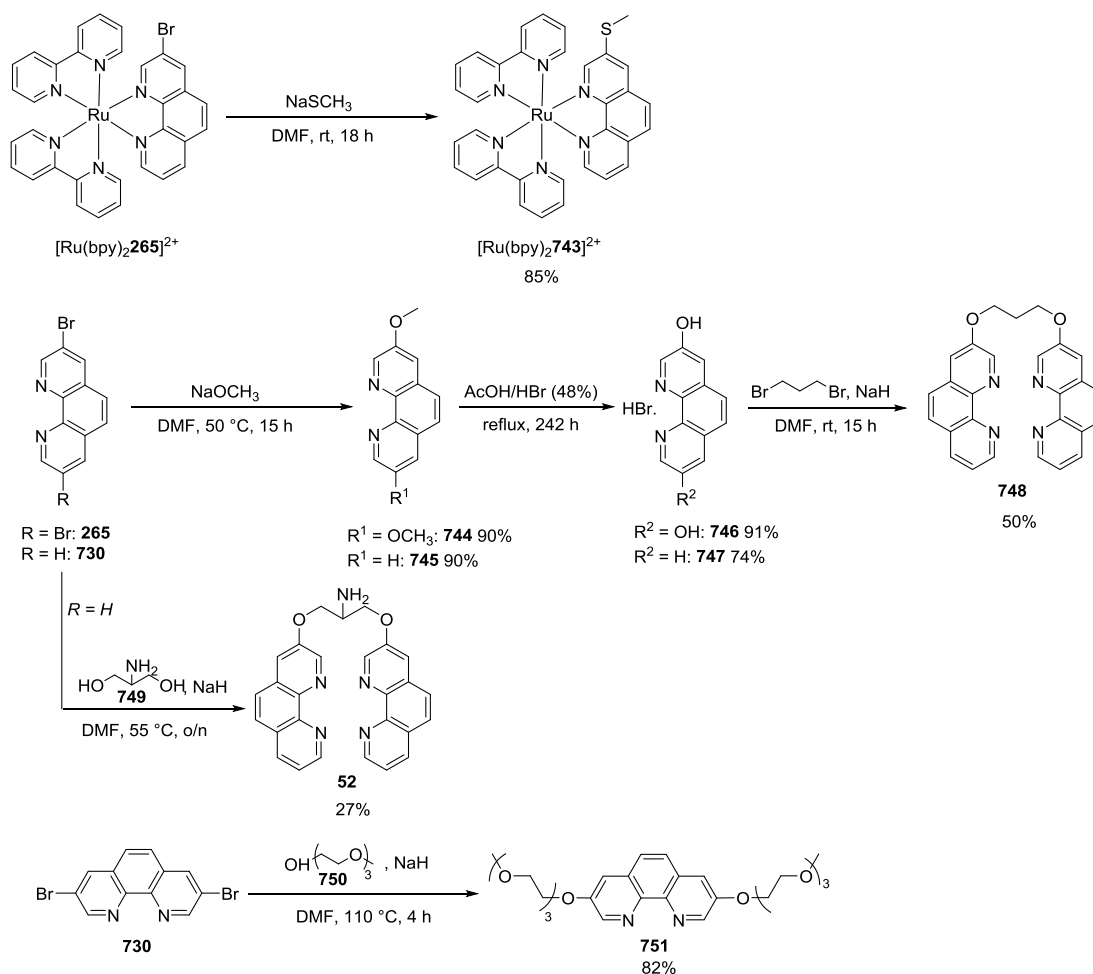
Scheme 122. Regioselective dimerization of phen catalyzed by palladium

3.2.2. Functionalization starting from 3- and 3,8-dihalogenated phen: aromatic nucleophilic substitutions

While positions (2,9) and (4,7) are electrophilic in nature, positions (3,8) are not and aromatic nucleophilic substitutions on **265** and **730** are reputed to be challenging.^{661–663} There are nevertheless a few examples where such reactions have been performed. Tzalis and Tor have pioneered the field by achieving the efficient substitution of Br in complexes $[\text{M}(\text{bpy})_2(\mathbf{730})]^{2+}$ and $[\text{M}(\text{bpy})_2(\mathbf{265})]^{2+}$ ($\text{M} = \text{Ru}$ or Os) by powerful nucleophiles methyl thiolate or fluoride (Scheme 123).^{661,662} In this case however, the C-Br bond is activated

thanks to the presence of the electrophilic ruthenium (or osmium) ion in the N[∧]N cavity of **265**. De-coordinating those inert ions from the chelating cavities is difficult and therefore methods to access more versatile free phen_{(3)sub} from **265** by aromatic nucleophilic substitutions have been implemented.

Meunier and co-workers have reported such method in 2001.⁶⁶³ Reacting **265** or **730** in DMF in presence of freshly prepared sodium methoxide (from NaH and methanol) lead to substituted compounds **744** and **745** respectively with high yields. Interestingly, the methyl groups can be removed affording hydroxy-functionalized phen_{(3)sub} and phen_{(3,8)sub} **746** and **747**. The latter are stable in their protonated forms (deprotonation probably leads to formation of quinone-like compounds). The reactivity of **746** has been further exploited to prepare phen dimer **748**. The same authors have applied their protocol to the preparation of other phen dimers, all prepared from **265** and (α,ω)-diols in presence of NaH^{664,665} e.g. “clip-phen” **52**). Importantly, the authors underline that the same reactions lead on **397** give target compounds with much higher yields,⁶⁶⁵ highlighting (i) the poor reactivity of C_{3,8}-Br with regards to aromatic nucleophilic substitutions, and (ii) the efficiency of the reductive hydrogenation of **265** by NaH as side reaction. Nevertheless, higher yields have been recently obtained for similar reactions, namely the synthesis of amphiphilic ligand **751**, designed for catalytic reactions in biphasic medium,¹⁹⁹ by increasing the temperature to 110 °C. Another method to achieve the aromatic nucleophilic substitution on **730** by sodium methanolate has recently been published by Housecroft, Constable and co-workers,⁶⁶⁶ replacing conventional heating by microwave irradiations.



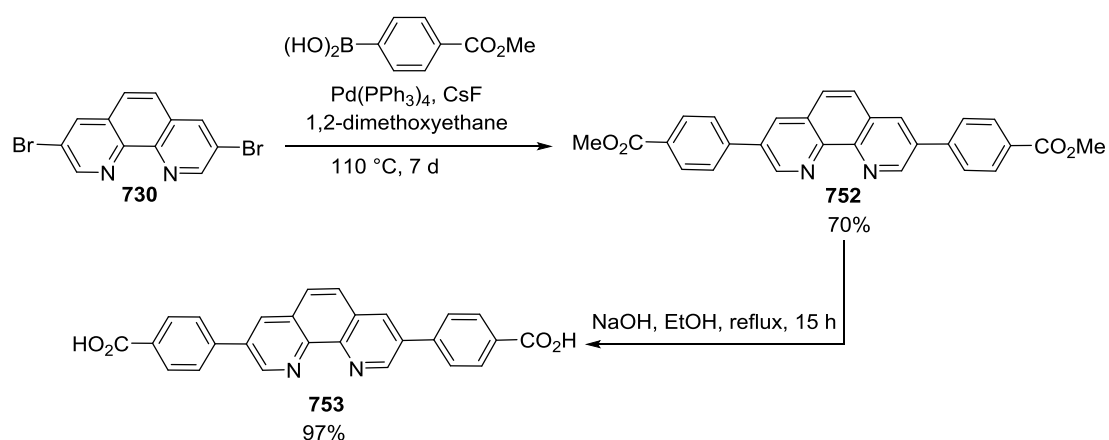
Scheme 123. Examples of aromatic nucleophilic substitutions on **717** and **718**

3.2.3. Functionalization starting from 3- and 3,8-dihalogenated phen: metal catalyzed C-C bond formation

Suzuki coupling

Functionalization at the position 3 is an important strategy that can be done by different metal catalyzed coupling reactions and Suzuki coupling is one out of several. The conditions of the Suzuki coupling reaction on halogenated (Br or I) phen₍₃₎sub or phen_(3,8)sub are similar to the ones developed on halogenated phen₍₂₎sub or phen_(2,9)sub.^{103,108,189,656,667–678} Among all examples, **753** (Scheme 123) is an important ligand which was used for the synthesis of different MOF.^{679,680} Feng et al.⁶⁸⁰ performed a double Suzuki coupling between the 3,8-

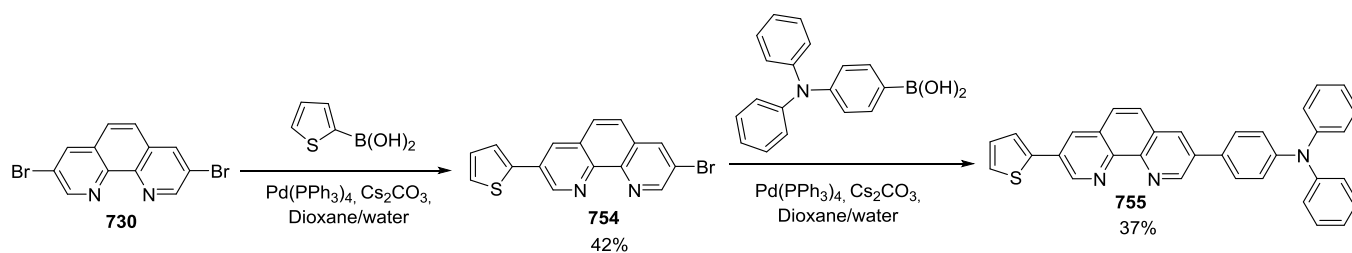
dibromophen and 4-methylcarboxylatephenylboronic acid. Basic hydrolysis of this ester produced di-acid modified ligand **753** with 97% yield (Scheme 124).



Scheme 124. Synthesis of 3,8-diacid substituted phen ligand **753**

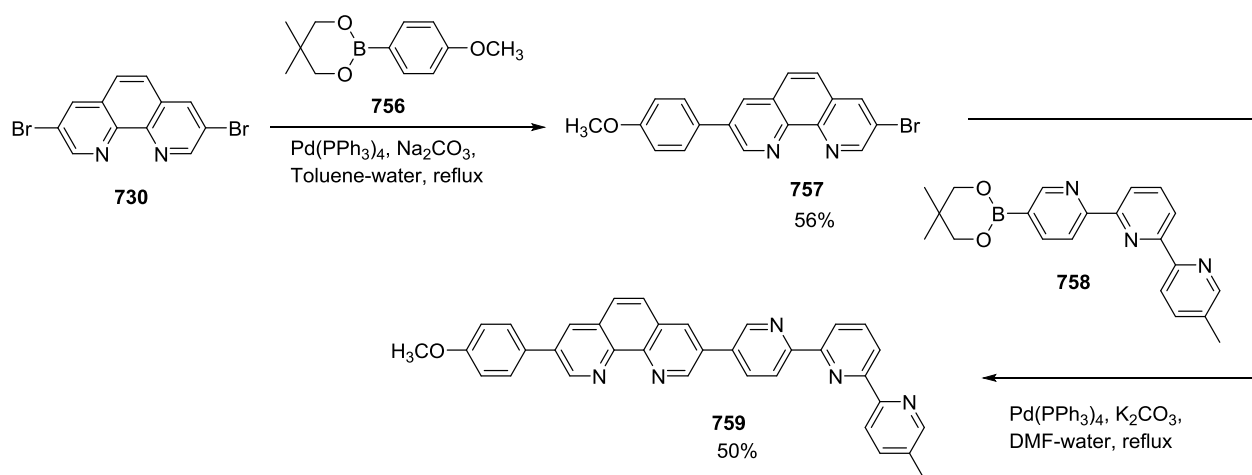
This ligand was coordinated with copper, rhenium or cobalt ions and two MOFs were prepared and were shown to be active in the photocatalytic hydrogen evolution and CO_2 reduction.

Besides, there are some examples where the Suzuki coupling condition was wisely used to design non-symmetrical phen_{(3,8)sub} ligand, i.e. positions 3 and 8 both are functionalized with two different aryl groups. As depicted in Scheme 125, **730** was subjected to Suzuki coupling with 2-thienyl boronic acid to produce **754** with 42% yield. Then, a second Suzuki coupling with 4-(diphenylamino) phenylboronic acid produced unsymmetrically substituted phenanthroline **755** with 37% yield.⁶⁷¹



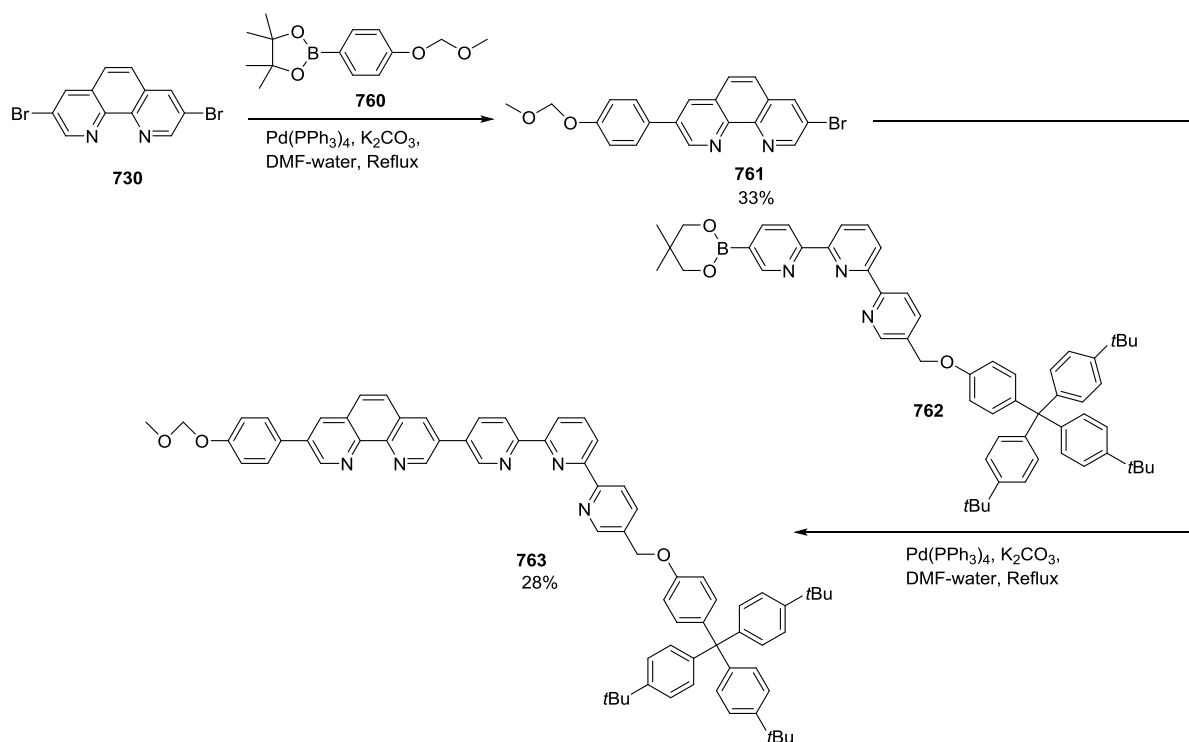
Scheme 125. Decoration of phen_{(3,8)sub} via successive Suzuki coupling reactions on **730**

Gaviña *et al.*⁶⁸¹ introduced p-anisyl-phenylboronic ester **756** by controlling the number of equivalent used and obtained **757** with 50% yield. Then, a second Suzuki coupling with borylated-ter-pyridine counter-part **758** yielded ligand **759** which was further utilized in supramolecular assemblies with Fe(II) ions (Scheme 126).⁶⁸²



Scheme 126. Synthesis of unsymmetrical phen_{(3,8)sub} **759** through Suzuki coupling reaction

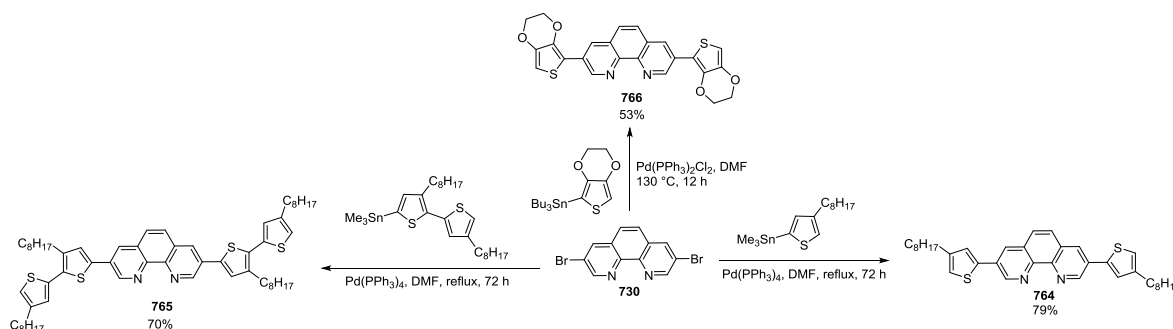
Coronado *et al.*⁶⁸³ disclosed the Suzuki coupling of **730** with 1 equiv. arylboronic ester **760** produced **761** and subsequent Suzuki coupling with substituted ter-pyridine moiety **762** resulted into ligand **763** which was further utilized to develop rotaxanes (Scheme 127).



Scheme 127. Synthesis of unsymmetrical phen_{(3,8)sub} **763** through successive Suzuki coupling reaction

Stille coupling

Stille coupling is another Pd-catalyzed cross-coupling, highly explored in common organic synthesis, but significantly less with **265** and **730**. This approach is mainly used when phenanthroline is substituted with 5-membered heterocyclic rings with chalcogens (thiophene and substituted thiophen in particular) (Scheme 128).^{684,685} This may be due to more easily accessible stannyl substituted chalcogen reagents.



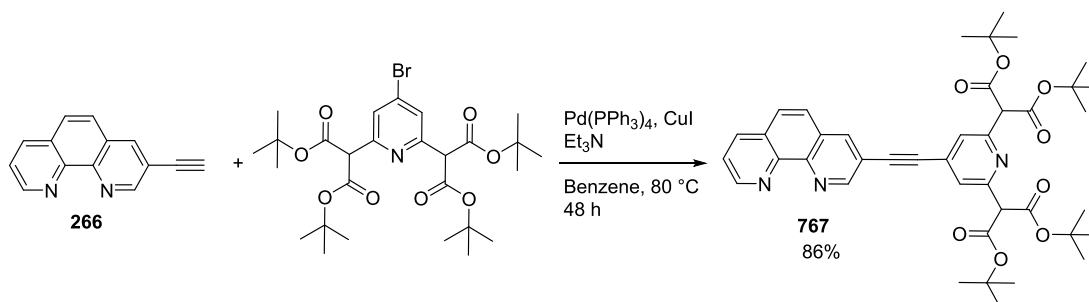
Scheme 128. Examples of functionalization of phen_{(3)sub} *via* Stille coupling on **730**

Ligands **764**, **765** and **766** after coordination with metal ions were used either as ruthenium complexes for DSSC (dye-sensitized solar cells)⁶⁸⁵ or as photoluminescent Europium conducting metallopolymer.⁶⁸⁴

Sonogashira coupling

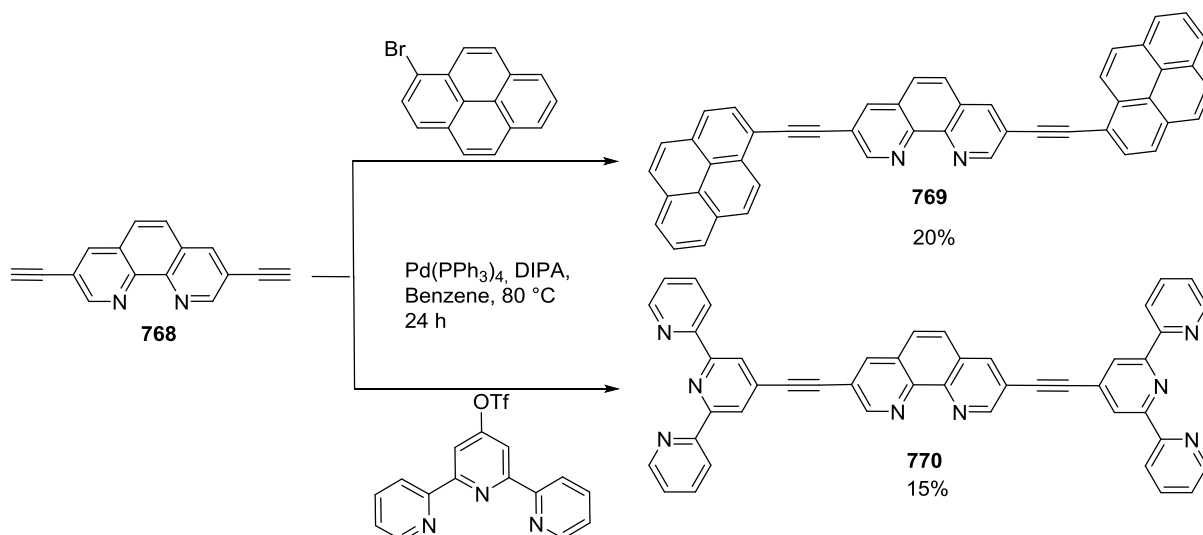
Pd-catalysed Sonogashira coupling was also employed to design phen_{(3)sub} and phen_{(3,8)sub} from brominated **265** and **730**.^{180,653,686–692}

For example, Jana et al.⁶⁹³ prepared the 3-ethynyl-1,10-phenanthroline **266** according to the procedure described by Michel et al.⁶⁸⁶ and performed a second Sonogashira coupling to obtain ligand **767** in 86% yield. This rigid ligand showed high potential for use in dual luminescence and magnetic resonance imaging and for optimization of d-f photoinduced energy-transfer (Scheme 129).



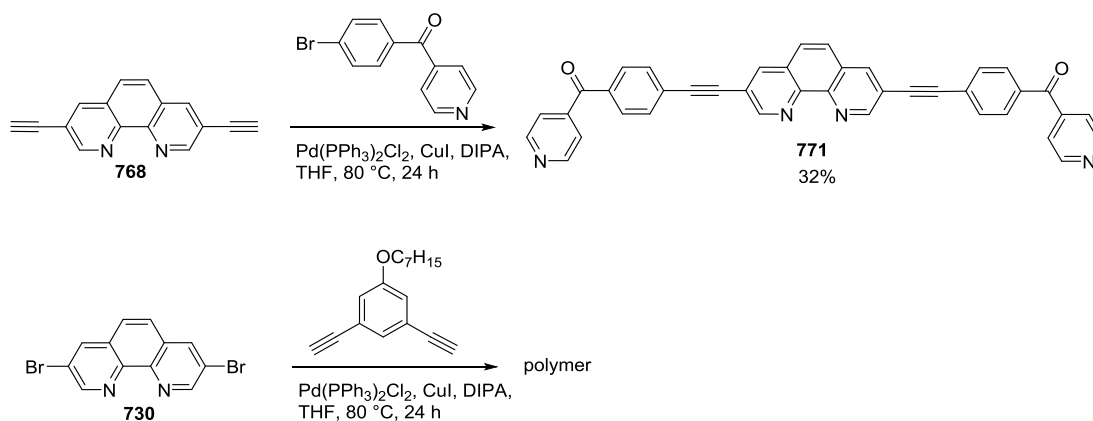
Scheme 129. Rigid ligand **767** developed by Jana et al. through a Sonogashira coupling⁶⁹³

Similarly, **768** has been prepared by a procedure described by Ziessel et al.⁶⁸⁷ and then a second Sonogashira coupling has been performed to obtain ligands **769** and **770** in 20% and 15% yield, respectively (Scheme 130).



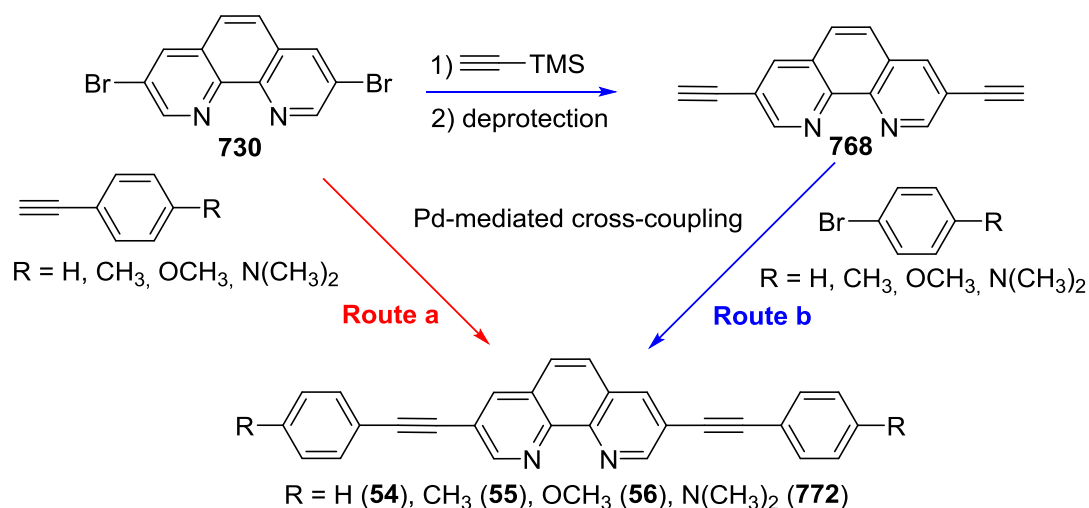
Scheme 130. Sonogashira coupling on **768** developed by Ziessel et al.⁶⁸⁷

Ponce et al.¹⁸³ used as well a Sonogashira coupling on 3,8-diethynylphenanthroline **768** to synthesize two phen_{(2,9)sub} ligands bearing either a pyridine or a S-acetylthiobenzene group linked to the triple bond. Those ligands were further transformed into their copper(I) complexes to study the conductance of the complex immobilized between two electrodes. Sonogashira coupling of 4-(p-bromobenzoyl)pyridine with 3,8-diethynylphenanthroline **768** led to **771** in 32% yield (Scheme 131).⁶⁹⁴ The authors compared this synthesis with the direct Sonogashira coupling of 3,8-dibromo-1,10-phenanthroline **730** with 3,5-diethynylheptyloxybenzene under the same conditions that led in this case to an intractable polymer.



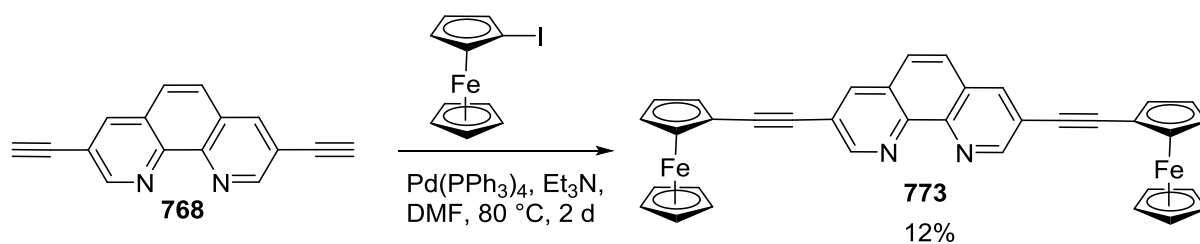
Scheme 131. Sonogashira coupling on **768** to obtain **771**⁶⁹⁴

Joshi et al.¹⁹³ utilized two routes to synthesize 3,8-bis(arylethynyl)phen **54-56** and **772** as novel fluorescent chromophores (Scheme 132). Route “a” (in red) consists in tethering substituted phenylalkynes onto **730**, while route “b” (in green) requires three steps: first the Sonogashira coupling of trimethylsilylacetylene to **730**, then deprotection and novel Sonogashira coupling of **768** on substituted aryl bromides. Both routes a and b work well but route b is nevertheless favored when alkynes are too unstable or highly volatile.



Scheme 132. Strategies to obtain 3,8-bis(arylethynyl)phen **54-56** and **772**¹⁹³

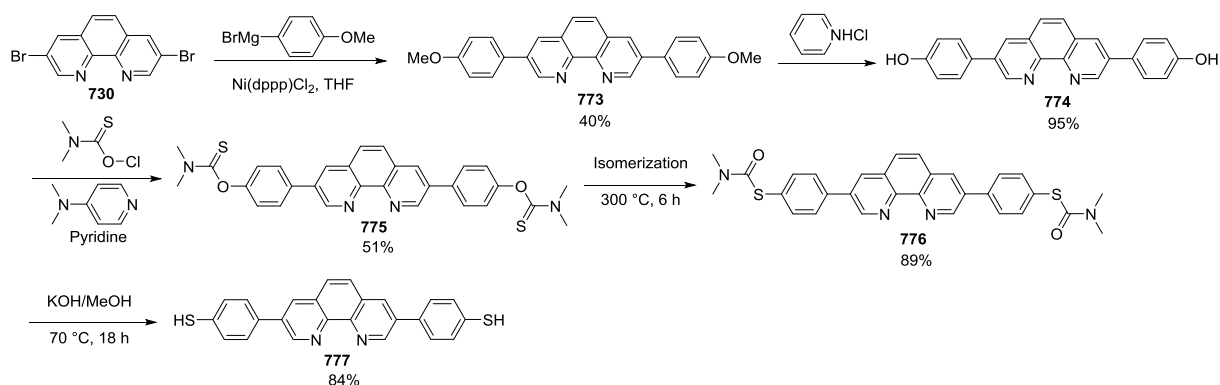
As last example, Shu et al.⁶⁹⁵ have prepared bis(ferrocenyl)phenanthroline **773** from **768** that underwent a Sonogashira coupling for 2 days in DMF with iodo-ferrocene (Scheme 133). The obtained redox active ligand has been used to design iridium complexes for the detection of cyanide and fluoride anions in aqueous solutions.



Scheme 133. Bis(ferrocenyl)phenanthroline ligand **773** developed by Shu et al.⁶⁹⁵

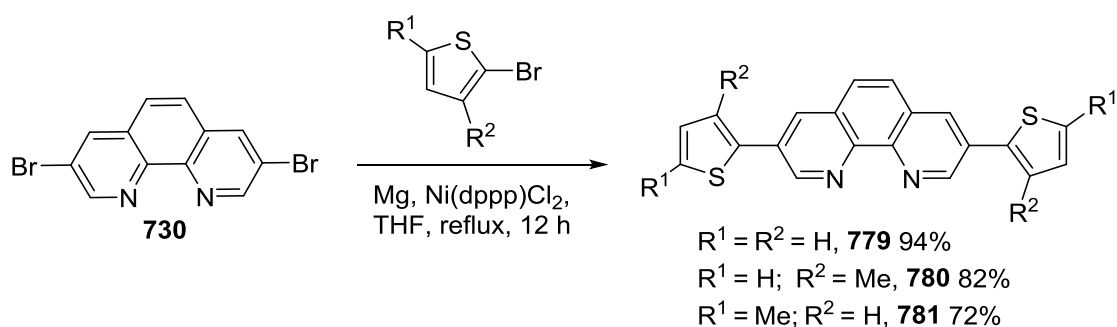
Kumada coupling

Kumada coupling is a nickel (or palladium)-catalyzed reaction which leads to a carbon–carbon bond formation by reacting a Grignard reagent and an organic halide. For example, Huang et al.⁶⁹⁶ developed a synthetic strategy to develop 3,8-bis(4-mercaptophenyl)-1,10-phenanthroline **778** (Scheme 134) in 5 steps with an overall yield of 14.5%. First Ni-catalyzed reaction between **730** and the Grignard reagent prepared from 4-bromoanisole and magnesium resulted in **774** that was treated with pyridinium chloride to yield **775**. Condensation with N,N'-dimethylthiocarbamoyl chloride in a catalytic amount of 4-N,N'-dimethylaminopyridine in dry pyridine followed by the Newman-Kwart rearrangement under argon atmosphere in a glass tube oven at 300 °C for 6 h and finally basic hydrolysis yielded 3,8-bis(4-mercaptophenyl)-1,10-phenanthroline **778**. This thiol group is very important for post modification and functionalization (e.g. on gold surfaces).



Scheme 134. Synthesis of 3,8-dimercapto substituted phenanthroline **777**

The Kumada coupling reaction has been particularly successful when applied to thiophenes,^{697,698} and therefore thiophene functionalized phen_{(3,8)sub} and phen_{(3)sub} have been synthesized by Ni-catalysed coupling on **265** or **730** (scheme 135).^{697–702}

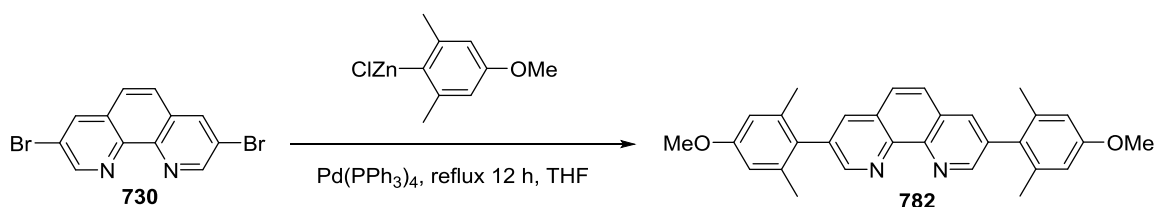


Scheme 135. Examples of the functionalization of phen_{(3)sub} and phen_{(3,8)sub} via Kumada coupling on **730**.

Ligand **779** has been complexed with Ru(II) ions and oligothiophene polymers bridging nanogap gold electrodes have been prepared by *in-situ* electropolymerization.^{699,700} From ligand **780**, further chemical modifications was performed to introduce nitrogen-containing heterocycles to form linear aromatic heterocyclic semiconducting fluorescent compounds.⁷⁰¹ Finally, ligand **781** after complexation with Zn(II) ions has been shown to be a cell-compatible fluorescent chemosensor.⁷⁰²

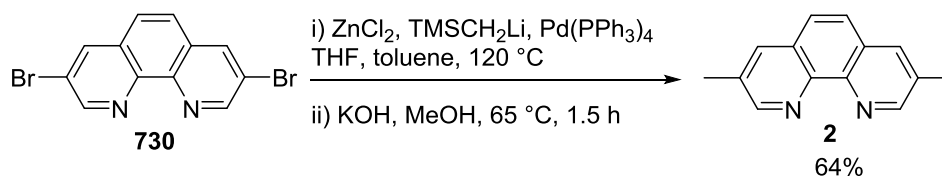
Other metal catalyzed cross-coupling reactions leading to C-C bond formation

Siegel et al.¹⁹⁵ have utilized aryl-Zn compound in the presence of Pd(0) catalyst to prepare 3,8-disubstituted symmetrical phenanthroline ligands (Scheme 136). First the Zn-aryl intermediate is prepared and then reaction with **730** yields the product **782** with 70% yield.



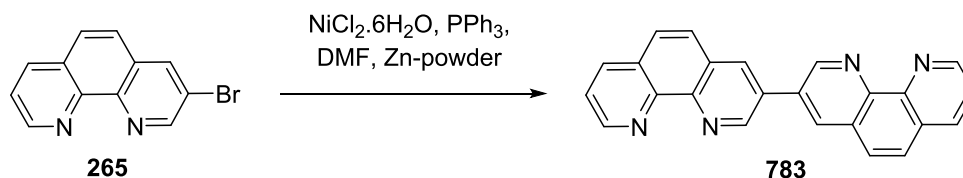
Scheme 136. Zn-catalyzed cross-coupling reaction to obtain phen_{(3,8)sub} **782**

In a similar way, Larsen et al.²⁶⁶ transformed **730** into **2** through a palladium catalyzed Negishi coupling using $\text{TMSCH}_2\text{ZnCl}$ as the nucleophile formed *in situ* through the reaction of ZnCl_2 and TMSCH_2Li . Then a basic treatment was performed to reach the product (Scheme 137).



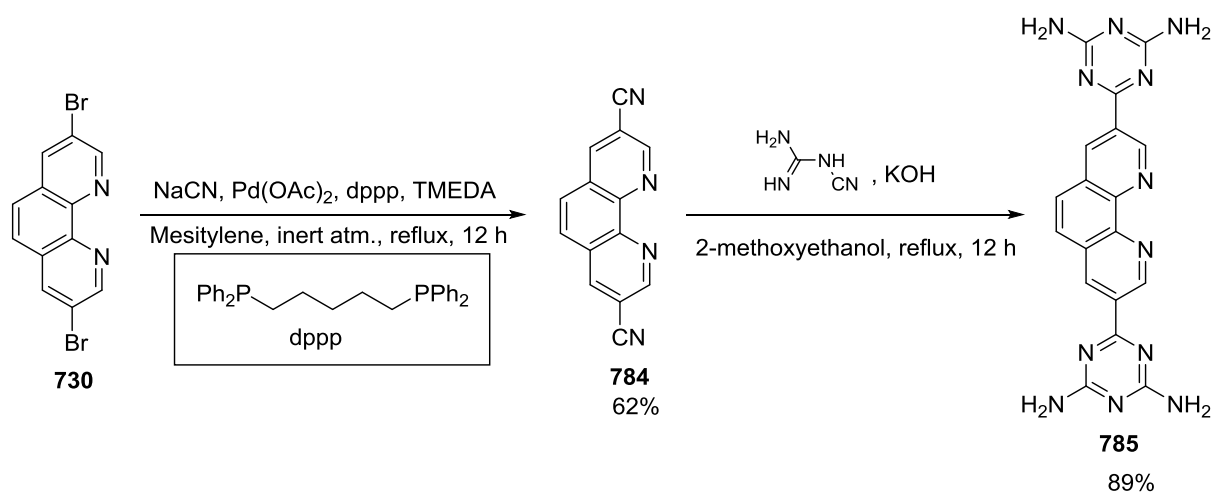
Scheme 137. Zn-catalyzed cross-coupling reaction to obtain 3,8-dimethyl phen **2**

Thummel et al.⁷⁰³ reported the synthesis of 3,3'-bis-1,10-phenanthroline **783** through Ni-mediated homocoupling. First $\text{Ni}(\text{PPh}_3)\text{Cl}_2$ was prepared *in-situ* by reacting NiCl_2 and PPh_3 in DMF at 50°C for 0.5 h. Later Zn dust was added followed by addition of **265** that provided **783** as white solid with 70% yield (Scheme 138).



Scheme 138. Ni-catalyzed homo-coupling reaction to form 3,3'-bis-1,10-phenanthroline **783**

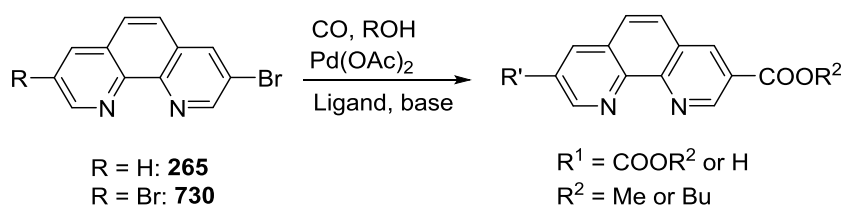
There are two important cases to mention, where the bromine atoms were replaced by pivotal functional groups *via* a metal-catalyzed cross coupling. First, when **730** is refluxed in mesitylene for 12 h with sodium cyanide, palladium acetate, 1,5-Bis(diphenylphosphino)pentane (dppp) and TMEDA, the precious 3,8-dicarbonitrile-1,10-phenanthroline **784** is obtained with 62% yield. Reaction with dicyandiamide gave compound **785** with 89% yield (Scheme 139).⁷⁰⁴

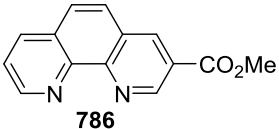
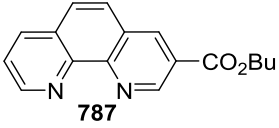
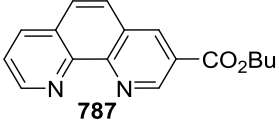
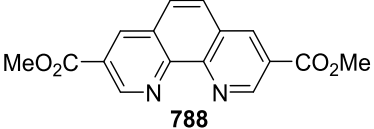
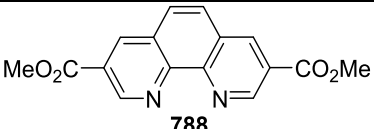
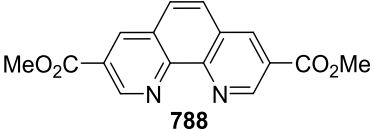
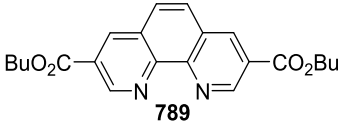
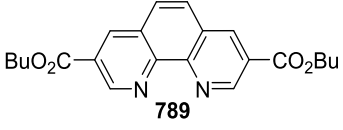


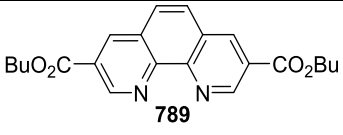
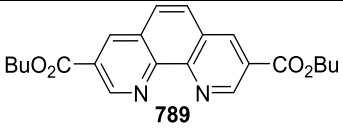
Scheme 139. Pd-catalyzed coupling of CN to **730** and reactivity of the obtained dinitrile **784**

The other important building block to mention is when COOH groups are tethered to positions 3 and 8. The COOH function is important for further decoration (*via* ester or amide linkage for example) or the development of metal organic framework (MOF). Abel et al. introduced COOR (R = methyl or *n*butyl) groups in position 3 and in positions 3 and 8 of phen *via* Pd-catalyzed alkoxy carbonylation (balloon with CO or bubbling CO in alcohol) on **265** and **730**, yielding the esters **786-789**. The corresponding acids can be obtained after hydrolysis. Different catalysts, bases, and overall reaction conditions have been tested to obtain the corresponding esters and some of them are listed in Table 17 including the conversion yield.⁷⁰⁵ The authors report that R = *n*butyl instead of methyl was necessary to achieve complete conversion of the dibromide into the diester. Otherwise, a mixture of mono and di- substituted products was obtained.

Table 17. Condition reactions and product of ester or acid substituted phen



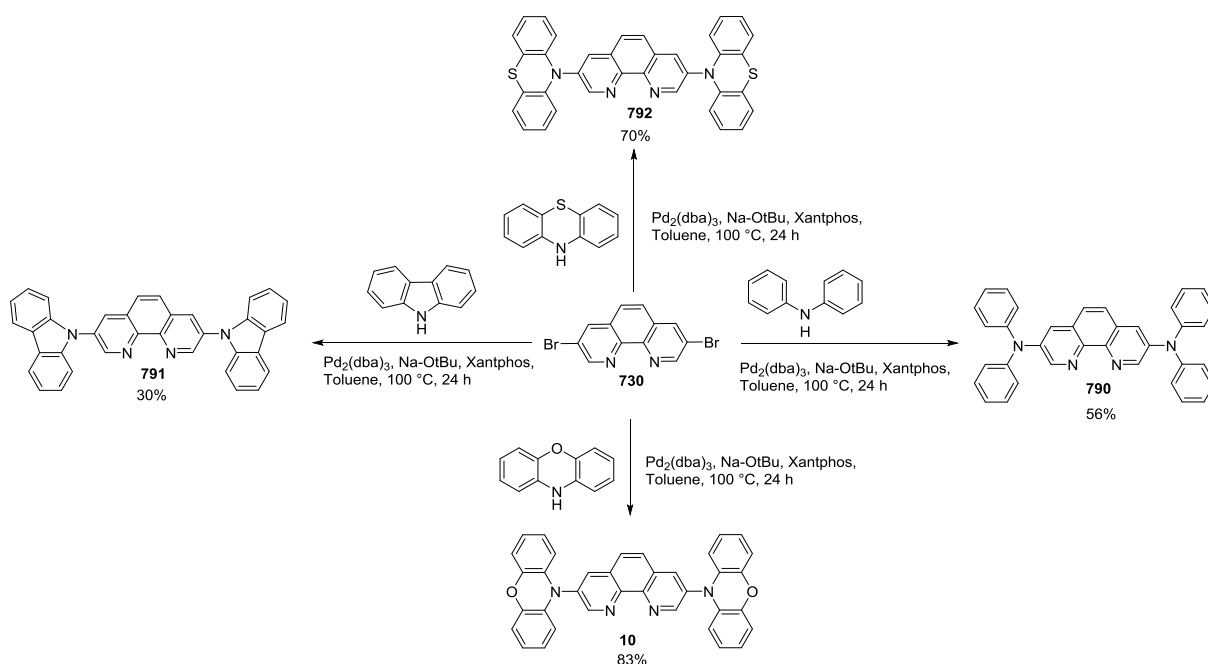
Product	ROH (eq.)	Base (eq.)	Ligand	T (°C)	Time (h)	Yield (%)
 786	MeOH (20)	NEt ₃ (30)	Xantphos	70	60	49
 787	n-BuOH (100)	NEt ₃ (30)	Xantphos	90	60	69
 787	n-BuOH (100)	K ₂ CO ₃ (30)	Xantphos	90	60	69
 788	MeOH (40)	NEt ₃ (30)	Xantphos	70	24	49
 788	MeOH (40)	NEt ₃ (30)	Xantphos	70	60	60
 788	n-BuOH (100)	NEt ₃ (30)	Xantphos	90	24	70
 789	n-BuOH (100)	NEt ₃ (30)	BINAP	90	12	70
 789	n-BuOH (100)	NaOAc (4)	Xantphos	90	3	49

 <p style="text-align: center;">789</p>	n-BuOH (100)	K ₂ CO ₃ (4)	Xantphos	90	3	70
 <p style="text-align: center;">789</p>	n-BuOH (100)	K ₂ CO ₃ (3)	BINAP	90	3	52

3.2.4. Functionalization starting from 3- and 3,8-dihalogenated phen: metal catalyzed C-heteroatom bond formation

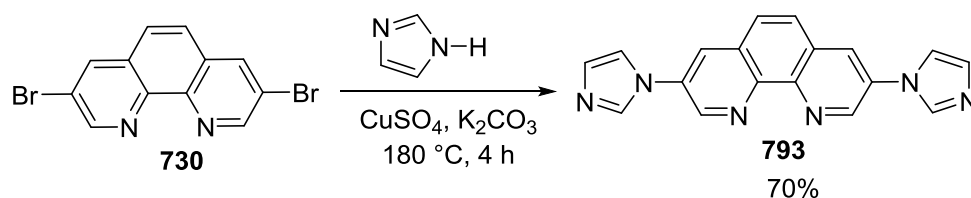
3.2.4.1. C-N bond formation

Pd-catalyzed C-N bond formation (Buchwald-Hartwig coupling) has also been explored to decorate **730**. Starting with halogenated phen, coupling with diphenylamine, carbazole, phenoxazine, phenothiazine gave wide range of donor-acceptor-donor type molecular scaffolds **10** and **790-792** which were used for thermally activated delayed emission (Scheme 140). In this type of coupling Pd₂(dba)₃ was used as a catalyst and phosphine ligands were explored such as the 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (Xantphos).⁷⁰⁶ In the case of **10**, other condition has been reported using Pd(OAc)₂, NaOtBu, (t-Bu)₃P.HBF₄, in refluxing DMF but the yield was much lower (36%).⁷⁵



Scheme 140. Examples of phen_{(3,8)sub} obtained via C-N coupling from amines and **730**

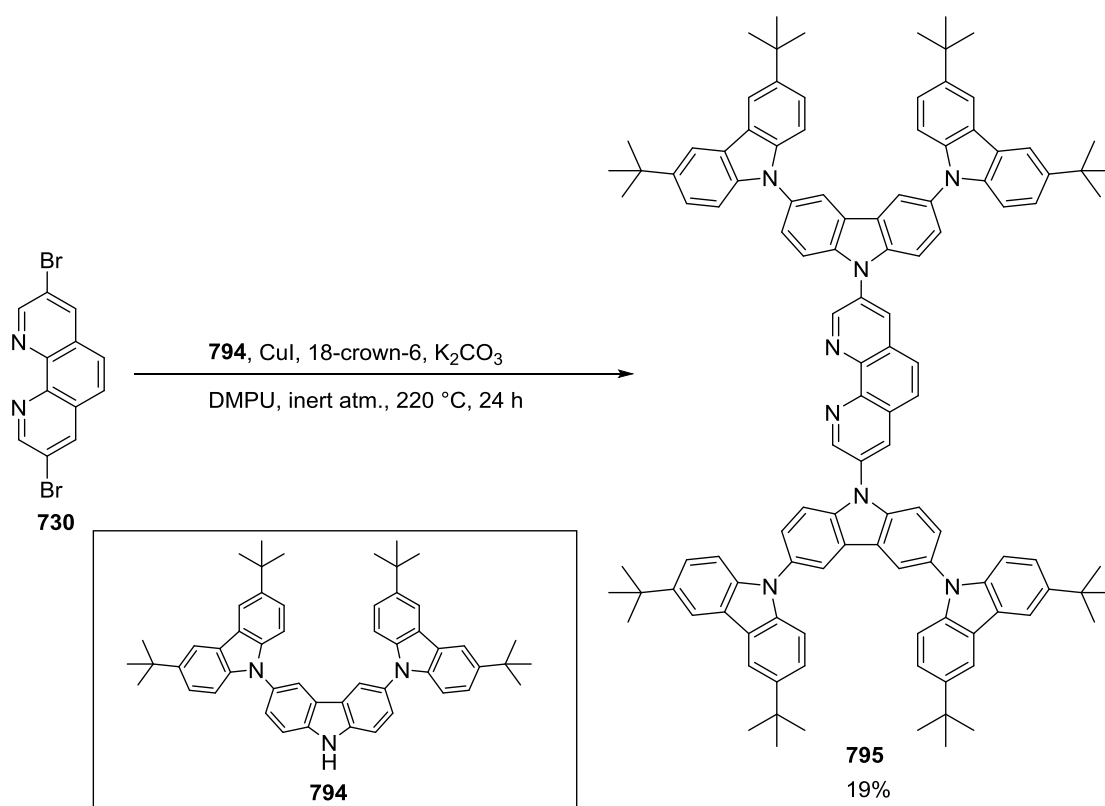
Wang et al.⁷⁰⁷ prepared 3,8-diimidazol-1,10-phenanthroline **793** via the carbon-nitrogen bond cross-coupling reaction between **730** and imidazole using Ullmann condensation methods. 3,8-dibromo-1,10-phenanthroline **730**, imidazole, K₂CO₃, and anhydrous CuSO₄ as the catalyst were mixed and heated at 180 °C under N₂ for 4 h. The final ligand was isolated with 70% yield (Scheme 141). Later this scaffold was demonstrated to be an efficient substrate for coordination polymer development with different metal ion.



Scheme 141. C-N formation through an Ullmann coupling

The Ullmann condensation conditions have allowed Su, Liao and co-workers to prepare **795** from **730** and dendrimer **794** (Scheme 142).¹⁹⁴ The corresponding iridium complex

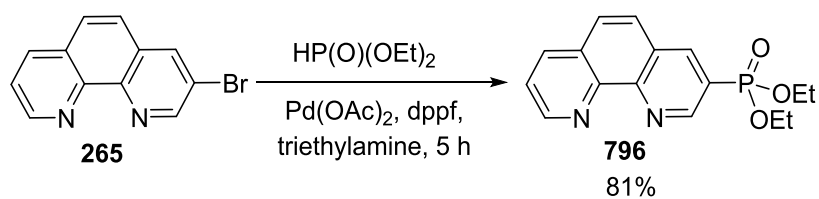
$[\text{Ir}(\text{ppy})_2\mathbf{795}]^+$ features aggregation induced emission, and has been used as luminescent probe in live cells.



Scheme 142. Ullmann coupling leading to extended $\text{phen}_{(3,8)\text{sub}}$ **795**

3.2.4.2. C-P bond formation

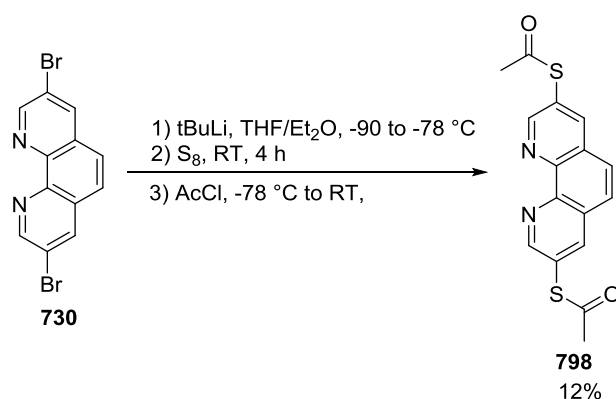
Phosphonate ester is an important functionalization because upon hydrolysis it produces phosphonic acid which is an important binding group for surface anchoring. Complexes of phen can be modified with phosphonic acid which can be further grafted on the surface of semiconductor/conductor surface for some photoelectrochemical/photochemical application. Hirao cross-coupling with **265** provided diethyl (1,10-phenanthroline-3-yl)phosphonate **796** with 81% yield (Scheme 143).⁴⁶⁰ Tetraethyl (1,10-phenanthroline-3,8-diyl)bis(phosphonate) **797** was prepared in the same conditions from 3,8-dibromo-1,10-phenanthroline **730** with yields varying from 70 to 90%.^{460,705,708,709}



Scheme 143. Synthesis of phosphonate ester substituted phenanthroline via an Hirao cross-coupling

3.2.5. Concluding remarks

The possibilities to functionalize phen in positions (3,8) are not as numerous as in the case of other positions. This is likely due to a lack of reactivity. However, the methods proposed in the literature are robust and many impressive structures have been prepared: nucleophilic substitutions and above all metal-catalyzed cross-coupling reactions. A last reaction is worth mentioning, and is based on the bromine-lithium exchange which takes place when **730** is put in presence of *tert*butyllithium, yielding a strongly nucleophilic bis-carbanion. The latter is quenched in presence of sulphur, giving compound **798** after treatment of the crude with acetyl chloride, however in very poor yield (Scheme 144).⁷¹⁰ This is an alternative way to obtain phen_{(3,8)sub} functionalized with thiols, and the reactivity of the bis-carbanion could be advantageously applied in many more cases, provided the organolithium reagent is unable to attack positions 2 and 9.



Scheme 144. Synthesis of **798** through the halogen-metal exchange reaction on **730**

3.3. Functionalization of phen in positions 4 or 7 / 4 and 7

As far as we can tell, there is no known method to prepare a phen₍₄₎sub or a phen_(4,7)sub molecule directly from phen by divergent methods. Otherwise, specific pre-functionalized synthons can be bought from various suppliers or synthesized by convergent methods, and can be further decorated to prepare extended phen₍₄₎sub or a phen_(4,7)sub. Those precious building blocks are given in Figure 27. The 4,7-dimethylphen **3** is the cheapest one (from 60 to 100 € according to suppliers) then the 4,7-dichlorophen **146** is in second place (from 150 to 300 € according to suppliers) whereas the 4,7-dibromophen **158** is more expensive (from 280 to 550 € according to suppliers). The 4-chlorinated phen **193** is not available in classical suppliers.

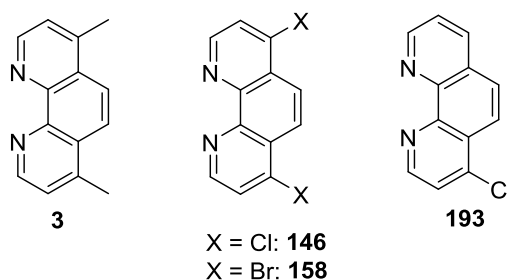


Figure 27. Structures of the three key synthons to elaborate extended phen_(4,7)sub

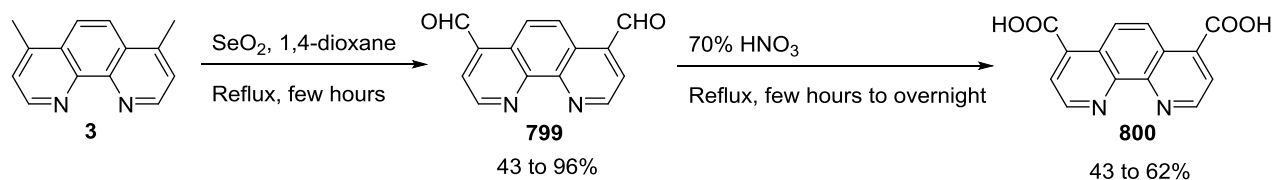
From these specific synthons, further transformations are possible and some examples will be presented in the section below illustrating the wealth of possibilities.

3.3.1. From 4,7-dimethylphen

3.3.1.1. 4,7-diformylphen, 4,7-dicarboxyphen and derivatives

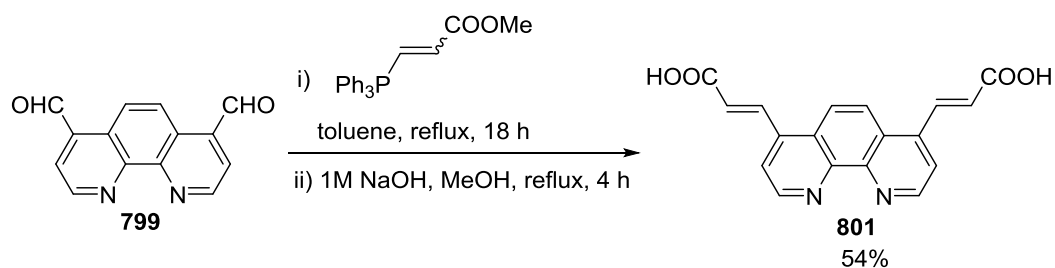
There is a kinship between the reactivity of neocuproine **1** and 4,7-dimethylphen **3**. From **3**, it is possible to oxidize the methyl groups with selenium dioxide in refluxing dioxane leading to bisaldehyde 4,7-diformylphen **799**, similarly to the oxidation of neocuproine into **565**.

Different yields have been reported from 43 to 96%.^{232,241,711-719} Then oxidation of the formyl group into carboxylic acid has been performed using nitric acid, leading to the 4,7-dicarboxylic acid phen **800** with 33%,⁷²⁰ 62%⁷¹¹ or 43%⁷¹³ yield (Scheme 145).



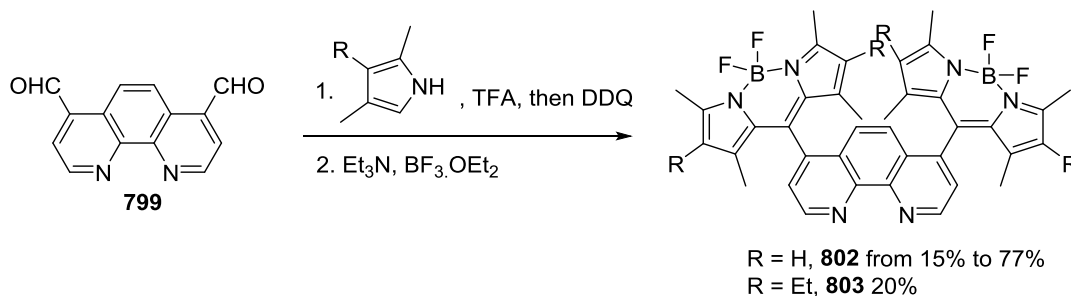
Scheme 145. Formation of 4,7-diformylphen **799** and 4,7-dicarboxylic acid phen **800**

Many functionalization reactions are possible from those two key-synthons. For example, Oh et al.⁷¹¹ performed a Wittig reaction on the 4,7-diformylphen **799**. Saponification of the two ester groups yields 4,7-bis(E-carboxyvinyl)-1,10-phenanthroline **801** (Scheme 146). The two COOH groups can be used as remote conjugated anchors to oxides, a particularly appealing feature for the design of photosensitive complexes for dye sensitized solar cells.



Scheme 146. Formation of the 4,7-bis(E-carboxyvinyl)-1,10-phenanthroline⁷¹¹

From the 4,7-diformylphen **799**, several groups functionalized phen with a BODIPY moiety (BDP-phen, Scheme 147).



Scheme 147. Functionalization of the 4,7-diformylphen with a BODIPY moiety

The Pd(II) complex of BDP-phen **802** was formed and used as a photocatalyst in the Sonogashira photo-assisted C-C cross-coupling reaction.⁷²¹ The BDP-phen **803** was used as sensor for Cd(II) and Zn(II) ions.^{716,722} After further modifications, it was used as well as near-IR probe.^{723,724}

Other fluorescent probes have been formed from the 4,7-diformylphen **799**. For example, **799** reacted with fluorescein to form a new probe **804** for the detection of the hypochlorite ion in aqueous solution (Figure 28).⁷¹⁹ Algi et al.⁷¹⁴ reacted the 4,7-diformylphen with the 5-aminophen by forming an imine bond to obtain **805** (Figure 28). This new compound was used as a fluorescent sensor for Zn²⁺ and H⁺ in aqueous solution. Finally, Bazzicalupi⁷²⁵ reacted the 4,7-diformylphen with 1,3-diaminopropane to form the corresponding cyclic tetra-imine **806** that was further reduced by NaBH₄. The obtained new macrocycle was used as fluorescent sensor for Zn²⁺ and H⁺ (Figure 28).

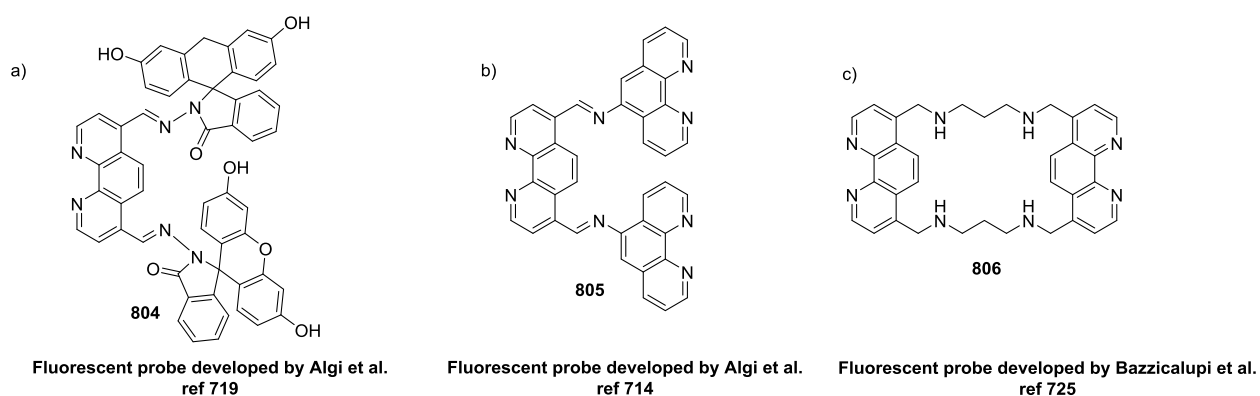
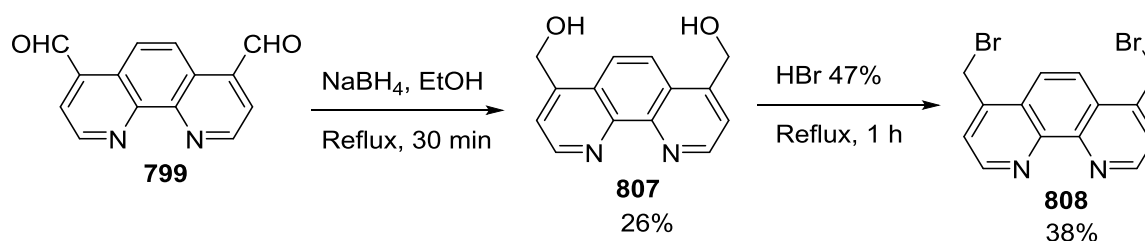


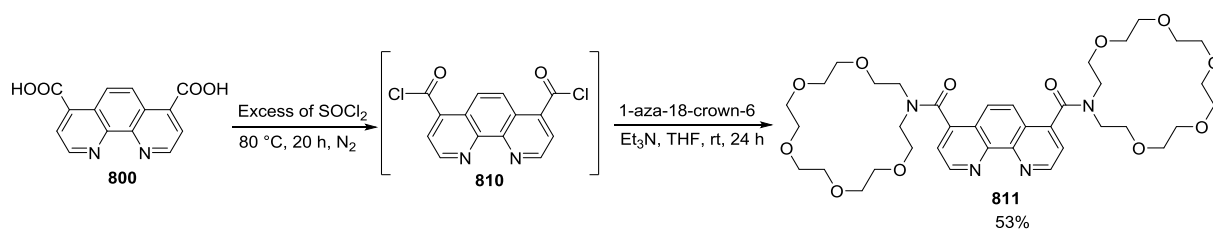
Figure 28. Fluorescent probes **804-806** functionalized in 4,7 position

Higashi et al.⁷¹⁷ reduced **799** into bis-alcohol **807** with NaBH₄. The obtained bis-alcohol features the classic reactivity of all alcohols (e.g. esterification),⁷²⁶ although this intermediate has been rarely used in the literature. Further reaction of **807** with an hydrobromic acid aqueous solution at reflux formed bis(bromomethyl)phen **808** (Scheme 148). The latter exhibits CH₂Br electrophilic sites, and nucleophilic substitutions on those positions is straightforward.⁷²⁷



Scheme 148. Synthesis of 4,7-bis(bromomethyl)phen **808**

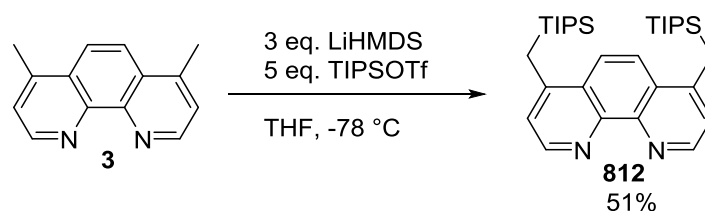
Synthon 4,7-dicarboxylic acid phen **800** exhibits the traditional reactivity of any aromatic acid. Bellusci et al.⁷²⁸ obtained the diethyl ester of **809** by refluxing for 5 days **800** with sulfuric acid in ethanol. The corresponding ester was obtained with 65% yield. Interestingly, **800** can be turned into the more reactive acyl chloride **810** as demonstrated by Boricha et al.⁷²⁹ Refluxing **800** with an excess of thionyl chloride under N₂ for 20 h yields the corresponding acyl chloride **810** which can be directly used in the next step and reacted with 1-aza-18-crown-6 **811** with 53% of yield (Scheme 149). The resulting heterotopic ligand has been coordinated to ruthenium ions (in the N[∧]N cavity) giving a photoluminescent sensor which luminescence is affected by the presence of cations in the crown ether rings.



Scheme 149. Phen-crown ether ligand **811** developed by Boricha et al.⁷²⁹

3.3.1.2. Deprotonation of the methyl groups of 4,7-dimethylphen

Larsen et al.¹²⁵ have deprotonated **3** using the strong base LiHMDS at $-78\text{ }^{\circ}\text{C}$. The resulting bis-carbanion exhibits a dark green color, which vanishes in presence of electrophilic triisopropylsilyl trifluoromethanesulfonate TIPSOTf. The double silylation reaction is thus achieved with a yield of 51% (Scheme 150) to obtain **812**.



Scheme 150. Silylation reaction on the **3**¹²⁵

Other bases than LiHMDS can be used to deprotonate **3**. Gimenez-Pedros et al.⁷³⁰ have used *n*-butyllithium to prepare the bis-carbanion of **3** and reacted it with 3-perfluorooctyl-1-iodopropane. The obtained perfluorinated ligand has then been coordinated with PdClMe(COD) and the resulting complex has been used in the catalyzed copolymerization of CO and *tert*-butylstyrene in supercritical carbon dioxide. This led to the obtention of polyketones ($M_w = 56\ 000\text{--}87\ 000\ \text{g mol}^{-1}$) with very narrow molecular weight distributions. Finally, lithium diisopropylamine (LDA) has been used as well as a base to deprotonate **3**, and the bis-carbanion further reacted with iodoalkyles (from C₉ to C₁₉, linear or branched) with yields from 31 to 61%.^{731,732}

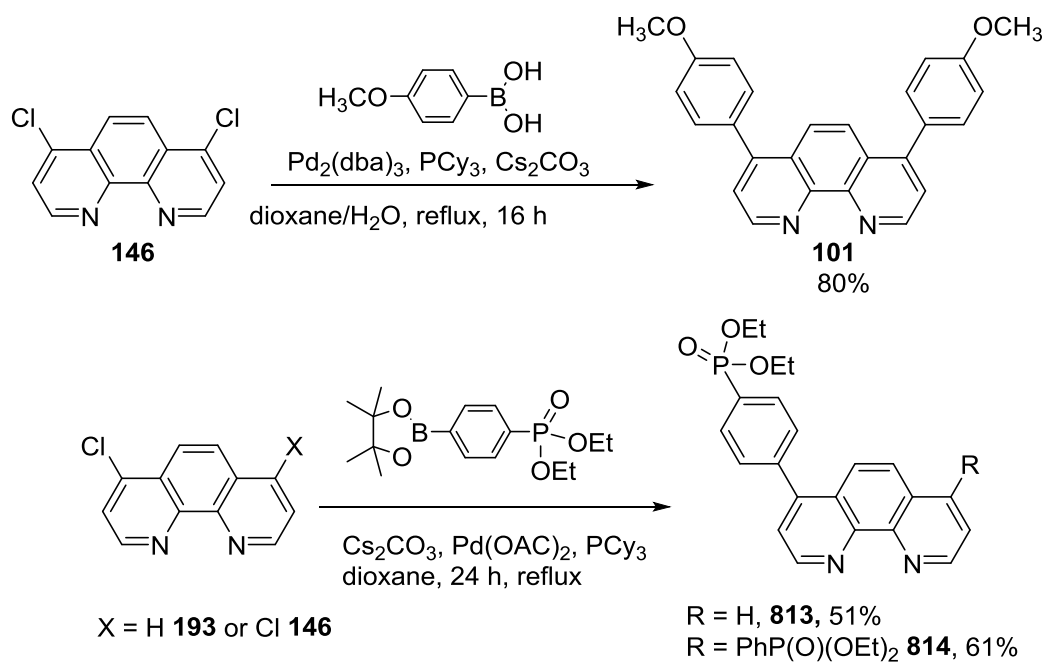
3.3.2. From 4-halogenated or 4,7-dihalogenated phen

Unsurprisingly, the vast majority of functionalization methods to synthesize phen_{(4)sub} and phen_{(4,7)sub} from 4-halogenated phen and 4,7-dihalogenated phen relies on metal-catalyzed cross-coupling reactions and aromatic nucleophilic substitutions.

3.3.2.1. Metal-catalyzed cross-coupling reactions

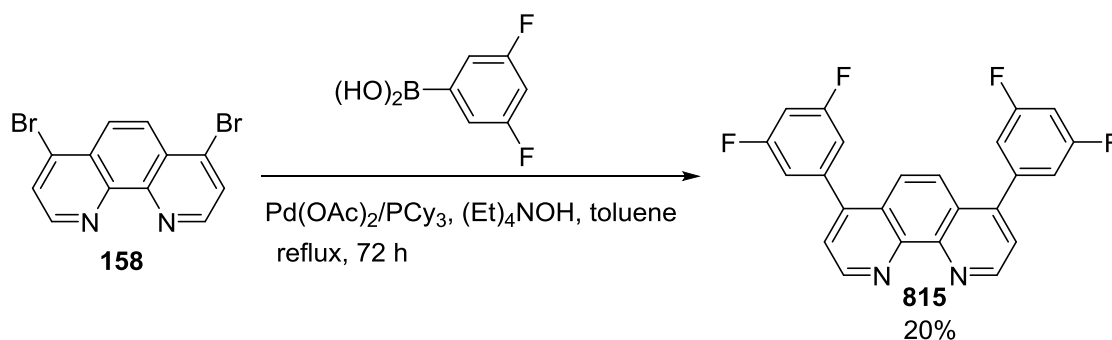
C-C bond formation by Suzuki coupling

4,7-dichlorophen **146** can undergo Suzuki reactions. For example, in the presence of 4-methoxyphenylboronic acid, Pd₂dba₃/PCy₃ and cesium carbonate in refluxing 1,4-dioxane/H₂O, the 4,7-bis(4-methoxyphenyl)-1,10-phen **101** is obtained after 16 h with 80% yield (Scheme 151).⁷³³ The corresponding Cr(III) complex was proven to be a good photocatalyst in the dearomative (3+2) cycloaddition between indoles and vinyl diazo (light = 23 W CFL (compact fluorescent light)). 4-*tert*-butylphenylboronic acid has been used in association with Pd(dba)₃/PCy₃ and cesium carbonate in refluxing 1,4-dioxane/H₂O to reach the final product with 84% yield.⁷³⁴ Morozkov et al.⁶⁷² has studied the position and influence of phosphonate group on Ru(II)-phen complexes that were used in the photooxidation of 4-methoxythioanisole to the sulfoxide product. The phosphonate substituted phen have been obtained through Suzuki couplings. The 4- or 4,7-dichlorophen **193** or **146** reacted with diethyl 4-BPin-phenylphosphonate in the presence of Pd(OAc)₂/PCy₃, cesium carbonate in refluxing dioxane (Scheme 146). It has been observed that the best TON of 1 000 000 for the oxidation of 4-methoxythioanisole is obtained when the Ru catalyst is prepared from the 4-substituted phen and the 4,7-disubstituted phen **813** and **814** rather than parent phen_{(3)sub} and phen_{(5)sub} or plain phen.



Scheme 151. Suzuki coupling performed on **146** or **193**

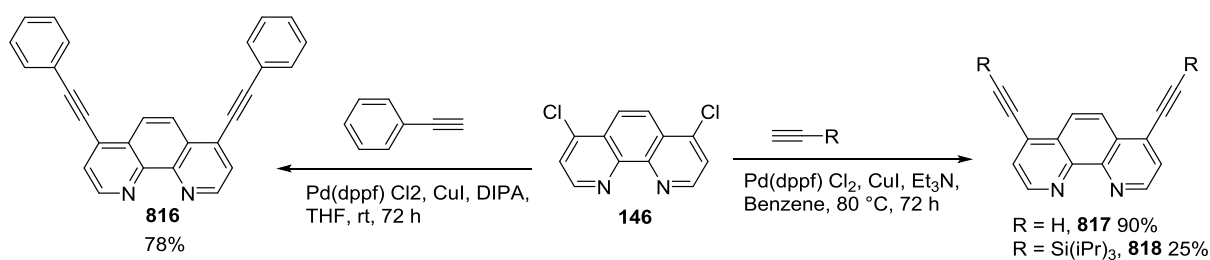
4,7-dibromophen **158** has been successfully involved in Suzuki coupling too. Zhu et al.²⁶³ mixed the 4,7-dibromophen with 3,5-difluorophenylboronic acid, $\text{Pd}(\text{OAc})_2/\text{PCy}_3$ in refluxing toluene for 72 h. The 4,7-di(3,5-difluorophenyl)-1,10-phenanthroline (4,7-dfpphen) **815** is obtained with 19% yield (Scheme 152). The corresponding ruthenium complexes exhibit a more intense and red-shifted emission band (compared to the parent, unsubstituted complex) thanks to the presence of the electron-withdrawing difluorophenyl groups.



Scheme 152. Suzuki coupling performed by Zhu et al.²⁶³

C-C bond formation by Sonogashira coupling

Classical Pd-catalysed Sonogashira coupling was also employed to design 4,7-substituted phen (Scheme 153).^{735,736}

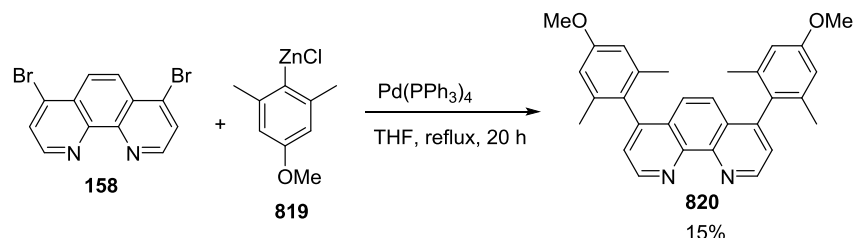


Scheme 153. Examples of Sonogashira coupling performed on 4,7-dichlorophenanthroline **146**.

Despite the fact that examples in Scheme 153 involve **146**, 4,7-dibromophen **158** has been used too in Sonogashira coupling reactions. As expected, reactions performed on **158** feature higher yields than those performed on **146**. For example, phenylacetylene has been coupled to **146** and **158** yielding the same bis-coupled compound **816** with 87%⁷³⁷ and 95%⁷³⁸ yields respectively. Nevertheless, the higher price of **158** does not entirely justify the use of the latter vs. cheaper **146**, for straightforward cross-couplings. It is interesting to notice that long reaction times are necessary to reach the highest yields. In some cases, significantly high amounts of CuI are added (0.6 equivalent^{735,736} instead of the usual catalytic amount of ca. 0.05 equivalent).⁷³⁷ The reason behind this matter is that copper(I) ions are efficiently coordinated by phen and this may affect the catalytic cycle. Nevertheless, let us precise that Sonogashira couplings of phenylacetylene on **146** has been performed in both conditions and afforded the target compound in good yields (with a slight advantage for the low loading in CuI).^{735,737} Accordingly, washings of the crude by cyanide aqueous solutions is always performed to destroy remaining copper-phen complexes and retrieve the highest amount of free ligand from the reaction mixture.

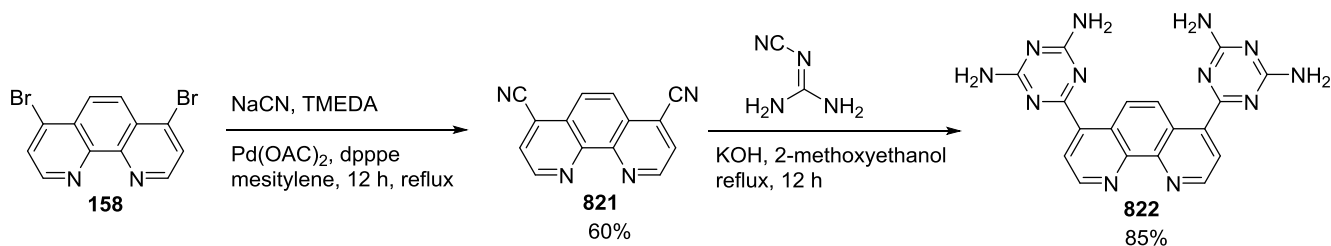
Other metal-catalyzed cross-coupling reactions

The Negishi cross-coupling reaction has been performed on the **158** using the organozinc reagent **819** in refluxing THF (Scheme 154). Compared to other positions, the yield is very low and only 15% yield was obtained for **820**.¹⁹⁵



Scheme 154. Negishi coupling on **158** described by Loren et al.¹⁹⁵

Duong et al.⁷⁰⁴ reacted **158** with sodium cyanide, palladium acetate, 1,5-bis(diphenylphosphino)pentane, tetramethylethylenediamine in mesitylene and refluxed for 12 h the mixture. The corresponding 4,7-dicarbonitrile phen **821** was obtained with 60% yield (Scheme 155). The efficiency of this coupling is not affected by the position of the bromine atoms ((4,7) or (3,8)) since a very comparable yield has been obtained for the synthesis of **800** (Scheme 141). Likewise, **821** was further transformed into 4,7-disubstituted diaminotriazinyl (DAT) phen **822** using dicyandiamide and KOH in refluxing 2-methoxyethanol.

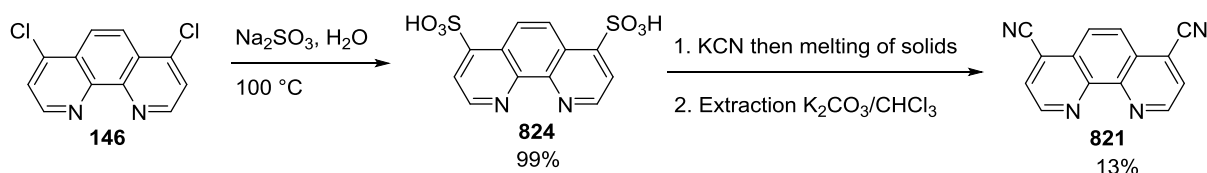


Scheme 155. Synthesis of **821** and **822** described by Duong et al.⁷⁰⁴

In an effort to improve the yield of the cyanation reactions, Staehle et al.⁷³⁹ compared the palladium-catalyzed cyanation of **193** or **146** under classical and microwave conditions using Zn(CN)₂ as the cyano group precursor and Pd(dba)₃/dppf. Under classical conditions, at 150

°C in dimethylacetamide for 5 h, the 4-cyanophen **823** was obtained with 70% yield. Under microwave conditions, the same yield was obtained but working in DMF for 1 h at 130 °C. **821** was obtained with 60% yield with the same microwave conditions.

A 2 steps process⁷⁴⁰ has been described as well to obtain **821** (Scheme 156): first **146** reacted with sodium sulfite in refluxing water to yield quantitatively **824**. The latter was then dried and mixed with dry potassium cyanide to obtain a fine powder. The mixture of finely mixed solids was then heated until melting occurs and then this viscous liquid was extracted with potassium carbonate and chloroform to yield **821** with 13% yield.



Scheme 156. A 2 steps process to obtain **821**

There are thus several efficient means to prepare **821** and yet, the molecule has been very rarely used for its reactivity compared to 2,9-dicyanophenanthroline **567**, for no obvious reason.

To the best of our knowledge, there is only one published work reporting the formation of a C-heteroatom bond, namely a C-P bond *via* an Hirao cross-coupling involving 4-bromophen **825**, which provided diethyl (1,10-phenanthroline-4-yl)phosphonate with 30% yield when a 10/20 loading of $\text{Pd}(\text{OAc})_2/\text{dppf}$ was used for 20 h or 52% yield with the same loading but dioxane was used instead of toluene. The reaction worked with a higher yield of 71% when **158** was used in toluene.⁴⁶⁰ The same reaction was conducted on the **146** in refluxing toluene with 80% yield.⁷⁰⁹

Apart from this last example, most C-heteroatom bond formations are achieved with favorable aromatic nucleophilic substitutions.

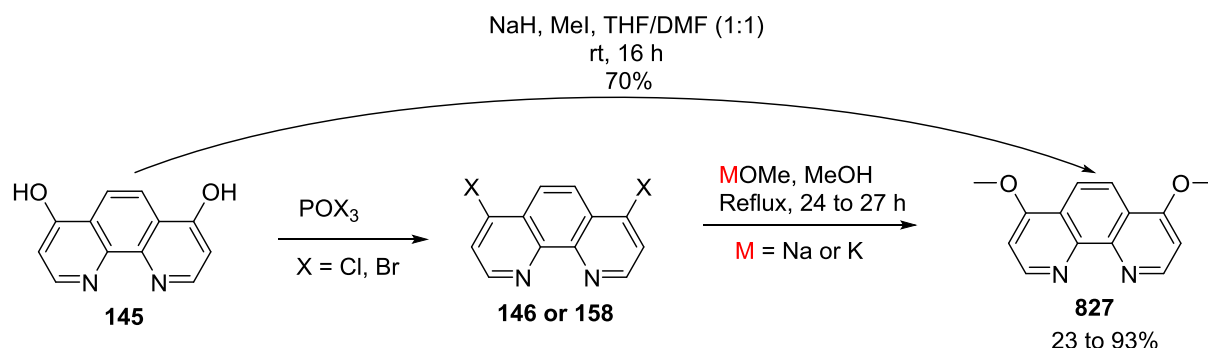
3.3.2.2. Aromatic nucleophilic substitutions

Nucleophilic aromatic substitutions are easily performed on 4,7-dihalogenated phen because C₄ and C₇ are electrophilic by nature. Several nucleophiles can be envisioned.

Oxygenated nucleophiles

Oxygen-bearing nucleophiles have been used in presence of 4- or 4,7-dihalogenated phen to form C-O bond. For example, **193** was treated with sodium methoxide in refluxing methanol for 27 h to obtain 4-methoxyphenanthroline **826** with 87% yield.^{261,275}

4,7-dihalogenated phen can as well undergo nucleophilic aromatic substitution. 4,7-dimethoxyphen **827** (Scheme 157) can be obtained using sodium methoxide^{86,220,261,741-743} or potassium methoxide⁷⁴⁰ in refluxing methanol.



Scheme 157. Synthesis of **827**

Those ligands exhibit stronger σ -donating abilities thanks to the electron-rich methoxy groups and were used for the copper-catalyzed N-arylation of various imidazoles,⁸⁶ in the palladium-catalyzed cyclization to obtain thienopyrroles,²⁶¹ or as nickel catalysts for asymmetric Ni/Cr coupling reaction.²⁶⁴ The ethoxy group was introduced too on **146**, generating potassium ethoxide from ethanol and a solution of *tert*-BuOK in THF. The purification of phen and

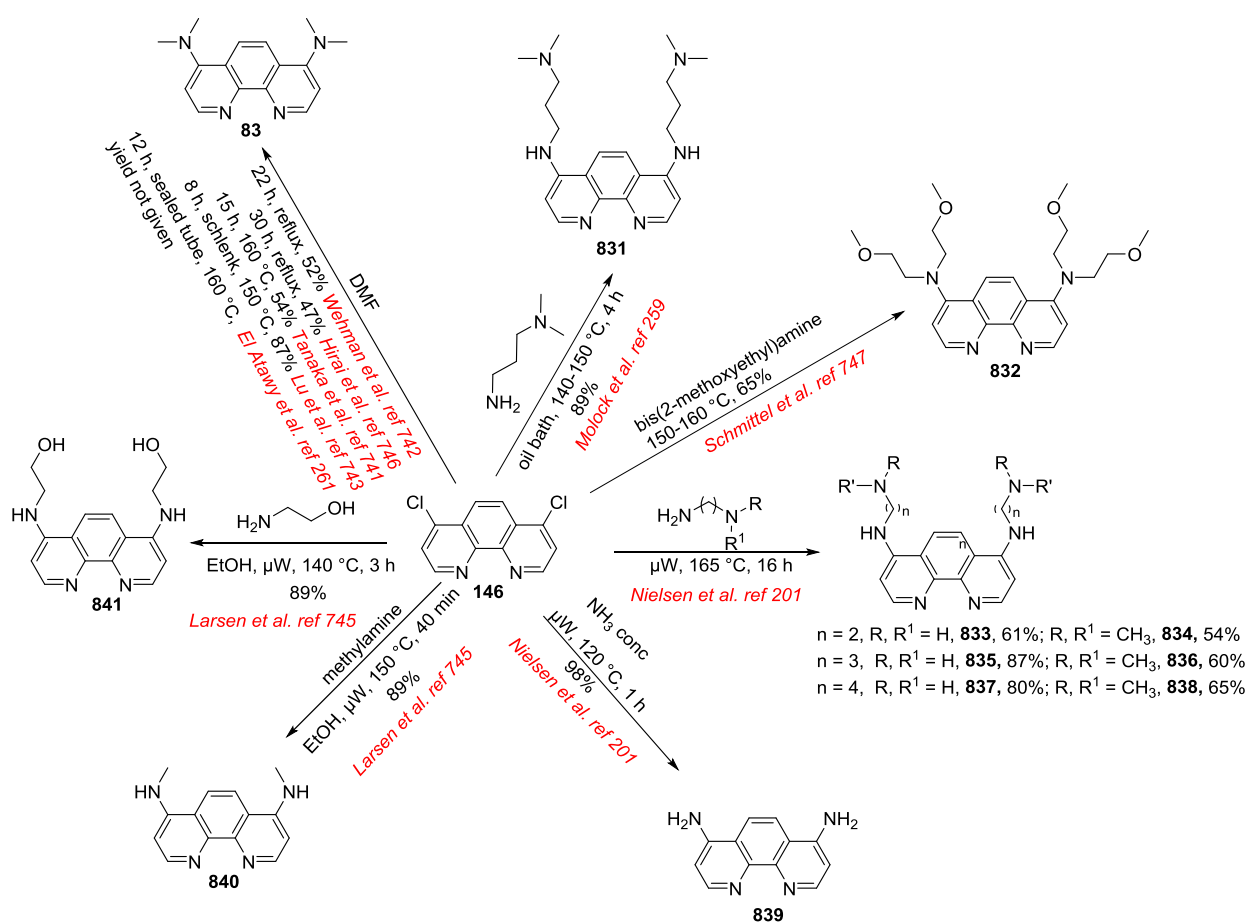
phen_{sub} by common liquid chromatography can be challenging because the N[∧]N cavity strongly interacts with the static phase. Interestingly, the authors report that the purification of the crude is efficiently achieved here on an amino-functionalized silica gel to yield quantitatively the 4,7-diethoxyphen **828**.⁷⁴⁴ A phenol group can be introduced on **146** using milder basic conditions (KOH) since phenols are more acidic, and the 4,7-diphenoxyphen **829** has been obtained with yields varying between 70% to 87%.^{220,740,741}

Unsurprisingly, the aromatic nucleophilic substitutions can take place on coordinated 4,7-dihalogenated phen. Aksakal et al.²⁶² have formed the Ru(II) complex of **146** and then substituted the chlorine atom with a bis(perylene-diimide) bearing a phenol in bay position. This complex has proven to be an active photosensitizer for *in vitro* photodynamic therapy. Amphiphilic PEG-functionalized phen was obtained by using triethylene glycol monomethyl ether, NaH in DMF at 100 °C for 6 h and the ligand was obtained with yield over 94%. This phen_{(4,7)sub} ligand (and phen_{(2,9)sub} and phen_{(3,8)sub} parent molecules) has been used in the Cu-catalyzed aerobic oxidation in water with molecular oxygen as the oxidant to obtain various 9-fluorenones.⁸⁹

Formation of C-N bond

Various aliphatic amines (Scheme 151) or N-containing heterocycles (Scheme 152) have been used as a nucleophile. 2-aminoethanol, methylamine, ammoniac, 1,2-dimethylalkanediamine, various diaminoalkane, bis(2-methoxyethyl)amine and even poorly nucleophilic DMF have been used to perform the nucleophilic substitution on 4,7-dihalogenated phen either under microwaves irradiation or conventional heating.^{201,259,261,741,741-743,745-747} For example, the obtained ligands were used for the copper-catalyzed N-arylation of purines (Scheme 158, Larsen et al.)⁷⁴⁵ or as G-quadruplex stabilizers (Scheme 158, Nielsen et al.).²⁰¹ When using 3-dimethylaminopropylamine and heating the reaction in an oil bath at 140-150 °C for 4 h, the product **830** (Scheme 158, Molock et al.)²⁵⁹ is obtained with 89% yield (by microwave, yield

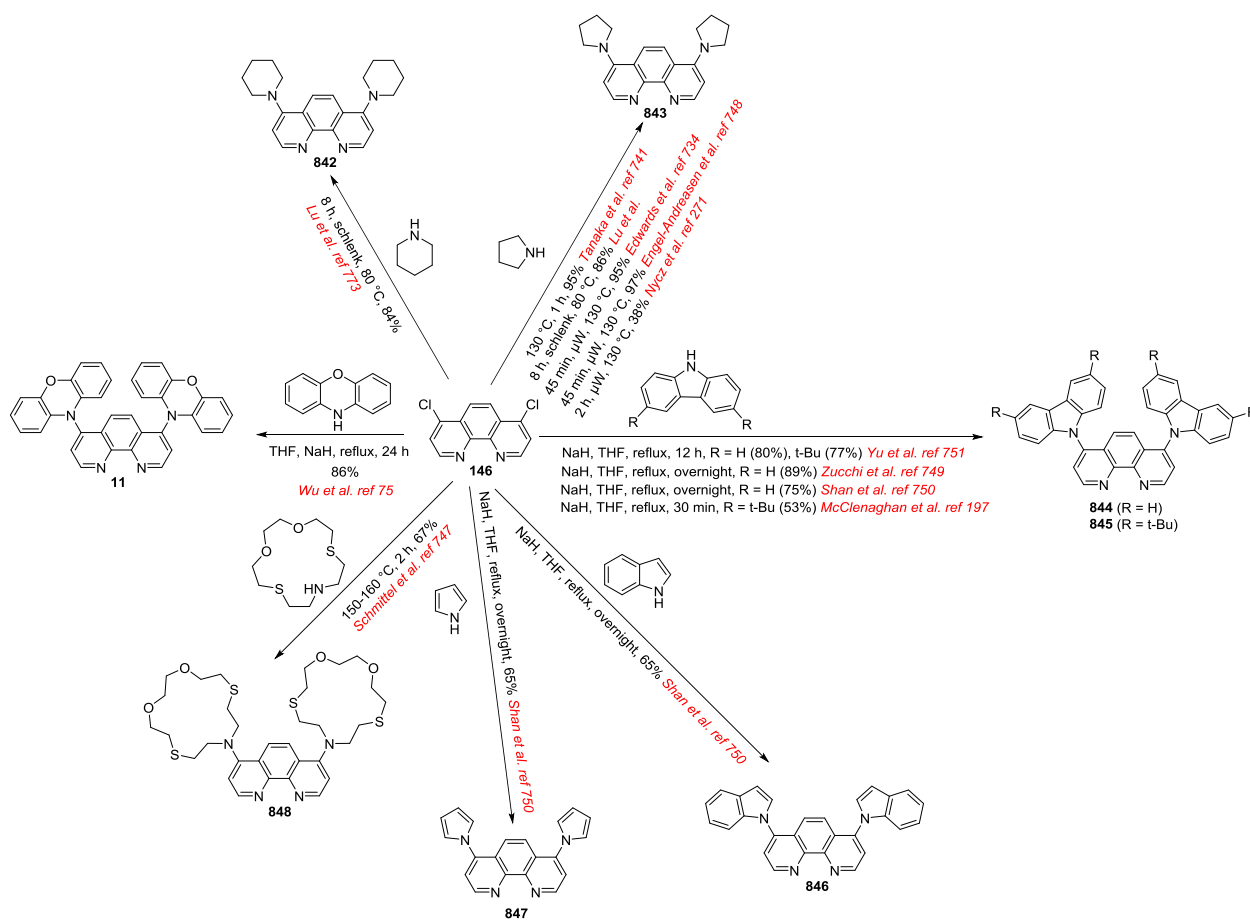
= 60%). The Mn complex of the **830** has been used to perform the esterification of tertiary amides (Scheme 158, Hirai et al.).⁷⁴⁶ DMF is used as pro-nucleophile, degrading into dimethylamine in the reaction conditions. This trick permits to avoid the use of very volatile dimethylamine (ebullition point at 7 °C). Tethering dimethylamine on phen allows to study the influence of electron donating substituents on the ligands and improves the palladium-catalyzed reductive carbonylation of nitrobenzene (conversely, electron-withdrawing chlorine atoms deactivate the catalyst)⁷⁴² or the catalytic α -oxidation of carboxylic acids.⁷⁴¹



Scheme 158. Nucleophilic aromatic substitution with various aliphatic amines

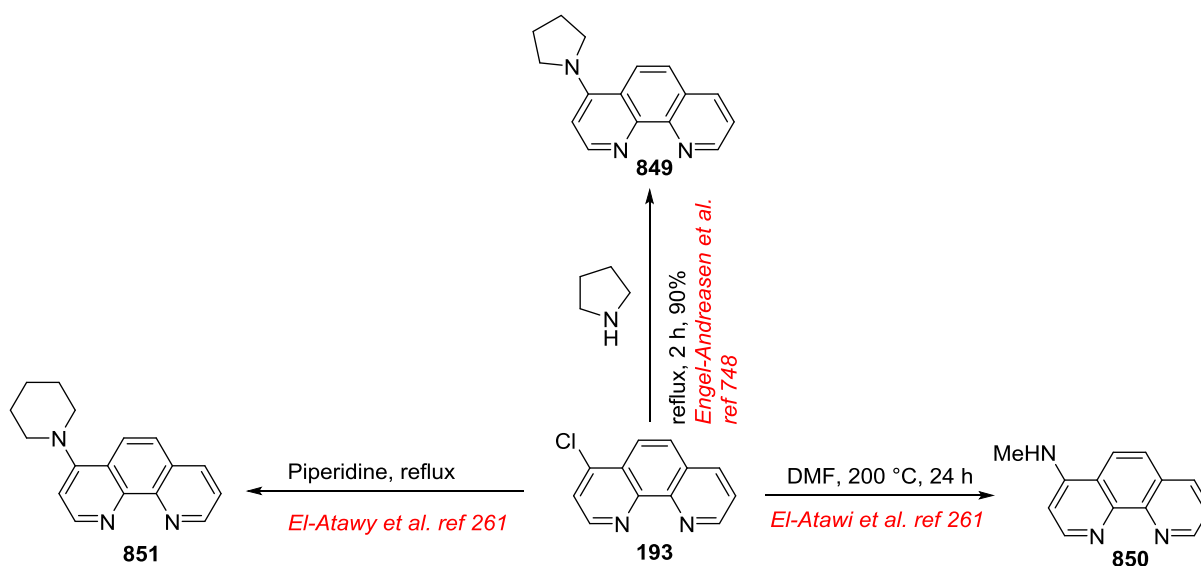
Regarding cyclic amines, pyrrolidine^{271,734,741,743,748} and piperidine⁷⁴³ have been introduced under classical conditions (reflux or Schlenk) or under microwaves irradiation with very good yields (Scheme 159). When refluxing phenoxazine and **146** in THF and in presence of NaH,

11 was obtained with 86% yield and was an efficient chromophore used in organic light emitting devices (Scheme 159, Wu et al.).⁷⁵ Schmitt et al. used a crown ether-type cycle to form in a good yield the corresponding substituted phen **848** (Scheme 159, Schmitt et al.).⁷⁴⁷ The corresponding iridium complex is an efficient sensor for Ag⁺ ions in aqueous media. Finally, pyrrole, indole and carbazole have been added for improved photophysical properties.^{197,749–751}



Scheme 159. Nucleophilic aromatic substitution on **146** with various cyclic amines

Similar reactions have been conducted on **193**. Piperidine and methylamine have been added in the reported conditions but no yields have been given.²⁶¹ Engel-Andreasen et al. introduced pyrrolidine with 90% yield (Scheme 160).⁷⁴⁸



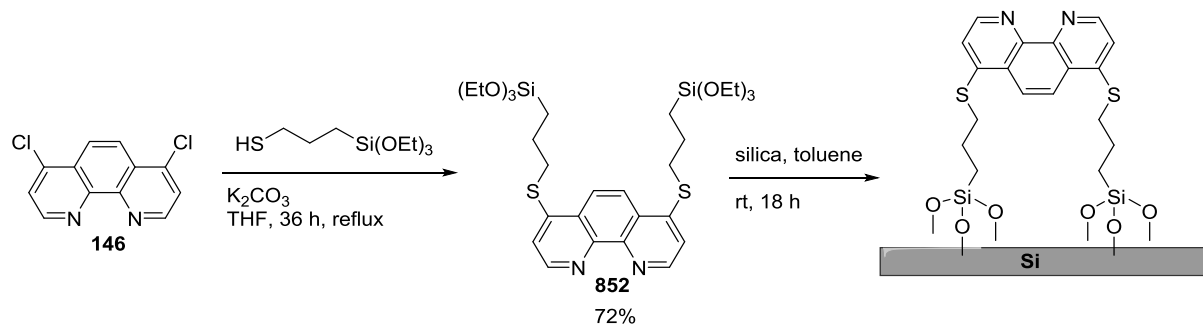
Scheme 160. Nucleophilic aromatic substitution on the 4-chlorophen with various amines

Finally, it is worth to mention that the 4,7-diaminophen **839** was obtained by reacting the 4,7-diphenoxyphen **829** (obtained from **146**) with ammonium chloride at 300-320 °C for 30 min. To purify **839**, the easiest way was to prepare the corresponding dihydrochloride salt that could be recrystallized in ethanol. Unfortunately no yield was given.²²⁰ Complexes of this ligand with rhenium⁷⁵² and europium⁷⁵³ have been prepared and studied for their anti-cancer and luminescence properties respectively. Surprisingly, the reactivity of this albeit very interesting synthon, has never been explored so far.

Formation of C-S bonds

Few examples can be found for the substitution of the chlorine or bromine atoms on 4,7-dihalogenated phen by sulfur atoms. Kabehie et al.⁷⁵⁴ have used 3-mercaptopropyltriethoxysilane and potassium carbonate on **146** in refluxing THF (Scheme 161). The ligand **852**, with reinforced σ -donating ability thanks to electron rich thioether groups, can be further immobilized on silica and used to design self-assembled copper(I) rotors immobilized on a surface. Likewise, **158** efficiently reacts with sodium thiomethoxide

to afford 4,7-bis(thiomethyl)-1,10-phenanthroline **853**. Corresponding heteroleptic copper(I) complexes (with diphosphine ligands) featured long lived and intense luminescence properties.⁶⁶⁶



Scheme 161. Immobilized ligand developed by Kabehie et al.⁷⁵⁴

4,7-bis(phenylthiol)-1,10-phenanthroline **854** is obtained with 83% yield by reacting **146** with thiophenol and finely powdered potassium hydroxide at 100 °C for 16 h.⁷⁴⁰

3.3.3. Concluding remarks

The reactivity of the 4,7-dihalogenated phen is versatile and has been well-exploited, although to a lesser extent than **396** or **405**. The synthesis of the 4,7-diiodophen is curiously not documented (although the 2,9-dimethyl-4,7-diiodo-1,10-phenanthroline is known).⁷⁵⁵ The high reactivity of the chlorinated and brominated ligands is however sufficient as demonstrated above.

It is important to remind that the 4,7-dihalogenated phen come from **145** obtained by convergent method. Interestingly, **145** can react directly with NaH and MeI to reach **827** with 70% yield (Scheme 157). This alternative method seems the simplest way to reach **827**, avoiding the unnecessary synthesis of 4,7-dihalogenated phen with toxic POX₃ (X = Cl or Br). However, efficient side reactions can take place with this strategy. For instance, Ballesteros et al.⁷⁵⁶ have attempted to alkylate **145** with benzyl chloride, sodium hydroxyde,

tetrabutylammonium bromide and benzene but a low yield is obtained because N-alkylation occurs as well on one of the nitrogen atom of the phen. To overcome this issue, **146** has been used as the starting material that reacted with benzyl alcohol under phase transfer catalysis at 120 °C for 2 h to obtain the target product with 63% yield.

Finally, decoration of phen in positions 4 and 7 can take place from specifically designed synthons obtained very often through convergent methods, as demonstrated in the dedicated section (section 2). There are numerous examples (a small sample is given in Figure 29) showing very traditional reactivities, and reviewing them all would be lengthy and inappropriate because not specific *per se* to phen chemistry.

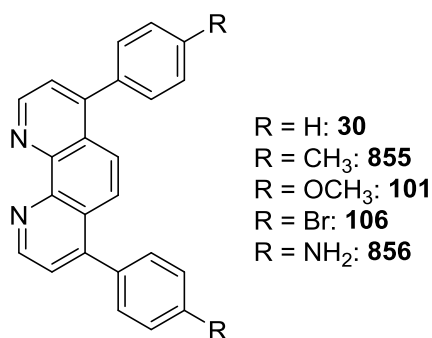
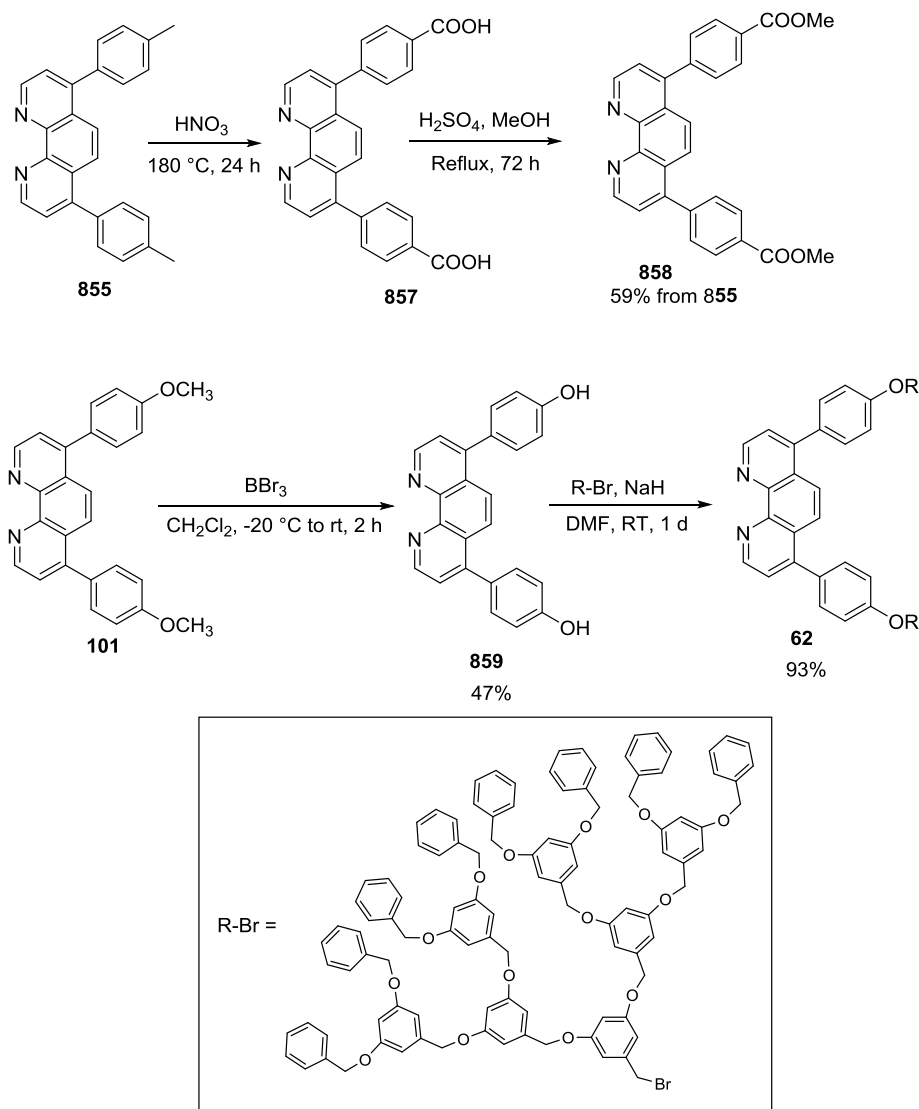


Figure 29. Examples of interesting phen_{(4,7)sub} synthons obtained by convergent methods

A few examples are nevertheless given in Scheme 162 for the readers consideration. The methyl groups of **855** are easily oxidized in carboxylic acids affording anchor-bearing **857**.⁷⁵⁷ Finally, Stephan et al. have obtained the 4,7-oxybathophen **859** through convergent methods.¹⁹⁸ Then the hydroxy group are deprotonated with sodium hydride and reacted with dendrons either highly branched (the corresponding Fréchet-type dendrons carrying a benzylic bromide function, Scheme 155)¹⁹⁸ or having ethylene glycol units.⁷⁵⁸ Those new dendritic phen ligands were shown to be able to extract Cu(II) ions from water.



Scheme 162. Examples of extended phen_(4,7)sub structure obtained from building blocks prepared by convergent methods

3.4. Functionalization of phen in positions 5 or 6 / 5 and 6

As mentioned in the introduction, substituents tethered to positions 5 and 6 of phen are likely to be a bit less influent on the overall properties of phen than the same substituents grafted at other positions. The first reason for this is they are remote from the N $\widehat{\text{N}}$ coordinating cavity. In addition, empiric observations tend to demonstrate that electronic effects from substituents in positions 5 and 6 are less prominent on the overall properties of the phen_(5,6)sub molecule and its complexes. From the reactivity point of view, C₅ and C₆ are electrophilic, as illustrated

by the large spin density on C₅ and C₆ in the HOMO of phen.⁷⁵⁹ Like in all the previous cases, all functionalization reactions in positions 5 and 6 rely on a few pivotal synthons obtained from naked phen, given in Figure 30. The syntheses of all those synthons and their use for further decoration of phen in positions 5 and 6 will be exposed in the following.

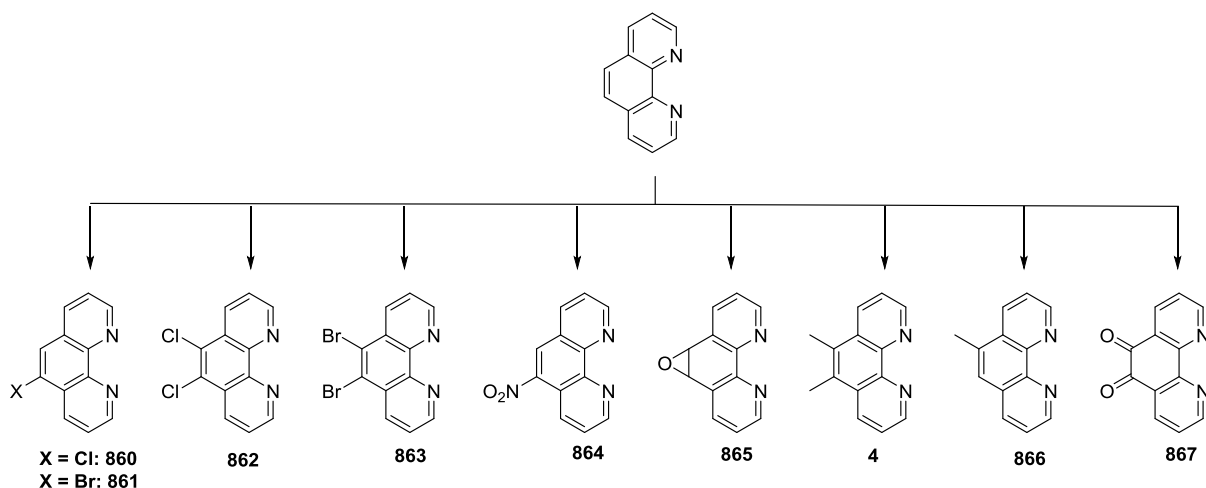
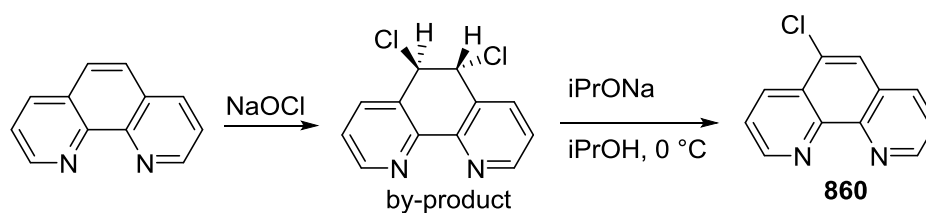


Figure 30. Structures of the pivotal phen_{(5,6)sub} synthons obtained from phen

3.4.1. 5- and 5,6-halogeno-1,10-phenanthroline synthons

3.4.1.1. Synthesis

The 5-bromo **861** and 5-chloro phen **860** are commercially available (between 100 € to 300 € for 1 g according to the suppliers) and the dihalogenated phen can be bought from custom chemical industries. These raw materials are quite expensive and considering to synthesize 5-halogeno-1,10-phenanthroline is therefore worthwhile. Surprisingly, only one paper⁷⁶⁰ describing the divergent synthesis of **860** was found. The authors used the by-product formed during the epoxidation reaction of the C₅=C₆ double bond using aqueous sodium hypochlorite. The by-product formed is 5,6-dichloro-5,6-dihydro-1,10-phenanthroline and when treated with a base, elimination of HCl occurs and **860** is formed but no yield was given (Scheme 163).

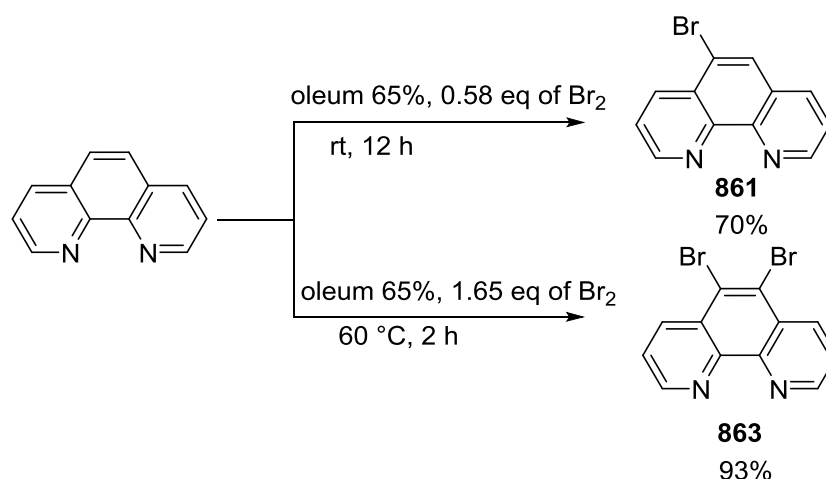


Scheme 163. Synthesis of 5-chloro-1,10-phenanthroline described by Antkowiak et al.⁷⁶⁰

There are many more published protocols to synthesize 5-bromo-phen **861** from phen. In all cases, the reaction requires the use of bromine and oleum and temperatures ≥ 120 °C. Depending on the authors, different conditions have been published, with varying yields. Usually, lower yields are due to the formation side products 5,6-dibromophen **863** and the phen-5,6-dione **867**. The good control of the conditions is necessary to limit the formation of those byproducts and obtain **861** in the highest yields.

Hissler et al.⁷⁶¹ have proposed a protocol in the 2000's adapted from the seminal experiment described by Mlochowski et al.⁷⁶² where they optimized the yield of **861**. More precisely, 20 mmol of phen is placed in a sealed tube, in an ice bath. While stirring, 12 mL of 15% oleum (fuming sulfuric acid) and 0.58 equivalent of bromine are added. Then, the mixture is heated up to 135 °C for 23 h. **861** is isolated after work-up and recrystallization in hot diethyl ether with 90 % yield. Importantly, the authors emphasize that the amount of bromine used, the reaction time and temperature (higher temperatures increase the formation of **863** and **867**) must be carefully controlled to reach high yields. For instance, when increasing the concentration of oleum (30%) and bromine (2.7 equivalents), the temperature (150 °C) and the reaction time (72 h), Yang et al.⁷⁶³ obtain **861** with 42% yield, after an Al₂O₃ column chromatography (eluent: CHCl₃) and recrystallization from a *n*-hexane-dichloromethane (1/1, v/v) solution. Doistau et al.⁷⁶⁴ used a 22-30% oleum solution and 0.47 eq of bromine and heated at 135 °C for 16 h and performed the recrystallization using CH₂Cl₂/EtO₂ to obtain the product with 42% yield. The lower yields obtained in the last two cases is probably partly

assignable to the higher concentration of oleum, which appears to be a particularly crucial parameter.⁸¹ Finally, Stumper et al.⁷⁶⁵ have developed a new synthetic protocol to obtain with high yield either **861** or 5,6-dibromo-phen **863**. The reaction is performed in 30 mL of a 65% oleum solution, 0.58 eq of bromine on 20 mmol of 1,10-phen hydrate at room temperature and normal pressure for 16 h. After work-up and after removal of the unreacted phen by stirring in hot ether for 12 h (column chromatography failed), a recrystallisation in chloroform (to remove **863**) allowed to obtain **861** with a satisfying yield of 70%. When the reaction is performed at 60°C using the same amount of oleum solution but a slight excess of bromine (1.65 eq) for 2 h, after the same treatments and purification steps, **863** is obtained with a very high 93% yield (scheme 164).



Scheme 164. Synthesis of 5-Bromo-phen **861** and 5,6-dibromo-phen **863** ligands according to Stumper et al.⁷⁶⁵

Previous attempts to reach **863** were slightly less successful. In the paper published in late 70's by Denes et al.,⁷⁶⁶ the bromination reaction was performed in thionyl chloride and in presence of 6 eq of bromine. The mixture was refluxed for 24 h (no need of an autoclave or sealed tube). The authors obtained a mixture of 5,6-dibromo-, 3,5,6-tribromo-, and 3,5,6,8-tetrabromo-phen. After different work-up and recrystallisation, they isolated **863** with a 6%

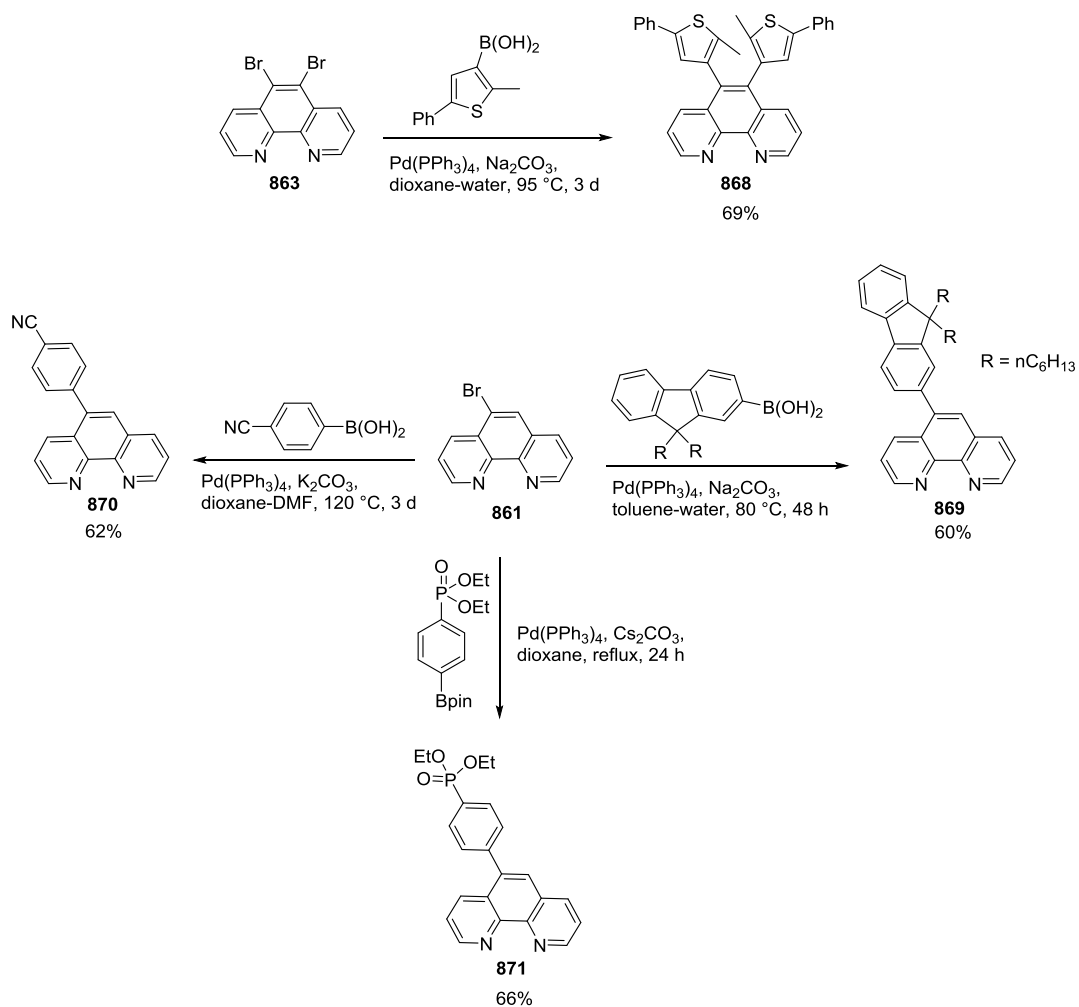
yield. Feng et al.⁸⁷ have obtained the target molecule in 65% yield by heating up phen in 30% oleum solution with 0.2 eq of bromine at 120 °C for 12 h in a sealed tube and recrystallisation in ethanol. Finally, Chesneau et al.⁷⁶⁷ have used 20% oleum solution and 2 eq. of bromine and heated the reaction mixture at 150 °C for 60 h. After a purification by column chromatography on deactivated alumina using CH₂Cl₂ as the eluent, **863** is obtained in 62% yield.

3.4.1.2. Functionalization starting from 5- and 5,6-halogenated phen

Metal catalyzed cross-couplings are the most documented reactions allowing to decorate 5-halogeno phen and 5,6-dihalogeno phen.

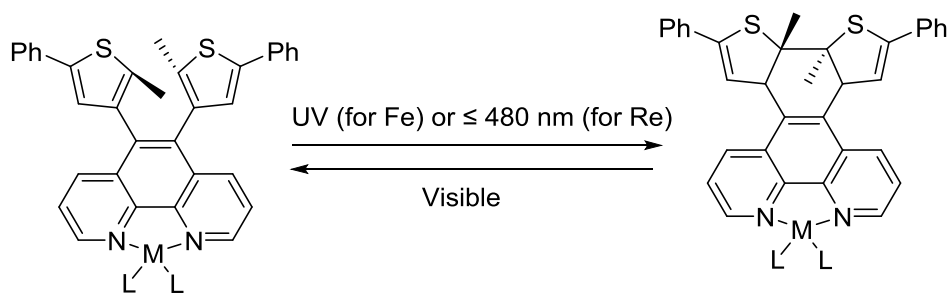
Suzuki coupling

Suzuki couplings can be performed on 5-bromo- and 5,6-dibromo-phen and the reported yields of the Suzuki coupling to produce functionalized phen_{(5)sub} or phen_{(5,6)sub} are satisfactory (Scheme 165).^{672,768–771}



Scheme 165. Examples of functionalization of **861** and **863** via Suzuki coupling.

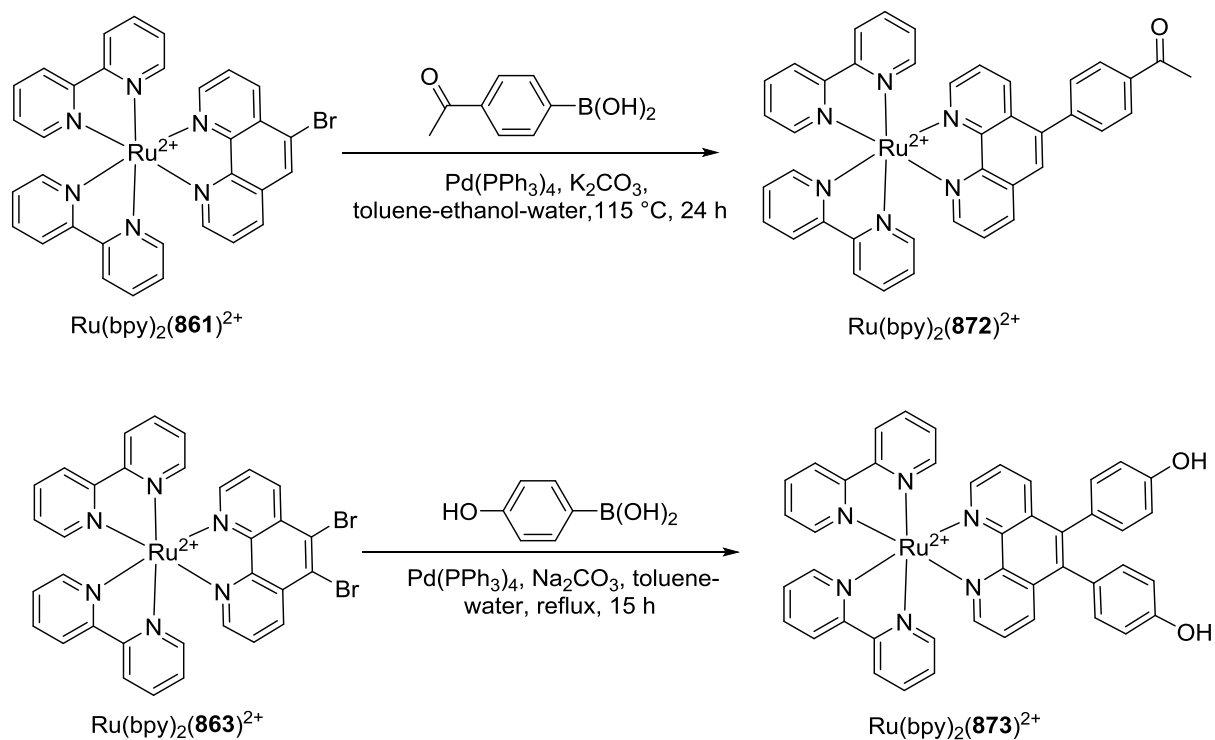
For **868**, the photophysical properties of the corresponding metallic (either rhenium or iron) complex were studied in the frame of molecular switches. Upon selective UV irradiation, ring closure takes place between the two thiophene moieties and under visible light, the system turns back to the open-ring isomer (Scheme 166). The switching between the two structures impacts the overall properties of the complexes. A similar molecule to **868** has been obtained *via* a Stille coupling.



Scheme 166. Molecular switches developed by Mörtel et al.⁷⁶⁸ after a Suzuki coupling

Jana et al.⁷⁷¹ synthesized through a Suzuki coupling on **861** 4-(1,10-phenanthrolin-6-yl) benzonitrile **870** and then hydrolyzed the nitrile group into carboxylic acid group (Scheme 165). This ligand was then used to synthesize an inorganic coordination polymer (either using cobalt or manganese ions) and Pd nanoparticles were incorporated into the polymer. This new Pd@MOF was proven to be effective as a heterogeneous catalyst in Suzuki reaction.

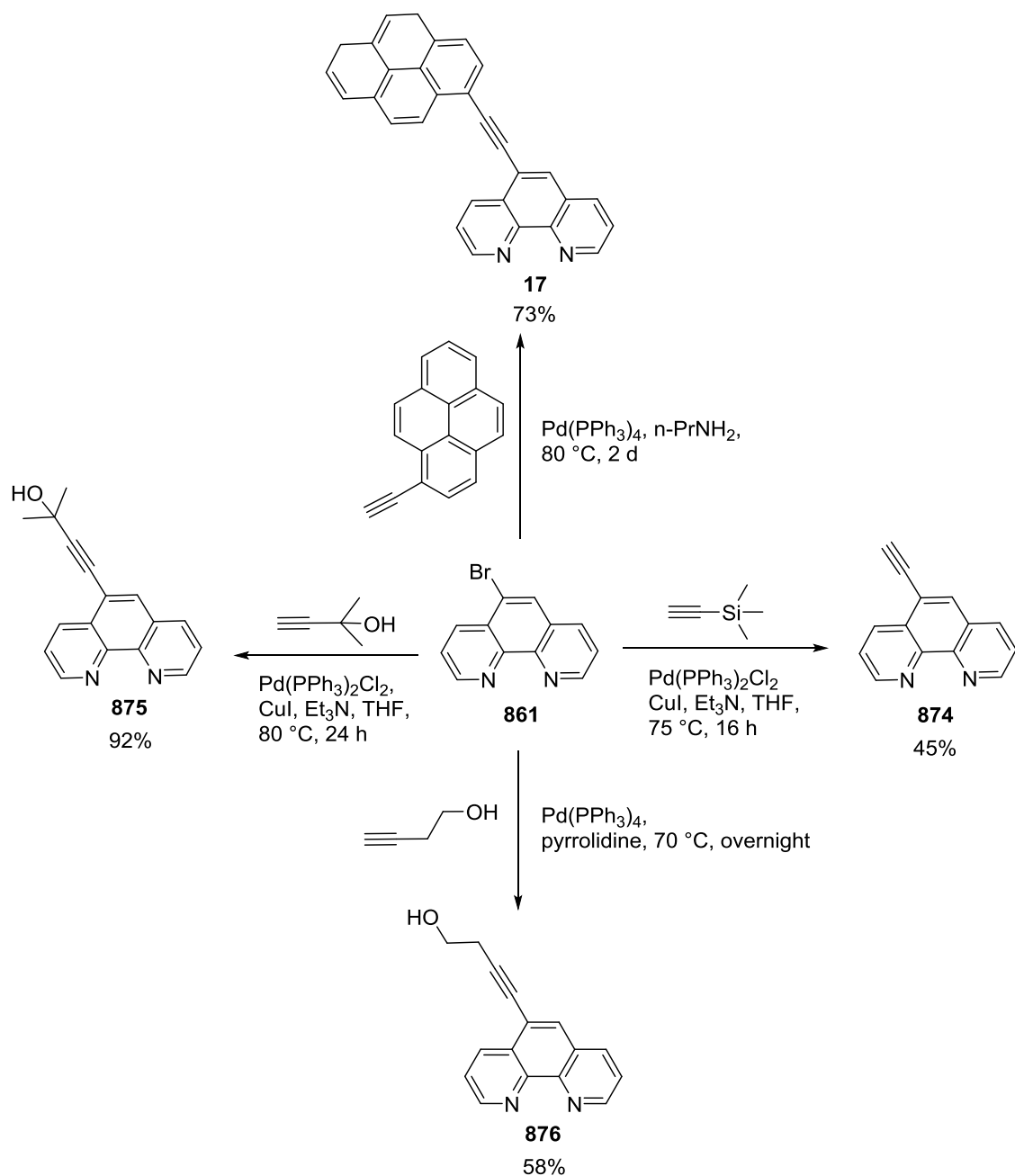
Interestingly, Stumper et al.⁷⁶⁵ were not able to perform a Suzuki coupling reaction on **863** or **861** using either 4-acetylphenylboronic acid or 4-hydroxyphenylboronic acid. The Suzuki reaction was only successful on the corresponding ruthenium complexes (Scheme 167). A possible explanation is that coordination of the N[^]N cavity by electrophilic Ru²⁺ ions activates the C₅-Br bond towards the oxidative addition. We note that **860** has not been involved in any Suzuki coupling, probably because the C₅-Cl bond is too unactivated vs. oxidative addition on Pd as well.



Scheme 167. Chemistry on the complex : Suzuki coupling necessitating the coordination of the Ru(II) ion.

Sonogashira coupling

Pd-catalyzed Sonogashira coupling has also been employed with 5 or 5,6-bromo (**861** and **863**) or chloro phen (**860** and **862**) and some examples on **861** are given in Scheme 168.^{688,764,772,773}



Scheme 168. Examples of Sonogashira coupling on **861**.

Monro et al.⁶⁸⁸ have synthesized **17** to prepare the corresponding Ru(II) complexes. Their photobiological properties were evaluated for photodynamic therapy. Interestingly, the same complex bearing the pyrenylethynylene fragment in position 3 of phen has been studied in parallel. Both complexes photocleave DNA when irradiated with visible light but the Ru(II)

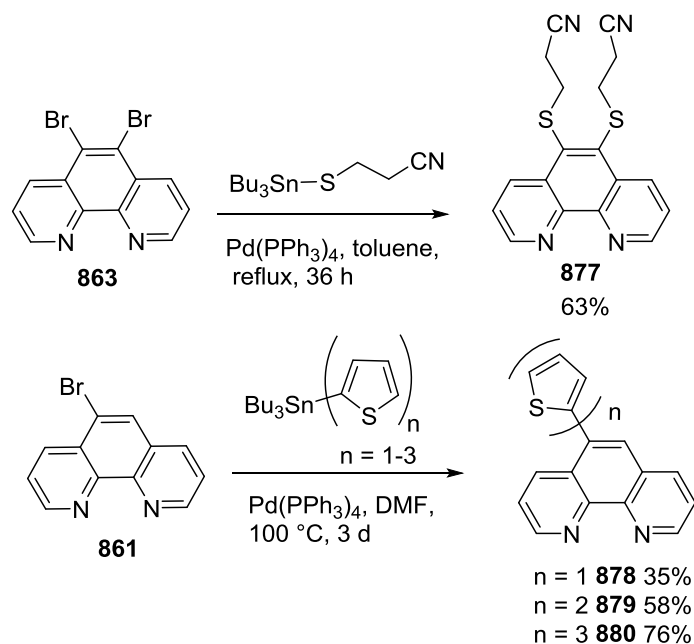
complex with the pyrene group attached in position 3 is more efficient (i.e. causes more damage to DNA).

Contrary to the Suzuki coupling, **860** has been successfully utilized as substrate to perform Sonogashira couplings^{737,774} with phenylacetylene. However, the yield of the reaction is mediocre (16%) in conventional conditions and much higher when performed on **861**⁴⁴ instead (interestingly, using copper-free Sonogashira conditions allows to reach the same target molecule with a significantly better yield (60%)).¹⁰⁴

The reactivity of the C₅-Cl bond can be improved when the **860** is coordinated by Ru²⁺ ions. Indeed, operating the coupling of phenylacetylene on [Ru(bpy)₂(**860**)]²⁺ instead of the free ligand, in similar conditions, allows to increase the yield to 65%,⁷⁷⁴ probably for the same reasons than above (activation of C₅-Cl bond towards oxidation addition). Another example of coupling-on-the-complex is provided by Hissler et al.⁷⁶¹ who have performed a Sonogashira coupling reaction directly on the platinum complex bearing **861** as a ligand, and using ethynylbenzene as alkyne.

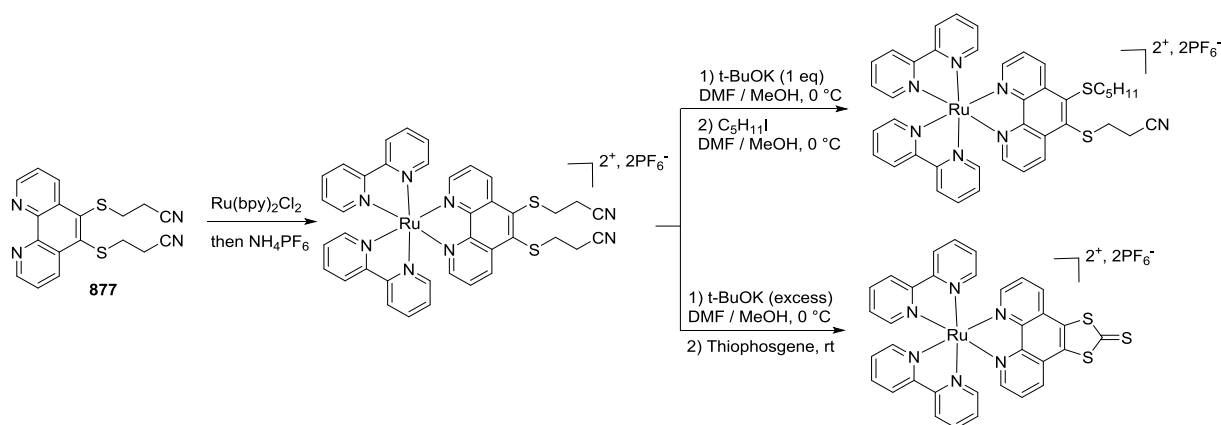
Stille coupling

Stille coupling, even though less explored, has been described on **861** or **863** (Scheme 169).^{767,775,776}



Scheme 169. Examples of synthesis of phen_{(5)sub} and phen_{(5,6)sub} *via* Stille coupling on 5-halogeno-phen **861** and 5,6-dihalogeno-phen **863**.

C₅-C and C₆-C bonds are formed rather efficiently using the Stille coupling conditions. Rau and co-workers notably report that the coupling of thiophenes onto **861** is challenging and that Stille coupling has proven to be a very efficient alternative to other metal-catalyzed cross-couplings.⁷⁷⁵ Moreover, Chesneau et al.⁷⁶⁷ have achieved an interesting C-S coupling reaction and obtained 5,6-bis(2-cyanoethylsulfanyl)-1,10-phen **877** building block after a Stille reaction involving **863** and 3-[(tributylstannyl)thio]propanenitrile. Then, after formation of the corresponding Ru(II) complex, one of the appended thioether bonds can be selectively hydrolyzed leading, after quenching of the thiolate by 1-iodopentane, to a Ru complex bearing an unsymmetrical phen_{(5,6)sub} ligand (scheme 170). Alternatively, both thioether bonds can be hydrolyzed into thiolates and quenching with thiophosgene results in the formation of 1,3-dithiole-2-thione derivative with potentially interesting redox properties.

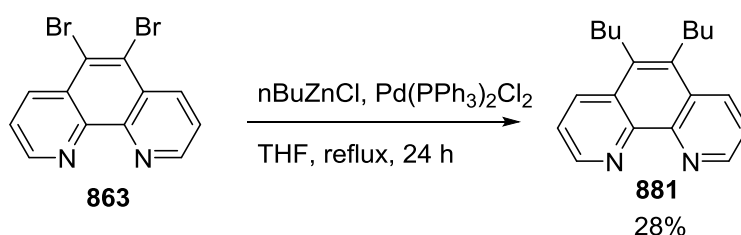


Scheme 170. Synthesis of unsymmetrical Ru(II) complex developed by Chesneau et al.⁷⁶⁷

Stille couplings from **860** could not be found during our literature survey, possibly because of the lack of reactivity of the C₅-Cl bond as experienced in the other cross-coupling reactions.

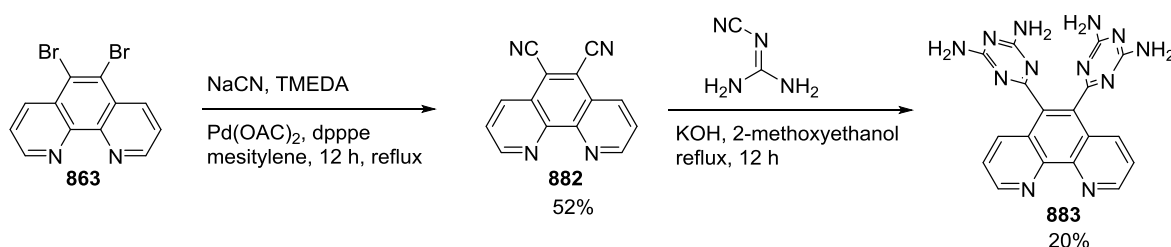
Concluding remarks

Other rarer metal-catalyzed cross-couplings have been performed on halogenated phen in positions 5 or 5 and 6. Feng et al.⁸⁷ have reported a C-C bond formation from **863** using a Negishi cross-coupling with BuZnBr catalyzed by a palladium source (Scheme 171). The Kumada coupling with the corresponding Grignard reagent has been tested by the same authors but this reaction is reported to be less effective.



Scheme 171. Formation of C-C bond from the 5,6-dibromo-phen **863** through a Negishi cross-coupling reaction⁸⁷

The Br atoms of **863** can be replaced by nitrile groups, when reacted with sodium cyanide, palladium acetate, 1,5-bis(diphenylphosphino)pentane, tetramethylethylenediamine in mesitylene and refluxed for 12 h. The target 5,6-dicarbonitrile phen **882** is obtained with 52% yield. The reaction of the latter with dicyandiamide leads to the diaminotriazine functionalized phen_{(5,6)sub} derivative **883** (Scheme 172), similar to the phen_{(4,7)sub} one described in Scheme 156. Let us notice the low yield (20%)⁷⁰⁴ of this reaction when performed on 5,6-dicarbonitrile phen **882** compared to 4,7-dicarbonitrile phen **821**. This could be due to the steric hindrance caused by the DAT groups.

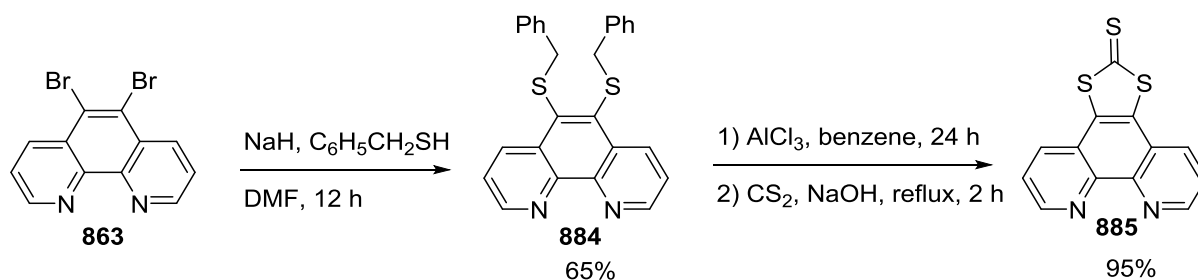


Scheme 172. Synthesis of 5,6-dicarbonitrile-phen **882** and reactivity of the latter in presence of dicyandamide.

Finally, it is interesting to notice that, to the best of our knowledge, no C-P formation was reported on the 5,6-halogeno-phen. However, on **861**, the corresponding phosphorylated phen was formed through an Hirao cross coupling using classical conditions: diethylphosphite, Pd(OAc)₂/dppf, triethylamine in refluxing toluene and yields from 80 to 90% were obtained.^{460,708,709}

Although the aromatic nucleophilic substitutions are very common on halogenated phen_{sub} in positions (2,9), (3,8) and (4,7), they are comparatively very rare on 5- or 5,6-halogeno-phen. Keniley et al.⁷⁷⁷ reported the reaction between **863** and sodium benzylthiolate (generated *in situ* from the corresponding thiol and sodium hydride). Then, the dithiolate dianion formed *in*

situ reacted with CS₂ under basic conditions to form the free ligand 1,3-dithiole-2-thione-phen **885** (Scheme 173).



Scheme 173. Formation of C-S bond by aromatic nucleophilic substitution on **863**⁷⁷⁷

At the end of this section, there is an array of presumptions pointing to the fact that C₅-Halogen and C₆-Halogen are indeed less reactive than the other C_n-Halogen bonds (n = 1-4 and 7-9). Original methods are sometimes necessary to circumvent this lack of reactivity. As a last example, Galopini et al.⁷⁷⁸ have published an original and efficient way to prepare 5-(4'-phenylacetylene)-1,10-phenanthroline **886**, by generating *in situ* a reactive alkyne-borane derivative (from the corresponding acetylide and B-methoxy-9-BBN) which is coupled to **861** using Pd(PPh₃)₄ as catalyst. In these conditions, a high yield of 90% has been reached.

3.4.2. Nitration and amination of phenanthroline in position 5

The 5-nitro-1,10-phenanthroline **864** is commercially available at reasonable prices from classical suppliers (for 1 g: from 28 to 88 €). On the contrary, 5,6-dinitro-1,10-phenanthroline **887** is not commercially available and no synthesis has been described.

The seminal work on the nitration has been published by Hammett et al. in 1934⁷⁷⁹ who have dissolved 1 g of phen in 10 mL of concentrated nitric acid, and this solution was added to 20 mL of 95% sulfuric acid solution. The mixture is heated up at 115-120 °C for 1 h. After precipitation and recrystallization in water, **864** is obtained with 26% yield. Smith et al.⁷⁸⁰ have improved the synthesis by replacing sulfuric acid solution by a 25% oleum solution.

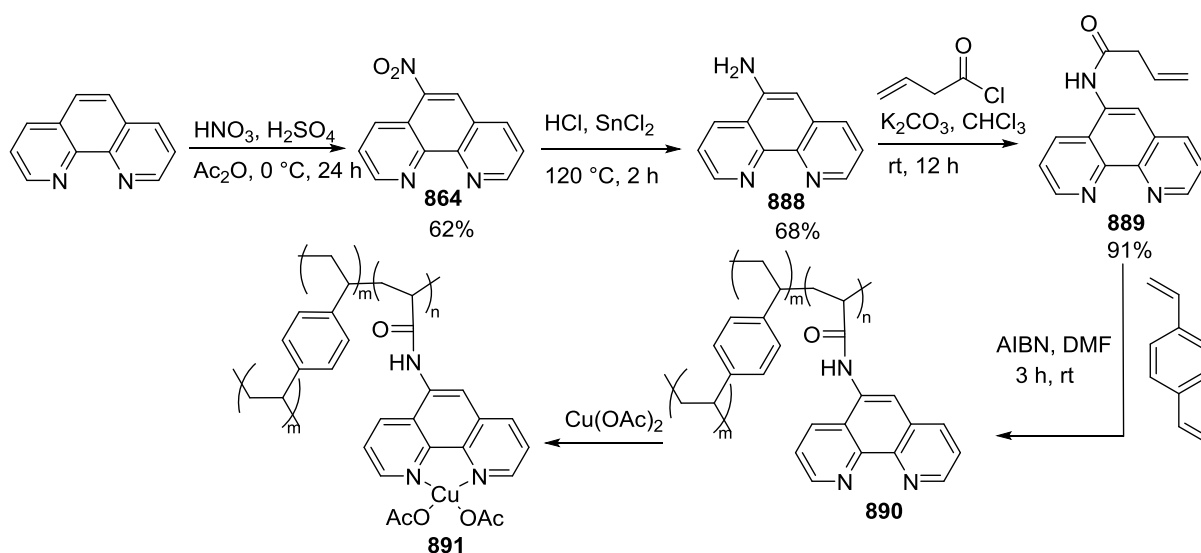
Thus, 30 g of phen monohydrate is dissolved in 150 mL 25% oleum solution, 80 mL of concentrated HNO₃ solution is added and the reaction is heated at temperatures close to 170 °C for ca. 30 min. The best yield (90%) was obtained when the temperature was 165 °C. Above and below that temperature, the yield started to decrease meaning that the temperature of the reaction is a critical parameter to control. While performing this reaction, the formation of by-products has been noticed and attributed to the formation of phen-5,6-dione **867**.

More recently, Ji et al.⁷⁸¹ have described the synthesis of **864** with 99% yield using concentrated sulfuric acid with a solution of fuming nitric acid at 160 °C. The temperature is maintained for 3 h. Algi⁷¹⁴ has followed almost the same conditions but heated up the mixture for 3 h at 120 °C and obtained **864** with 65% yield after recrystallization in 95% ethanol. Patel et al.⁷⁸² have used a protocol very close from Smith et al.. They have dissolved the phen in oleum solution and added dropwise a solution of 70% of nitric acid while keeping the temperature just below 170 °C. After the addition of nitric acid, the heating of the reaction is continued for 30 more min. They obtained **864** with 64% yield. All the other protocols are basically similar, with variations of yields due to variations of temperature and heating time.^{783–787} However, one different protocol has been published in 2013 by Sun et al.⁷⁸⁸ where the synthesis of **864** is performed using this time 10 mL of concentrated nitric acid and 60 mL of cool acetic anhydride with 1 mL concentrated sulfuric acid (98%), onto which is added 1 g of 1,10-phenanthroline. The resulting solution is stirred at 0 °C for 24 h. After work-up and recrystallization in water, **864** is obtained with 62% yield.

864 is usually transformed into 5-aminophen **888** for further transformations and various applications. The reduction of the nitro group is conducted using hydrazine hydrate (from 1.2eq to 5 eq) with 5% or 10% Pd-C as a catalyst in reflux in EtOH for 2 to 10 h^{714,781,783–787,789–793} or in MeOH.⁷⁹⁴ Yields of this reduction vary from 31 to 92%. Deviations from those classical conditions consist for instance in using Raney-Ni as reduction catalyst (yield =

51%)⁷⁹⁵ or using tin chloride in concentrated HCl as a reductive agent at 120 °C for 2 h (yield = 68%).⁷⁸⁸ Incidentally, Garcia-Fresnadillo et al.⁷⁹⁰ have tested hydrazine or tin chloride or Na₂S₂O₄ as the reductive reagents but the yields were lower with SnCl₂ or Na₂S₂O₄ compared to hydrazine.

The amine tethered to position 5 can be involved in several classical reactions. For example, Sun et al.⁷⁸⁸ have reacted **888** with acryloyl chloride to form a peptide bond and connect polymerizable acrylamide to phen. The latter undergoes copolymerization with divinylbenzene affording the polymer **890** bearing pendant phen cavities, able to coordinate Cu(II) ions. This polymer-supported copper catalyst was found to be active in the Glaser coupling reaction and in the Huisgen cycloaddition /reaction (Scheme 174).



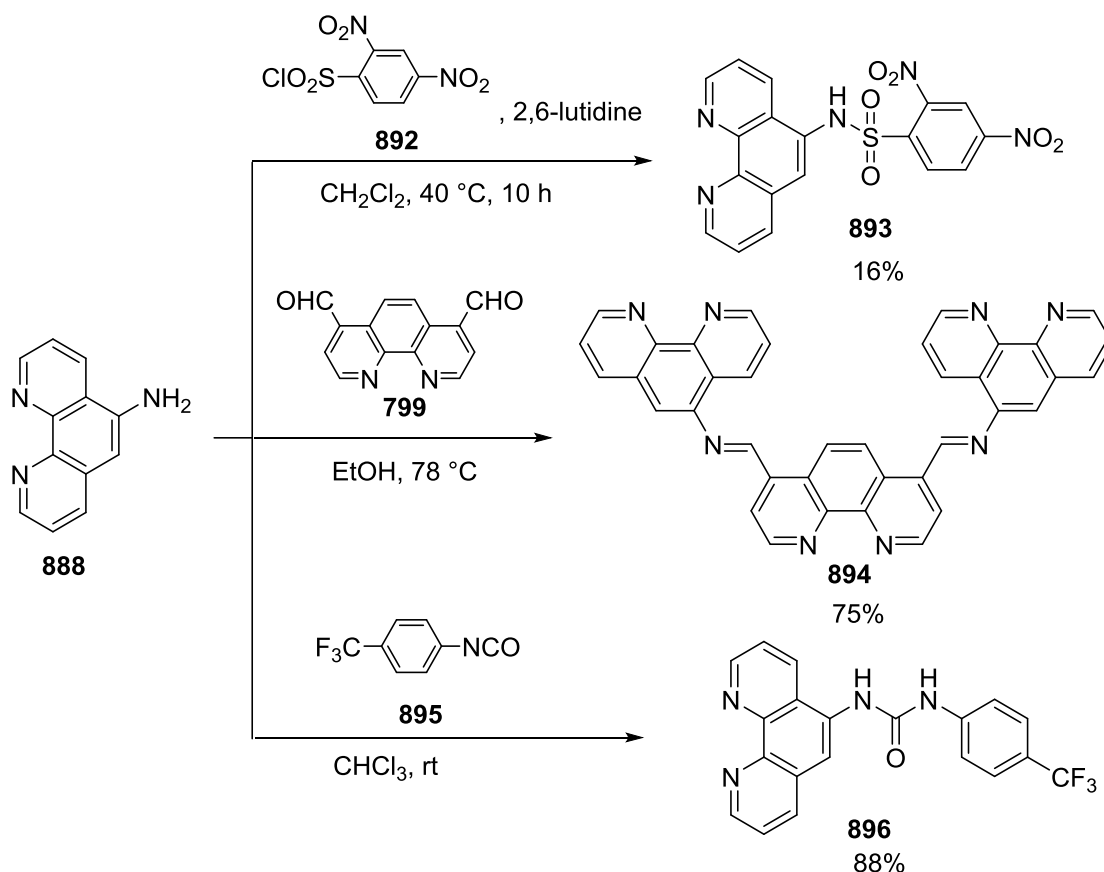
Scheme 174. Synthesis of a polymer-supported copper catalyst active in the Glaser coupling reaction and in the Huisgen cycloaddition reaction⁷⁸⁸

Ji et al.⁷⁸¹ have reacted **888** with 2,4-dinitrobenzenesulfonyl (DNBS) chloride and used the obtained ligand **892** to form a Ru(II) complex [Ru(phen)₂**892**]²⁺ acting as thiol luminescent sensor (Scheme 175). Indeed, the [Ru(phen)₂**892**]²⁺ complex is non-luminescent (due to an efficient photo-induced electron transfer from the Ru(II) ion to the dinitrobenzene moiety)

but in the presence of a thiol, the DNBS is cleaved and luminescence is restored. Interestingly, peptide couplings are performed mainly with acyl chloride or anhydrides,⁷⁹⁶ but there are a few examples where coupling agents (DCC,^{797,798} EDC⁷⁹⁹) have been used to reach the target molecules.

Other types of reactions are feasible with synthon **888**. Algi⁷¹⁴ has reacted **888** with **799** and this ligand **893** can be used as a selective fluorescent Zn²⁺ sensor (Scheme 175). **888** is sufficiently nucleophilic to readily react with isocyanates too. For example, ligand **896** obtained by reacting trifluoro-p-tolyl isocyanate **895** with **888** is proven in this case to be a selective fluorescent probe for chloride anion (Scheme 175).⁷⁹³ Kabehie et al.⁷⁵⁴ reacted **888** with 3-(triethoxysilyl)propyl isocyanate that yielded the product with 39% yield. This ligand was then immobilized on silica using toluene as the solvent.

Hossein-Beyki et al.⁷⁸⁴ developed a core-shell magnetic chitosan biopolymer where shell chitosan is grafted with 5-acrylamido-phenanthroline and was cross-linked to the magnetic core (Fe₃O₄ nanoparticles) with glutaraldehyde. This new biopolymer has proven to be effective to remove Pb and Cu ions from environmental samples. Jiang et al.⁷⁹¹ developed as well a new material to remove heavy metals from water based on chitosan and **888**.



Scheme 175. Imine and urea bond formation on **888**

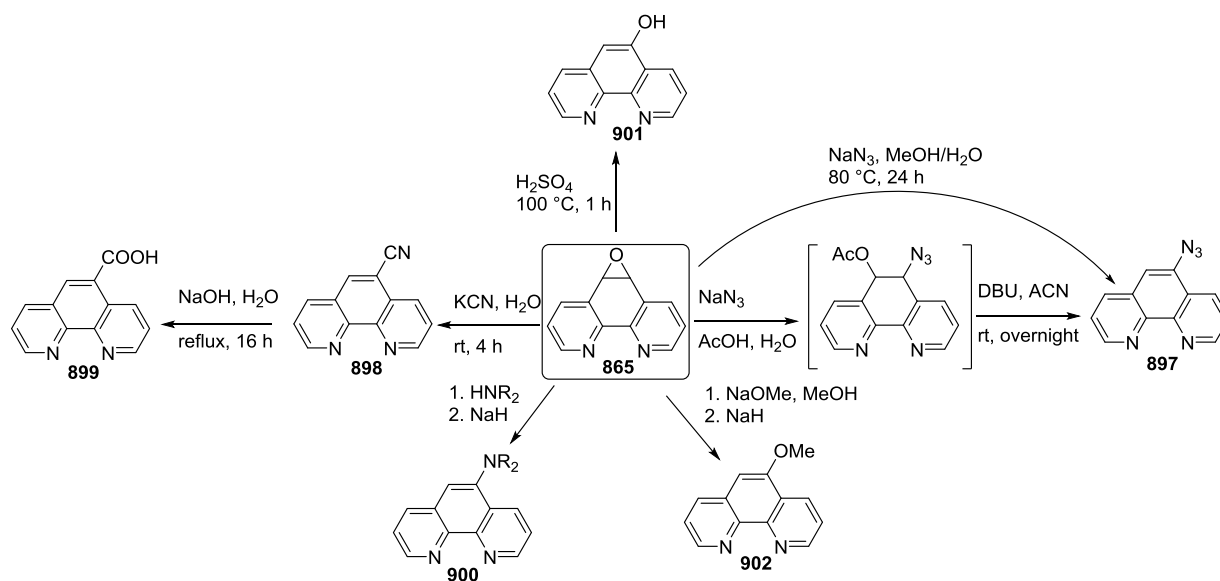
3.4.3. Synthesis of the phen-5,6-epoxide

Phen-5,6-epoxide **865** is not a phen_{(5,6)sub} derivative *per se* because the C₅=C₆ double bond has been reduced. However, it is a very versatile synthon giving access to a wealth of important phen_{(5)sub} building blocks.

One of the seminal works on the formation of **865** has been reported by Krishnan et al.⁸⁰⁰ The synthesis consists in reacting phen with aqueous sodium hypochlorite in the presence of a phase transfer catalyst (tetrabutylammonium hydrogen sulfate) while keeping the pH between 8 and 9 (adjusted with concentrated HCl). **865** is obtained with 92% yield and no N-oxide by-product is observed. Then Moody et al.^{801,802} have used commercially available bleach, water and tetrabutylammonium hydrogen sulfate while again adjusting the pH between 8 and 9 and have obtained **865** with 98% yield. From those works, very little modifications have been

made in the more recent experimental protocols (reaction time will vary depending on the bleach quality, and depending on the pH variation) and the yields varied from 50 to 93%.^{803–810}

As mentioned above, various versatile phen_{(5)sub} ligands can be obtained from the ring opening of **865** by nucleophiles (Scheme 176).



Scheme 176. Examples of ligands prepared from the phen-5,6-epoxide **865** through a nucleophilic attack followed by dehydration.

5-hydroxy-1,10-phenanthroline **901** can be obtained easily by reacting **865** in aqueous sulfuric acid solution at 100 °C.^{803,804,806,807,810} For example, galactopyranose has been efficiently coupled to **901** through a nucleophilic attack of the hydroxyl group on the appropriate brominated derivative. The ligand is used to assemble an iridium complex serving as a probe for ovarian carcinoma cells.⁸¹⁰ Alternatively, the deprotonated hydroxyl group of **901** (with K₂CO₃) performs a nucleophilic attack on ethylene oxide to obtain alkoxyated ligand that is in turn grafted onto carbon nanotubes.⁸⁰⁶

901 and 5-alkylatedamino-1,10-phenanthroline **900** could be obtained by simply using sodium methoxide and dimethyl⁸⁰³ or diethylamine⁸⁰⁸ respectively in refluxing solvent. Those nucleophiles readily open the epoxide and form an intermediate that is rearomatized after elimination using NaH.

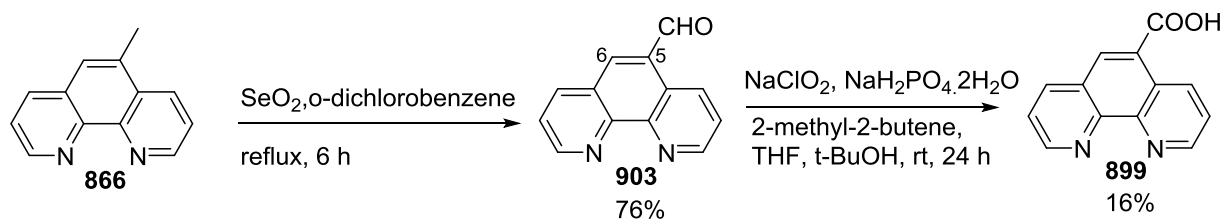
5-azido-1,10-phenanthroline **897** can be obtained from the azido-acetate intermediate prepared from a procedure described by Sanfilippo et al.⁸¹¹ and then rearomatized using a base.⁸¹² Alternatively, this ligand can be obtained directly from **865** using NaN₃ in refluxing MeOH/H₂O.⁷⁸⁵ For example, this ligand has been further used for the formation of luminogenic iridium complexes and of course in click chemistry.⁸¹²

5-cyano-1,10-phenanthroline **898** can be obtained by reacting **865** with potassium cyanide in water.^{803,809,813} Then, the cyano group can be hydrolyzed in refluxing soda to afford 1,10-phenanthroline-5-carboxylic acid **899**.⁸⁰⁹ The latter was used to form efficient ruthenium sensitizer for DSSC.⁸⁰⁹

*3.4.4. Reactivity of 5-methyl-1,10-phenanthroline **866***

5-methylphen **866** is commercially available or easily obtained by convergent synthetic methods. Interestingly, the reactivity of the methyl groups on phen is approximately similar regardless the position it is tethered to.

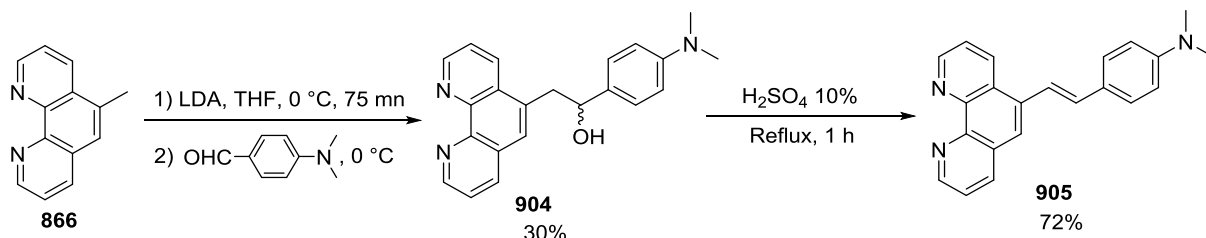
The methyl group of **866** can be oxidized by SeO₂ efficiently, but higher temperatures than usual are required. The reactivity of the CHO group has been exploited in a few cases (e.g. formation of imine bonds⁸¹⁴ with rhodamine, synthesis of benzimidazoles with diketones⁸¹⁵ or diamines⁸¹⁶). **903** can be further oxidized into **899** through by a Pinnick reaction (Scheme 177)⁸¹⁷ instead of the more conventional method (HNO₃ at reflux). We tentatively propose that HNO₃ may induce parasitic reactions on **903** such as undesired partial nitration in position 6.



Scheme 177. Synthesis of 1,10-phenanthroline-5-carboxylic acid **899** starting from **866**⁸¹⁷

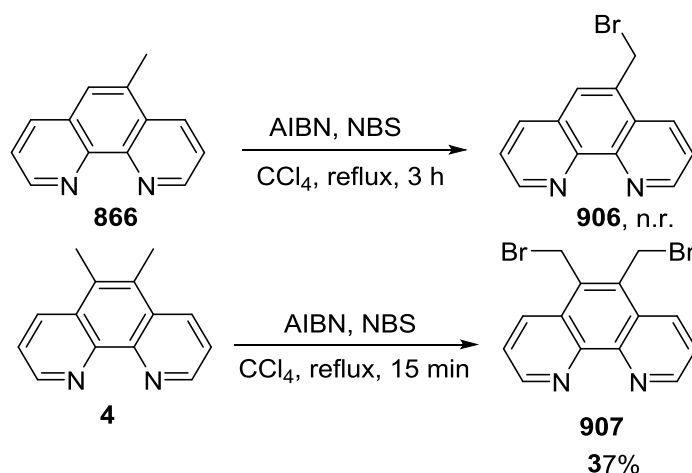
899 can be then coordinated to palladium ions and the resulting complex supported on amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin. This new catalyst proves to be effective in the palladium-catalyzed Friedel-Crafts-type alkylation of indoles in water.

Apart from the oxidation reaction, the methyl group of **806** can be deprotonated by LDA (Scheme 178).⁸¹⁸ The resulting carbanion efficiently reacts with *p*-(dimethylamino)benzaldehyde giving **904** which quickly turns into **905** after elimination of one molecule of water.



Scheme 178. Deprotonation of **866** and subsequent alkylation with *p*-(dimethylamino)benzaldehyde

Finally, bromination of **4**⁷¹⁷ and **866**⁸¹⁹ can be achieved with NBS in refluxing CCl₄ (Scheme 179). Importantly, the reported reaction time for the radical bromination of **866** is much longer than **4**. Polybromination of the methyl group is likely to happen but cannot be assessed since **906** has not been isolated nor characterized.



Scheme 179. Formation of 5,6-bis(bromomethyl)phen **907**

The CH_2Br groups are electrophilic and can thus react in presence of nucleophiles like trimethylamine⁸²⁰ or cyclam.⁸¹⁹ **907** has not been used for its reactivity, as a matter of fact this compound showed DNA intercalating and crosslinking activity, and was stable in aqueous solution thus making it a potential anticancer agent.

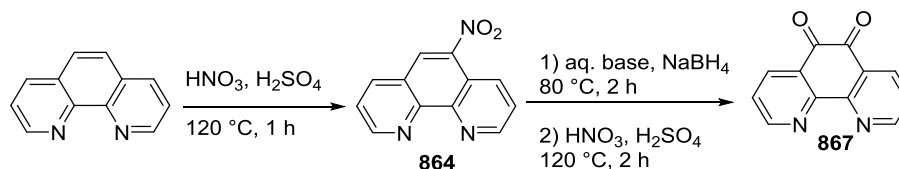
3.4.5. Synthesis and reactivity of the phen-5,6-dione (“phendione”) synthon **867**

Phendione **867** is probably one of the most versatile building blocks ever used to functionalize phen. A plethora of articles describes the synthesis of **867**.^{652,711,792,821–914} The common point to all the reported procedures is the strongly acidic (ensuring phen is protonated and increasing the solubility) and oxidizing conditions. Phendione can be further transformed into precious synthons for numerous applications. Only selected examples are presented below.

3.4.5.1 Synthesis of the phen-5,6-dione (“phendione”) **867**

The first synthesis of **867** was reported in the 40’s from the **864** but with very low yields (~1%).⁷⁸⁰ In 1970, Dickeson et al.⁸⁶⁴ improved the synthesis by reacting the **888** (obtained from the reduction of **864**) with concentrated sulfuric acid and fuming nitric acid and the mixture was heated up for 2 h at 120 °C. After work-up and recrystallization in MeOH, **867** is

obtained with 50% yield. The same year, Gillard et al.⁸²² described the same strategy but gave no final yield. But this strategy involved a curious three-step synthesis consisting of nitration in position 5 of phen, then reduction step and finally oxidation into **885** (Scheme 180).



Scheme 180. Three step synthesis to obtain phendione **867**

In 1990, Amouyal et al.⁸⁵⁰ has described the synthesis in one step from phen: phen monohydrate in 20% oleum solution is heated up at to 110-115 °C and nitric acid is added to the solution. The latter is then refluxed at 143 °C and nitric acid is added again over 30 min. At the end of the addition, the mixture is cooled to 115 °C and the solution is stirred for another 1 h 30. After work-up and recrystallization in methanol, **867** is obtained with 20% yield. Yamada et al.⁹¹⁵ has both simplified and improved this strategy by adding potassium bromide in the acidic mixture and heating the mixture only 2 h at 80-85 °C affording **867** with 86% yield. Although this was not rationalized, the formation of bromine is clearly observed and plays a crucial role in the synthesis of **867**. Hiort et al.⁸⁷⁸ have used sodium bromide instead of potassium bromide and refluxed the reaction mixture for 40 min and obtained 45% yield. They mentioned that the yield dropped to 20% when no sodium bromide was added, underlining the paramount importance of bromide ions for the completion of the reaction. Rosa Lopez et al.⁸²¹ describes the 2-step synthesis of phendione by first reacting phen with bleach and tetra-n-butylammonium hydrogensulphate. After the work-up, a crude intermediate is obtained and treated with a mixture of HNO₃ and H₂SO₄ at 90 °C. Phendione **867** is finally obtained with 53% yield after recrystallization in methanol. Even though no

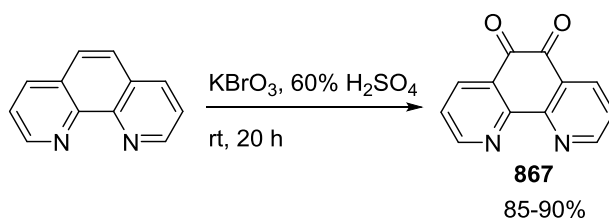
information is given on the intermediate compound, it is likely phen-epoxide is isolated first and then opened and oxidized in the acid oxidizing mixture to yield **867**.

From these pioneering works, some minor variations in this synthesis of **867** have been described. Some authors dissolve first phen in sulfuric acid then add sodium bromide and then nitric acid,^{827,835,875,881–883,885,905,916} other mixed first phen with potassium or sodium bromide and cool down the mixture before adding sulfuric acid and nitric acid at $-78\text{ }^{\circ}\text{C}$ ^{833,852,860,861,917} or $0\text{ }^{\circ}\text{C}$,^{826,831,832,834,836,844,848,851,854,858,865–867,877,886,888,890,891,900–902,904,910,911,913} others cool down the sulfuric acid solution at $0\text{ }^{\circ}\text{C}$ or $-78\text{ }^{\circ}\text{C}$ and add a mixture of phen and KBr or NaBr then add nitric acid.^{825,837,856,857,863,868,871,879,896–899} Other reports advise to cool down sulfuric acid and nitric acid at $0\text{ }^{\circ}\text{C}$, before phen and NaBr are added to the mixture and heated,^{823,892} or some directly prepare the phen and KBr solid mixture and add the latter to the acidic mixture before heating.^{839,912} Finally, some dissolved first phen in sulfuric acid then add potassium bromide and no nitric acid was used in this case before heating the reaction.^{893,894}

Although the experimental procedures look similar, the variations in the yields are important, from 25% to almost quantitative yield. It is likely that the most important parameter to control is the temperature at which the addition of the acids is performed. Indeed, Yamada et al.⁹¹⁵ have precised in their seminal paper that sulfuric acid should be added carefully to the cooled solution of phen and potassium bromide, through the ice-cooled wall of the flask. Not doing so entails a severe drop of the yield to 0%. The authors have tempted to rationalize this as follows: during the synthesis, bromine is produced by oxidation of bromide ions, but HBr is concomitantly formed and might be involved in side reactions. Adding carefully sulfuric acid at low temperature will limit the rapid formation of HBr. In 2019, Miltsov et al.⁸⁸⁰ have proposed to modify this protocol by changing potassium bromide to molecular bromine to avoid (or minimize) the formation of HBr. The best conditions to obtain the highest yield (ca. 70%) of the phendione are to disperse phen in Br_2 (2.5 eq) first; then the mixture is added

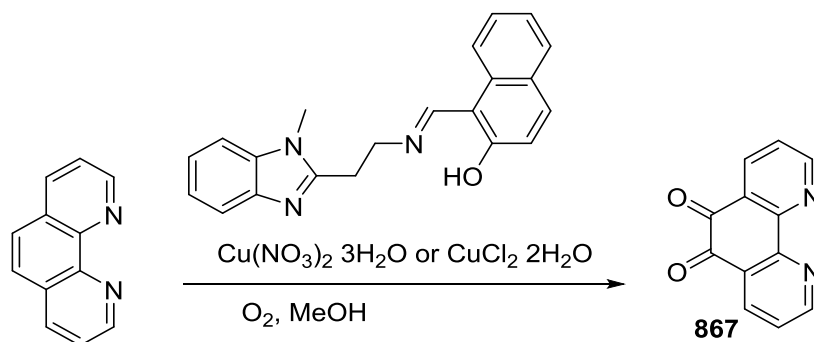
carefully into an iced solution of sulfuric acid (96%) and nitric acid (70%) in a ratio 2:1 v/v. Finally, the mixture is heated to 90-95 °C for 5 h (after 2 h of heating, 0.65 eq of bromine was again added).

Some variations in this synthesis have been reported. For example, Zheng et al.⁸⁶² have tested different oxidizing reagents such as H₂O₂, CrO₃, KMnO₄, MnO₂ instead of KBrO₃ but none was found effective. Besides, the authors have tested different concentrations for the sulfuric acid solution (from 20% to 80%) and 60% is reported to be the most suitable (Scheme 181). The drawback of this method is the use of potentially explosive bromate ions.



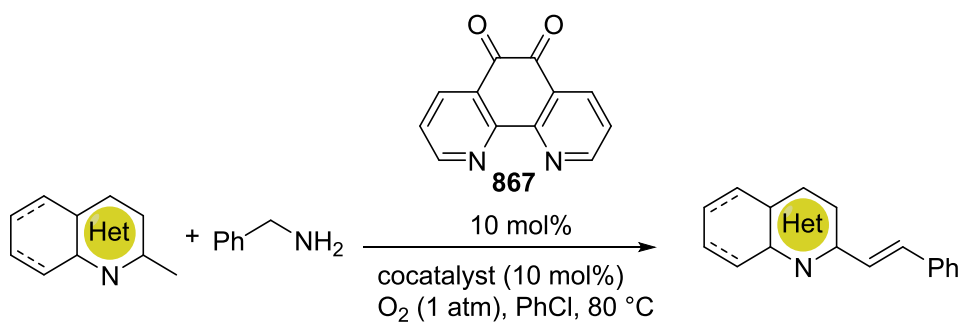
Scheme 181. New method to synthesize **867** at room temperature developed by Zheng et al.⁸⁶²

To finish, a very original method to produce **867** has been published by Kumar et al.⁸²⁴ who proved that Cu(II)-Schiff base complexes could catalyze the room temperature oxidation of phen in presence of molecular O₂ in methanol (Scheme 182). The reaction could easily be monitored by UV-vis spectroscopy. After optimization, the ratio catalyst/substrate of 1:10 was the best to obtain the highest conversion. A mechanism involving H₂O₂ is proposed.



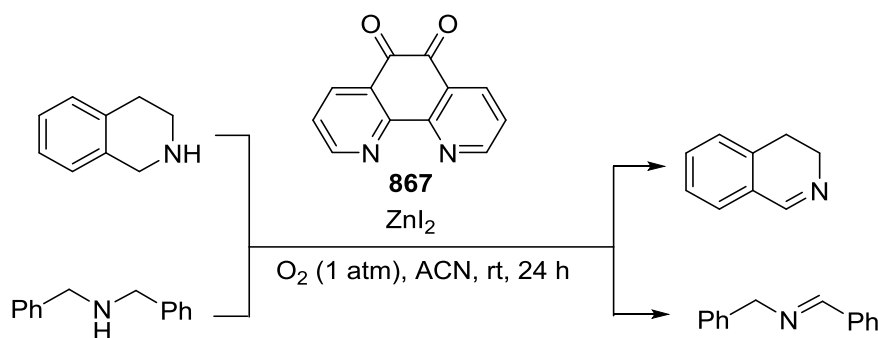
Scheme 182. Oxidation of the phen with Cu(II) complexes and molecular O₂ developed by Kumar et al.⁸²⁴

Phendione **867** is above all a precious and stable intermediate, but it has been directly used in a few instances for its properties. Thorve et al.⁹⁰² have used **867** directly as an organocatalyst in the deaminative olefination of methyl N-heteroarenes (Scheme 183). This reaction allows to avoid the use of precious metal, high temperature, to work under atmospheric pressure of oxygen. A Brønsted acid is required as a cocatalyst. Nine different classes of N-heteroarenes (pyrimidines, pyrazines, pyridines, quinolines, quinoxolines, benzimidazole, benzoxazoles, benzthiazole and triazines) could be modified, with only ammonia and water as byproducts.



Scheme 183. Deaminative olefination of methyl N-heteroarenes developed by Thorve et al.⁹⁰²

Wendlandt et al.⁸⁷⁴ have coordinated **867** with Zn²⁺ ions and have used this platform as a catalyst that performs the oxidation of secondary amines and nitrogen containing heterocycles. This catalyst has a dual role: the quinone part acts as an oxidation site whereas the coordinated Zn²⁺ acts as Lewis-basic site (Scheme 184).



Scheme 184. Phendione coordinated with Zn^{2+} ions as a catalyst for oxidation of secondary amines⁸⁷⁴

3.4.5.2 Transformations of the phendione

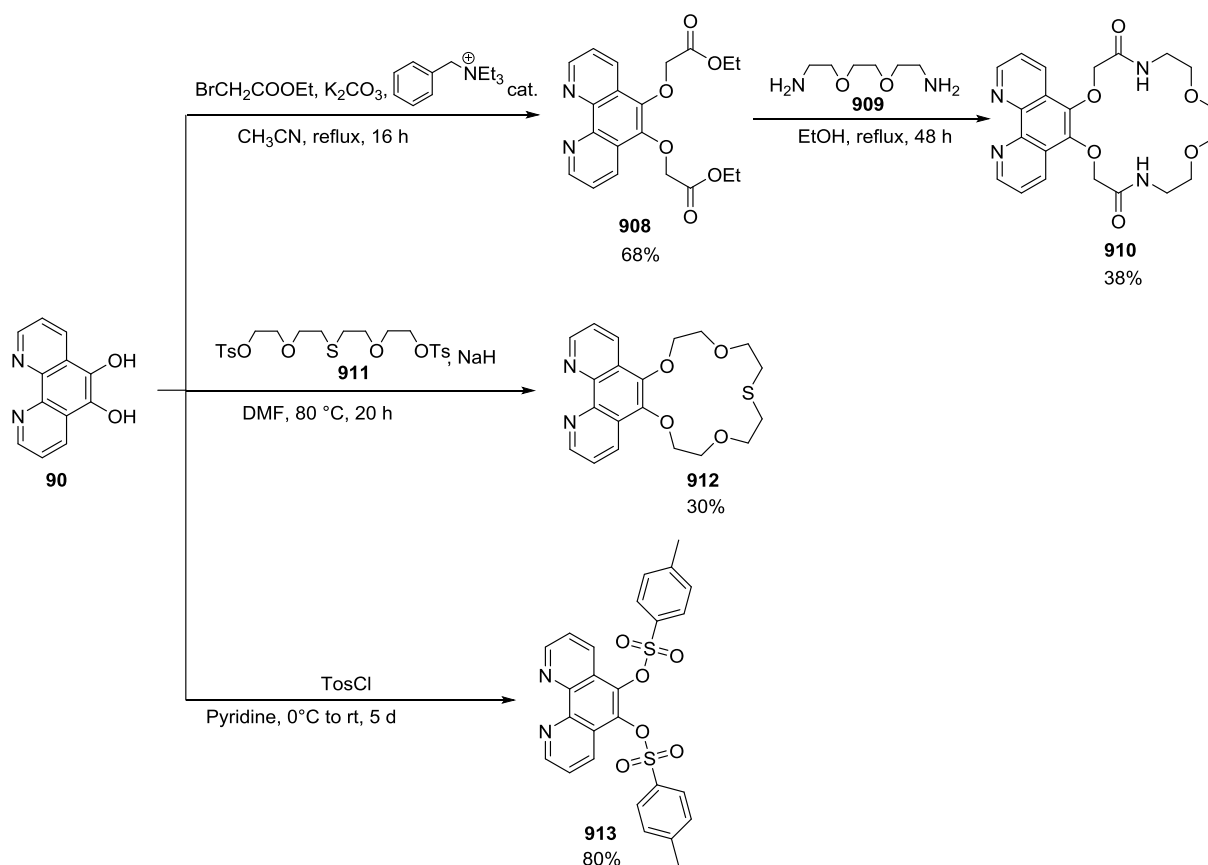
From **867**, a lot of structural variation can be found for various applications. The two major transformations are the formation of phenazine derivatives and the imidazole derivatives.

Synthesis and reactivity of the phendiol

The phendione **867** can be reduced into the 1,10-phenanthroline-5,6-diol **90** by using dithiooxamide in ethanol in 82% yield.^{891,913} **90** has been coordinated to copper(II) ions and those Cu(II) complexes have proven to be promising antitumor agents, outperforming cisplatin. In particular, $[Cu(1,10\text{-phenanthroline-5,6-diol})_2(OH_2)](ClO_4)_2$ has an IC_{50} value 37 times higher than cisplatin for the treatment of SK-MES-1, cell lines derived from human lung squamous carcinoma.⁸⁹¹ Habibi et al.⁹¹³ have demonstrated that **90** can anchor (like a catechol) on Fe_3O_4 magnetic nanoparticles, and that the so-immobilized ligands could accommodate Co(II) ions. The obtained heterogeneous catalyst is used in the N-formylation reaction of various amines by formic acid at room temperature. Besides, those complexes show antioxidant and antibacterial activities. There are other examples where the diol function has been exploited for its coordinating ability; as a matter of fact, **90** can be considered a heteroditopic ligand, with a soft $\widehat{N}N$ and a harder O-CH=CH-O chelating cavities. This has allowed to prepare homo- and hetero-dinuclear complexes.^{59,918,919}

The 1,2-diol group in **90** is nucleophilic, this feature has been exploited in a few cases. Halogeno-alkanes readily react with phendiol **90** in presence of a base leading to etheroxide linkages.^{920–924} For example, **908** comes from the reaction between **90** and ethyl bromoacetate, and further reaction with diamine **909** leads to the macrocyclic compound **910** in reasonable yield. The corresponding Ru and Re complexes have been used as anions sensors.⁹²² Yam and co-workers report too the one-step synthesis of macrocycle **912** from **90** and the appropriate bistosylated oligoetheroxide **913** (Scheme 185).

90 reacts too in presence of sulfonyl chloride to give **913**,⁹²⁵ but the obtained ditosylated phendiol has not been used in further reactions (such as aromatic nucleophilic substitutions).

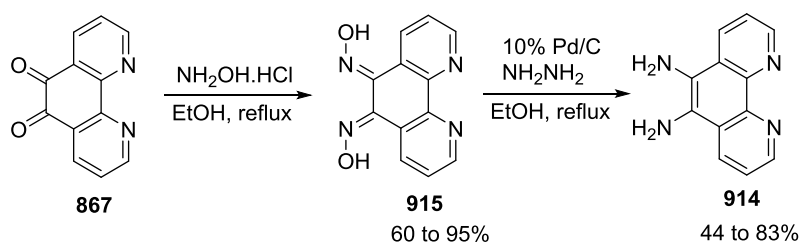


Scheme 185. Examples of reactions where phendiol **90** is used as nucleophile

During our literature survey, no example of esterification reactions between phendiol and a carboxylic acid has been found.

Synthesis and reactivity of the 1,10-phenanthroline-5,6-diamine **914**

The 1,10-phenanthroline-5,6-diamine **914** can be easily obtained in two steps, first by reacting the phendione **867** with hydroxylamine hydrochloride to reach the 1,10-phenanthroline-5,6-dioxime **915** that is further reduced using Pd/C, hydrazine in ethanol into the target compound (Scheme 186).^{859,879,917,926-931}



Scheme 186. Synthesis of the 5,6-diamino-1,10-phenanthroline **914** from the phendione **867**

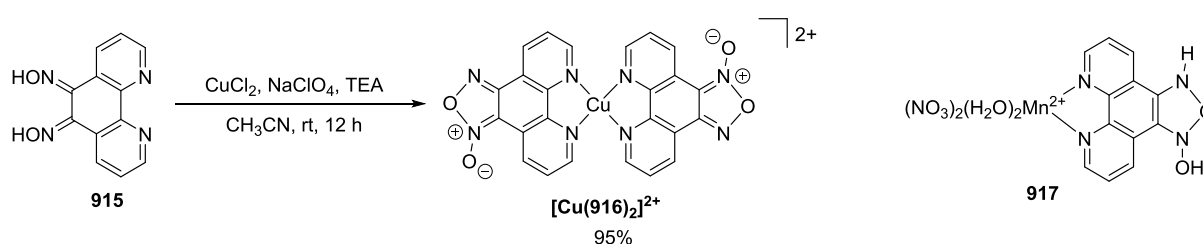
Classically, the dioxime was obtained by reacting **867** with hydroxylamine hydrochloride in the presence of calcium carbonate in refluxing ethanol for 4 h.⁹³² The authors precised that **915** was soluble in ether, alcohol and acids but insoluble in water. Later on, Bodige et al. reported that **915** was not purified because of its poor solubility in organic solvents.⁹²⁶ Oh et al.⁸⁷⁹ used sodium carbonate during the synthesis of the dioxime compound instead of calcium carbonate. Yields ranged between 60-85%.

Originally, to obtain **914** from **915**, Comba et al.⁹³³ reduced **915** with a solution of sodium dithionite in concentrated ammonia and **914** was obtained with 86% yield. They explored as well the use of thiourea dioxide in concentrated ammonia and the yield to obtain **914** was comparable (86%).

915 and above all **914** have been used to elaborate larger molecular arrays. The dioxime can act as a chelate, as demonstrated by Steiner et al. who prepared a mixed $\text{Ru}^{2+}\text{-Zn}^{2+}$ complex where Ru and Zn ions are respectively coordinated by the $\widehat{\text{N}}\text{N}$ and dioxime cavities.⁹³⁴ This dinuclear complex is a powerful fluorescent probe for the determination of acetyl phosphate in biological medium.

As other example of the coordinating ability of phendioxime, Shariatipour et al.⁸²⁵ have adsorbed phendioxime through the hydroxyl groups on partially reduced graphene oxide/oxidized multiwalled carbon nanotubes doped with Fe₃O₄ magnetic particles, where Pd(II) ions are coordinated and catalyze the Suzuki-Miyaura cross-coupling reaction.

From the reactivity point of view, in presence of copper(II) and triethylamine in acetonitrile, **915** turns into 1,10-phenanthrolinefuroxan **916** (Scheme 187).⁹³⁵ The free ligand is retrieved after NH₃ treatment; alternatively, a synthesis of the same molecule has been recently published, using iodobenzene diacetate as reagent.⁹³⁶ Finally, it is worth to mention that phendioxime condense into a fused five-membered ring in presence of manganese(III) nitrate, the acidic conditions of the reaction are invoked to rationalize this transformation. The resulting complex (**917**, Scheme 187) features a significant anti-tumor activity.⁹³⁷

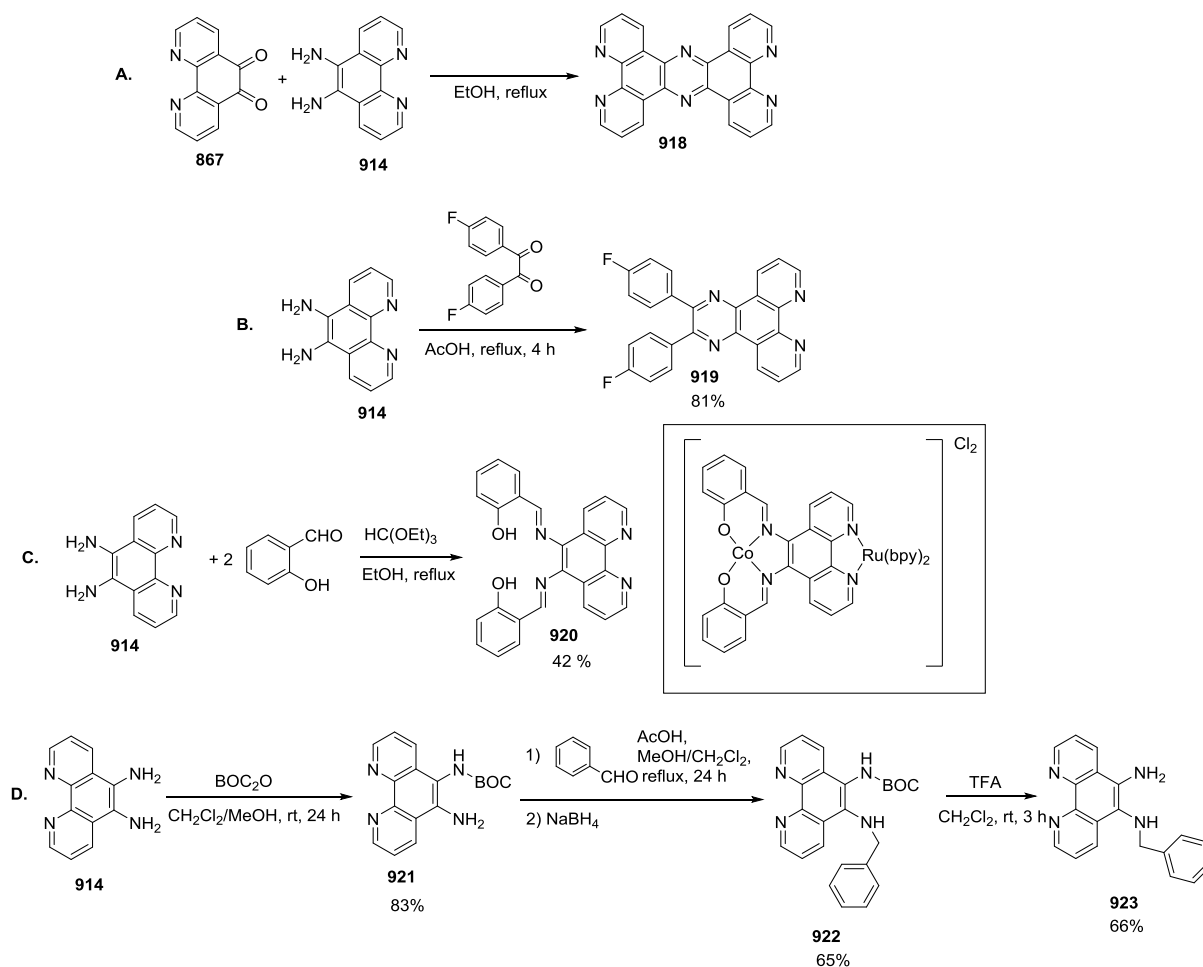


Scheme 187. Copper(II)-assisted formation of 1,10-phenanthrolinefuroxan **916** from **915** and structure of complex **917**.

Usually however, **915** is just an intermediate on the way to **914**. The coordinating ability of the diamines has been little explored, the amines are usually oxidized into imines with better chelating ability.^{938,939} The most frequently used synthetic strategy involving phendiamine **914** is the condensation of the latter on aldehydes and particularly on diketones.⁹⁴⁰⁻⁹⁴⁶ For example, the condensation of **967** on **914** affords the rigid aromatic ditopic ligand **918** (Scheme 188A) used to prepare numerous photosensitive homo- and hetero-metallic dyads.^{947,948} Similarly, Li et al.⁹⁰⁷ synthesized the conjugated ligand **919** by reacting **914** with

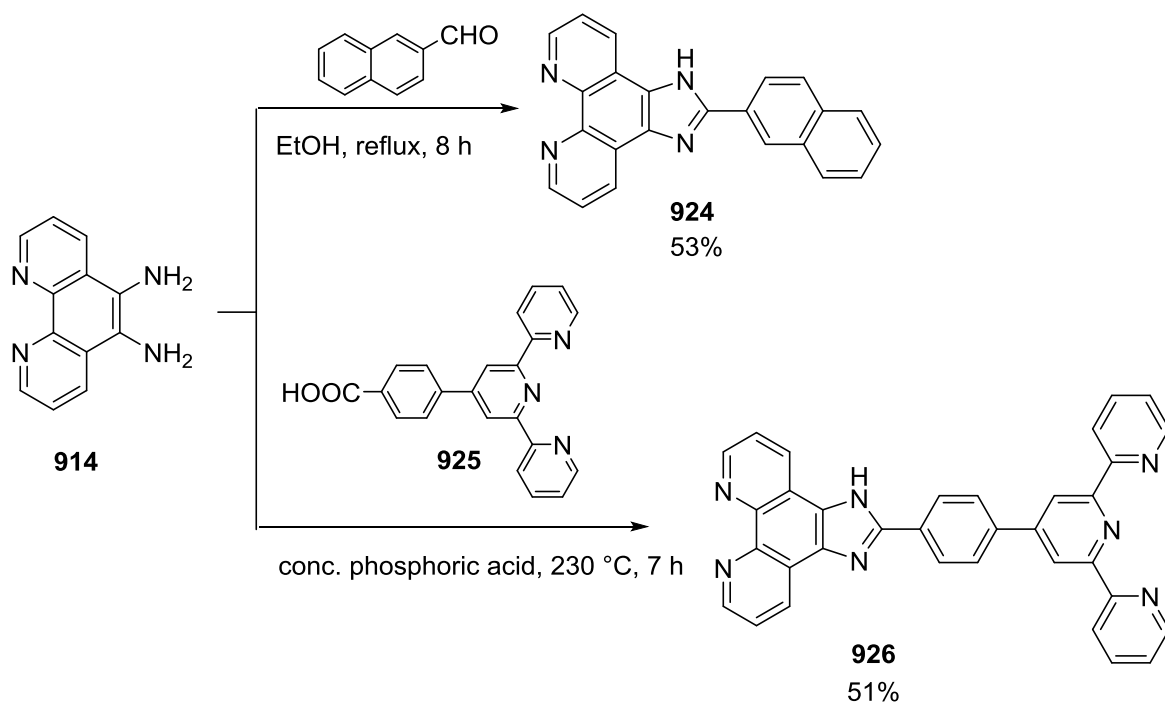
the commercially available 1,2-bis(4-fluorophenyl)ethane-1,2-dione in refluxing acetic acid (Scheme 188B). Oh et al.⁸⁷⁹ synthesized first a rhenium complex from **914** that was condensed with quinone moieties found on graphite edge planes. This new catalyst performed CO₂ reduction into CO with better selectivity and activity than the soluble molecular complex. Another example developed by Lopez et al.⁹²⁹ consists in condensing **914** with salicylaldehyde to obtain **920**, then metallation with cis-Ru(bpy)₂Cl₂ is performed before metallation with Co(II) ions with the salophen cavity (Scheme 188C). This dyad is proven relevant for light-driven water oxidation.

Mono-functionalization of one amino group may require an additional protection step.⁹⁴⁹ In presence of one equivalent of BOC anhydride, **921** is formed first, then the free amino group on **921** condense on benzaldehyde leading to **922** after reduction of the imine by NaBH₄. **922** is finally deprotected into **923** (Scheme 188D), the iridium complex of which is an efficient NO probe: in presence of NO, the mixed amine-benzylamine core rearranges into a triazine fused to the phenanthroline core.



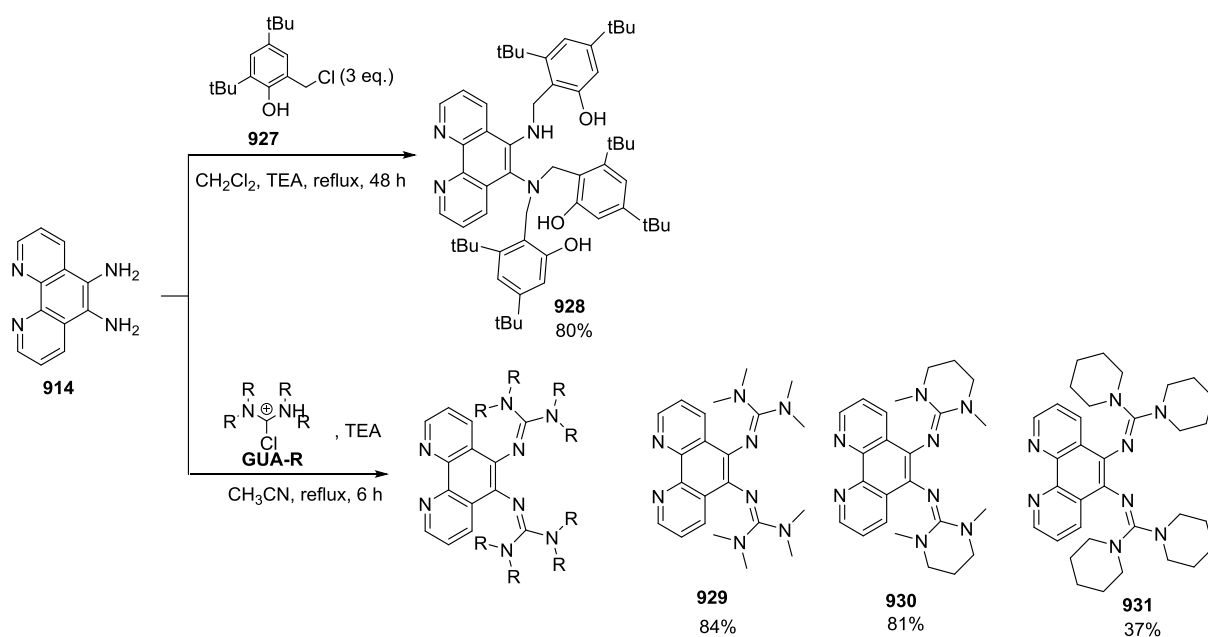
Scheme 188. Condensation of aldehydes and diketones on phendiamine.

The addition of one equivalent of aldehyde (e.g. 2-naphthaldehyde, Scheme 189) on phendiamine usually leads to the formation of imidazole derivatives such as **924**⁹⁵⁰ (Scheme 189) but those benzimidazole derivatives are more often obtained from **867** as will be presented below. Interestingly, aromatic carboxylic acids are known to react with **914** to afford benzimidazole compounds. For instance, **925** has been condensed on **914** leading to heteroditopic linear ligand **926**.⁹⁵¹ The conditions are however generally very harsh, using polyphosphoric acid at high temperatures,^{951–953} sometimes for long reaction time (e.g. days).



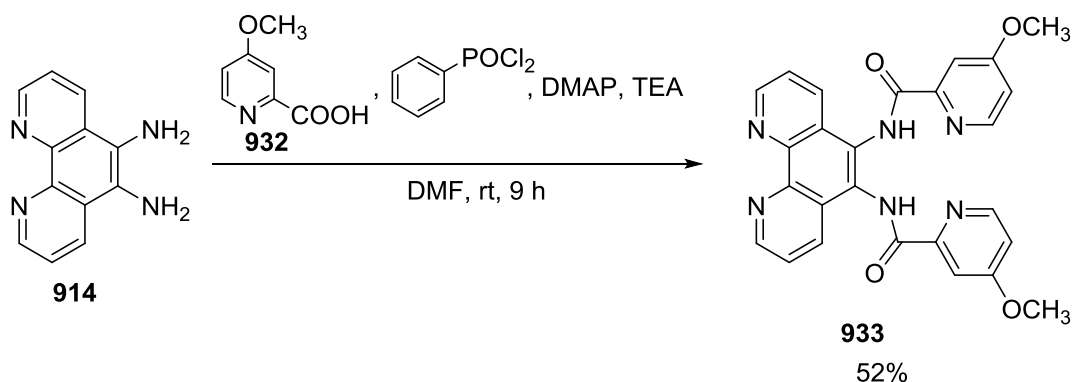
Scheme 189. Formation of benzimidazole spacers from phendiamine

914 can be used as nucleophile in nucleophilic substitutions (Scheme 190) in presence of appropriate electrophiles, such as **927**.⁹⁵⁴ The resulting ligand **928** offers two binding sites, the soft $\widehat{N-N}$ cavity and the harder N_2O_3 coordinating cavity connected to positions 5 and 6, well adapted for Fe(III) ions. Moreover, Vilsmeier salts are easily attacked by phendiamine leading to versatile coordinating ligands **929-931**.⁹²⁷



Scheme 190. Examples of nucleophilic substitutions from phendiamine **914**.

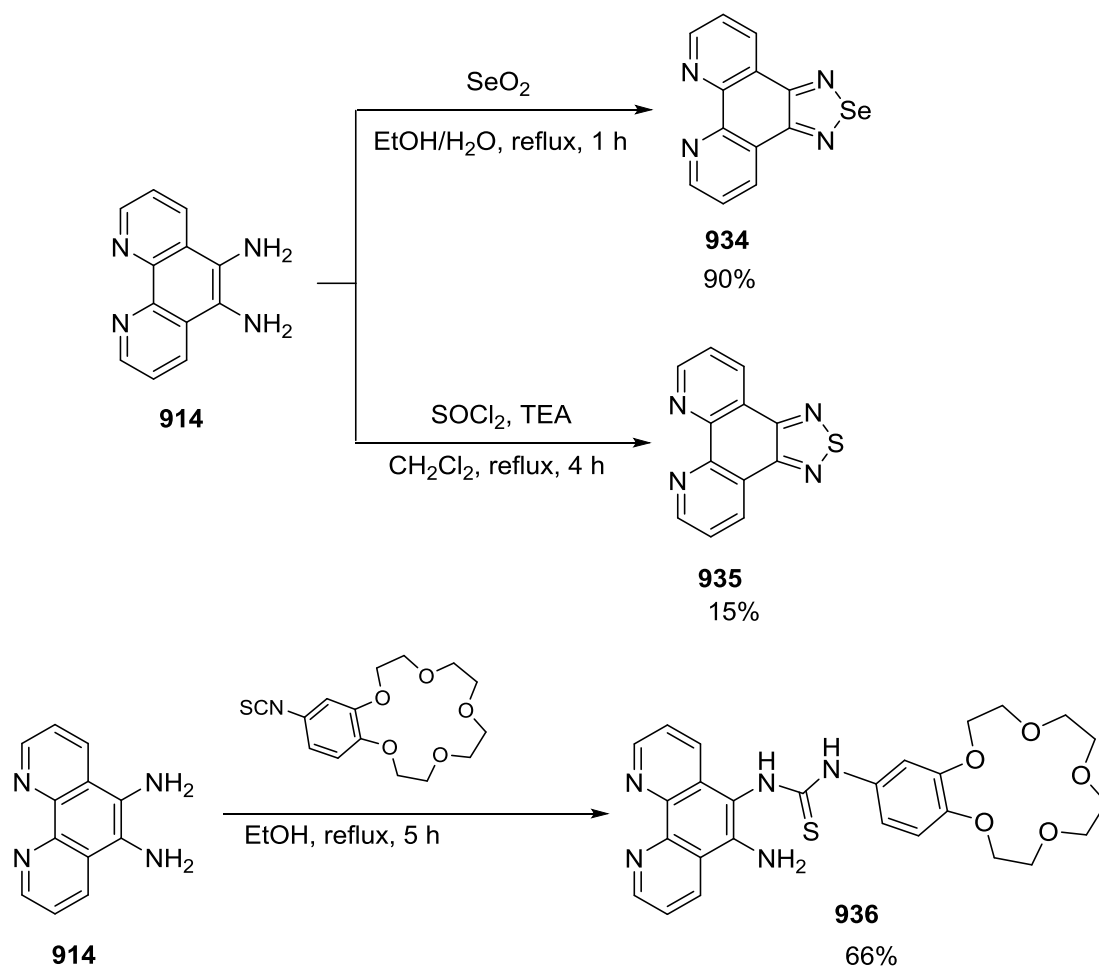
Quite unexpectedly, amide bonds have been rarely formed on phendiamine (Scheme 191). Comba and co-workers⁹³³ have nevertheless reported the synthesis of a heteroditopic ligand featuring the $\widehat{\text{N}}\widehat{\text{N}}$ cavity of phen connected to an amido-pyridine tetracoordinating N_4 chelate **933**. The authors clearly indicate that the amine functions of **914** are poorly reactive and the peptide coupling reactions with carboxylic acid **932** therefore require activation (in this case, a mixture of DMAP and phenylphosphonic acid dichloride). The corresponding Ru complex $[\text{Ru}(\text{bpy})_2\text{AMID}]^{2+}$ has been used as fluorescent sensor for copper(II) ions.



Scheme 191. Formation of amide on phendiamine.

Another work reports that oxalyl chloride efficiently reacts on phendiamine to give a bisamidation cyclic product.⁹⁵⁵ But the examples of amidation of **914** are scarce, probably because of the lack of reactivity of the amine functions, due to the strong electron withdrawing character of phen.

Nevertheless, other interesting reactions can be performed on **914** (Scheme 192). For example, refluxing phendiamine in presence of SeO₂ leads to **934** where a selenium heterocycle is fused to phen.⁹⁵⁶ The corresponding [Ru(bpy)₂(**934**)]²⁺ complex has been used as theranostic agent and presents a potential anti-cancer activity.^{957,958} Similar ligand **935** has been obtained too and the Re complex features high emission quantum yield and has been implemented in phosphorescent OLED devices.⁹⁵⁹ Remarkably, the reverse reaction (from **935** to **914**) is potentially feasible in acetic acid at 100 °C and in presence of zinc.⁹⁶⁰ Although demonstrated on a molecular system which significantly differs from **935**, the thiadiazole group could behave as a protecting group for the phendiamine.



Scheme 192. Other reactions allowing to modify phendiamine

Despite the weak nucleophilicity of amines, condensation on thiocyanate derivative crown-NCS has been reported, giving the heteroditopic ligand phen-crown.⁹⁶¹

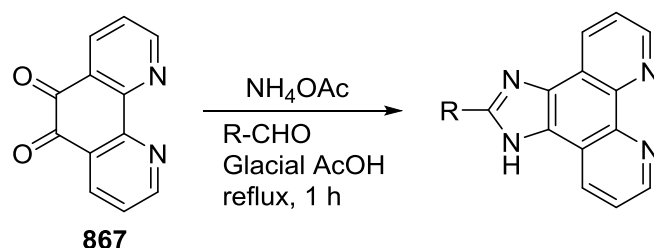
Synthesis of imidazole derivatives (imidazo[4,5-f][1,10-phenanthroline]) from phendione

An impressive collection of phen_{(5,6)sub} ligands, the imidazo[4,5-f][1,10-phenanthroline] ligands, where aromatic groups Ar are connected to phen through a fused imidazole spacer have been published. The reasons behind this fact are that the synthesis of those molecules is particularly easy from phendione and virtually any aromatic aldehyde, and that the resulting molecules have a linear geometry ensuring the appended Ar groups (potentially bearing other functional fragments or reactive functions) are located at fixed distance *via* a conjugated

linker. For those reasons, a section specially devoted to the synthesis of those molecules is presented here.

The design of the imidazo[4,5-f][1,10-phenanthroline] relies on the condensation of **867** and aromatic aldehydes. Many variations have been made on the aldehyde backbone for various applications (biology,^{831,832,840,843,844,865,877,890,900} detection/sensors,^{833,841,873,884,886,889,897,905} supramolecular chemistry,^{827–829,858,866,916} coordination chemistry,^{851,875,881–883,892,893,893} non-linear optics,⁸⁹⁹ photo-induced electron transfer^{711,847,872} ...), thus only selected examples will be presented.

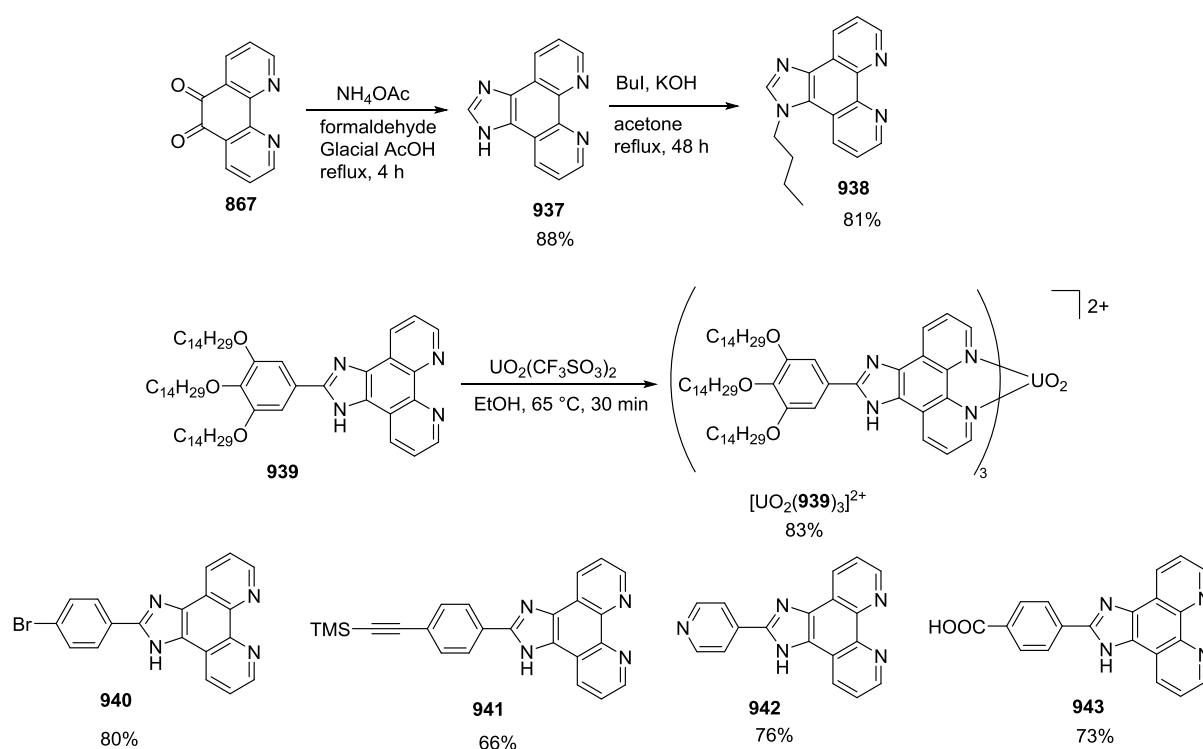
Classically, to form the 5-membered heterocyclic ring, the phendione will be mixed with ca. 20 eq of ammonium acetate in glacial acetic acid (0.15 M). Then, the corresponding aldehyde (1 eq) dissolved in glacial acetic acid (0.15 M) will be added to the mixture and the mixture will be refluxed for 1 h (Scheme 193).⁹⁶² After neutralization with an aqueous ammonia solution to pH = 7, a precipitate is formed and filtered to yield the desired product.



Scheme 193. Classical formation of imidazo[4,5-f][1,10-phenanthroline] derivatives described by Steck et al.⁹⁶²

Martins et al.⁸⁵¹ first performed the synthesis of a Ru(II) complex from **867** and [Ru(DMSO)₄Cl₂] and then they formed the imidazole ring in classical conditions. To form the unsubstituted imidazole ring **937**, Bagherzadeh et al.⁸⁹⁸ used directly an aqueous solution of formaldehyde. The formed imidazole can be alkylated, as demonstrated by the same authors, as they performed an alkylation reaction on the imidazole ring with iodobutane (**938**, Scheme

194). The same phenimidazole molecule **937** has been obtained by Zhong et al.,⁸⁸³ using hexamethylenetetramine instead of formaldehyde.



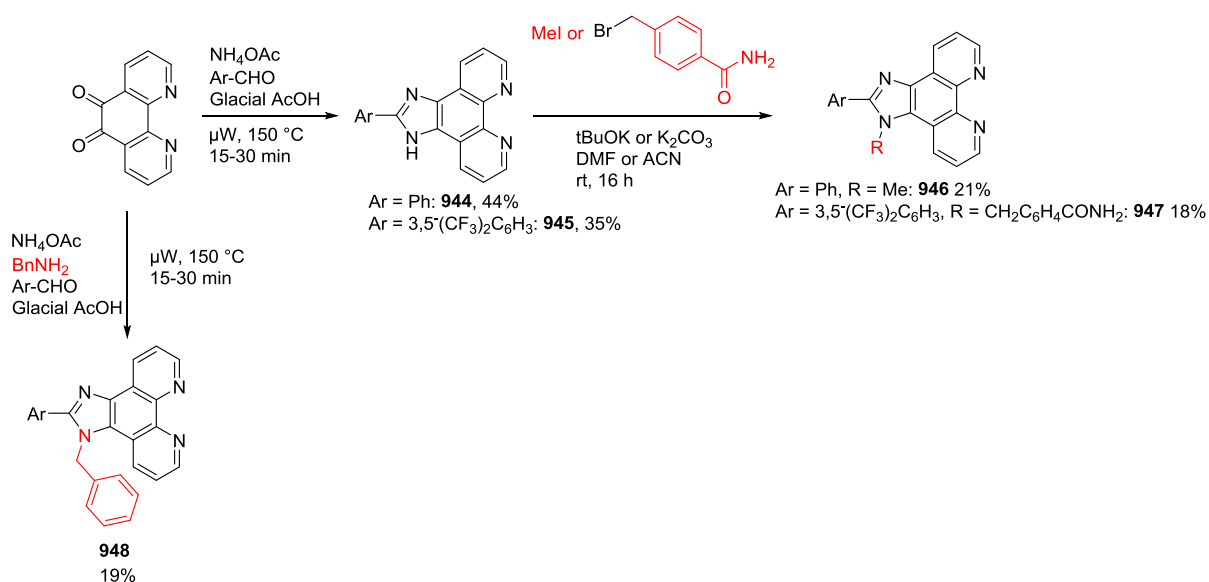
Scheme 194. Synthesis of the imidazo[4,5-f][1,10-phenanthroline] compound described by Bagherzadeh et al.⁸⁹⁸

Another example has been given by Cardinaels et al. who have developed imidazo[4,5-f]-1,10-phenanthroline ligands such as **939** bearing long alkoxy chains.^{827–829} Different transition metals or rare-earth metals such as uranyl, platinum, rhenium, yttrium, lanthanum, neodymium, samarium, europium have been coordinated to **939** to form various complexes. The authors have shown that those ligands were very versatile to design metal-containing liquid crystals (metallomesogens) thanks to the long alkoxy chains borne by the aromatic end group.

Sergeeva et al.^{865,900} studied the imidazole derivatives when R = 4-BrC₆H₄ (**940**) or 4-TMS-C≡C-C₆H₄ (**941**), or 4-pyridine (**942**). The corresponding europium complexes are synthesized, show fluorescence and could accumulate in the endoplasmic reticulum making

those molecules interesting cellular probes. Besides they were selective for cancer cells with high cytotoxicity, especially for the OE21 cell lines (oesophageal squamous carcinoma) making them potential candidates for cancer treatment. **943** has been obtained from 4-carboxybenzaldehyde (showing there is not interference from the COOH moiety during the reaction) and used for its interesting reactivity at the level of the COOH group. The latter has been notably used to design octa-arginine photoluminescent Ru complexes as cell-membrane permeable probes,⁹⁶³ through Merrifield peptide conjugation.

Variations of the traditional protocols can be found. For example, Patel et al.⁸⁹⁰ have used microwave to form the imidazole ring of **944** and **945** and the products are obtained after 15 min only at 150 °C under irradiation (300 W) (Scheme 195). They studied as well the alkylation of the imidazole ring either performing the alkylation in a second step after the ring formation (obtaining **946** and **947**) or in one spot from the phendione using directly a mixture of ammonium acetate, aromatic benzaldehyde and various substituted anilines (**948**, Scheme 195) as described in the 19th century by Debus⁹⁶⁴ and Radziszewski.⁹⁶⁵

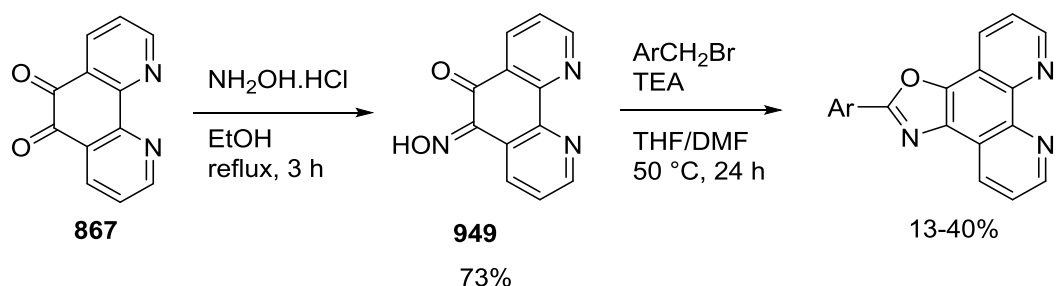


Scheme 195. Formation of imidazo[4,5-f][1,10-phenanthroline] derivatives using microwave irradiation described by Patel et al. and alkylation of the imidazole.⁸⁹⁰

The overall yield is better when performing the reaction in one step (even though this yield is low because of probable formation of side products, but no details are provided) than performing the alkylation in a second step. Bonello et al.⁸⁹² performed as well the reaction in one step to obtain the alkylated imidazole ring by refluxing in glacial acetic acid the mixture of ammonium acetate, aromatic benzaldehyde and various substituted anilines. No details were provided on this reaction and on the formation of the side-products. The authors nevertheless mention that they removed impurities by oxidation, making treatments of the crude with hypochlorite solution. Their yields varied from 28 to 90% depending on the substituted benzaldehyde and aniline.

We note that one article⁹⁶⁶ reports the very rapid and efficient solvent-free synthesis of imidazo[4,5-f][1,10-phenanthroline] ligands using ammonium acetate, **867** and aldehydes in presence of ionic liquids.

Importantly, the formation of the imidazole ring is sometimes accompanied by an oxazole by-product.^{962,967} In order to selectively synthesize the oxazole derivative, Zhu et al.⁸⁴¹ have developed a new pathway from phendione, by synthesizing the 1,10-phenanthroline-5-oxo-6-oxime product **949** that further reacted with various arylmethylbromide in the presence of triethylamine and in a mixture of THF/DMF affording phen-oxazole derivatives (Scheme 196) with yields in the range of 13 to 40%, probably due to byproducts resulting from ring opening.

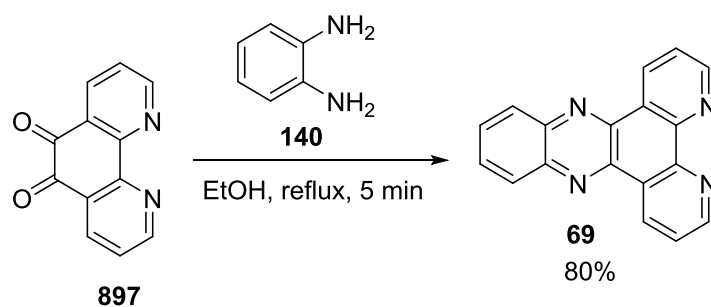


Scheme 196. Synthesis of 2-aryloxazolo[4,5-f]-1,10-phenanthroline derivatives described by Zhu et al.⁸⁴¹

To conclude, other aliphatic aldehydes (cinnamaldehyde, 2,4-hexanedial,⁹⁶⁸ terbutylaldehyde⁹⁶⁹ or butanal)⁹⁶⁶ have been condensed on phendione in conventional conditions, but the examples are scarce.

Synthesis of dipyrido[3,2-a:2',3'-c]-phenazine derivatives from phendione

Just as important than the previously described synthesis, one of the major reactions allowing to functionalize phendione and grow large phen_{(5,6)sub} structures is to add aromatic or non-aromatic diamine to form a pyrazine fused phen that leads to the formation of extended conjugate systems. The historical example is the synthesis of the dipyrido[3,2-a:2',3'-c]phenazine (dppz ligand **69**) described by Dickeson et al.⁸⁶⁴ although it was mentioned in a former paper by Nyquist et al.⁹⁷⁰ (but they did not start the synthesis from the phendione). Classically the dppz ligand **69** is obtained by reacting the phendione **867** with one equivalent of *o*-phenylene diamine **140** in refluxing ethanol (Scheme 197).

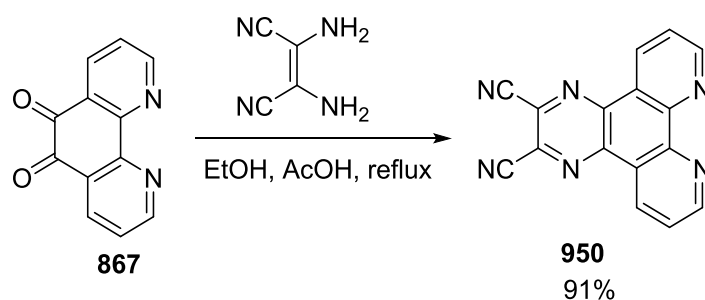


Scheme 197. Classical formation of the dipyrido[3,2-a:2',3'-c]phenazine (dppz ligand) **69** described by Dickeson et al.⁸⁶⁴

Chambron et al.^{850,971} showed that this ligand had attractive features. In metal complexes the phenazine part acts as an electron-withdrawing group, but is curiously electronically decoupled from the N[∧]N cavity. As such, the metal complexes bearing dppz have often been qualified as bichromophoric (a metal-N[∧]N complex associated to a phenazine spacer with

weak electronic communication in between).²⁰⁶ Consequently, and for example, the ruthenium(II) complex $[\text{Ru}(\text{bpy})_2(\text{dppz})]^{2+}$ exhibits a dyad behavior: under light excitation, an electron is ejected from the metal center towards the phenazine acceptor part, and the electron dwells there for an unusually long time for such simple molecular systems. Interestingly, the $[\text{Ru}(\text{II})(\text{bpy})_2(\mathbf{69})]^{2+}$ complex exhibits residual luminescence, quenched in presence of protic solvents and enhanced in apolar medium, a feature that has been extensively utilized for the design of intercalative DNA probes.²⁰⁹ The dppz ligand **69** or its derivatives have been described in a plethora of papers for various applications (biology,^{835,839,845,849,853,855,868–870,878,912} electron transfer,^{850,971} luminescence,^{826,871,887,910,972} organic electronics,^{823,856,896,907} sensors,^{904,906} electrochromism⁸⁴⁶ ...).

Other interesting conjugated ligands can be obtained from the reaction of phendione with diamines. Si et al.⁸⁷¹ have used a non-aromatic diamine, diaminomaleonitrile, with acetic acid as a catalyst in refluxing ethanol and obtained the 2,3-dicarbonitrilopyrazine[2,3-f]-1,10-phenanthroline **950** with 91% yield (Scheme 198).



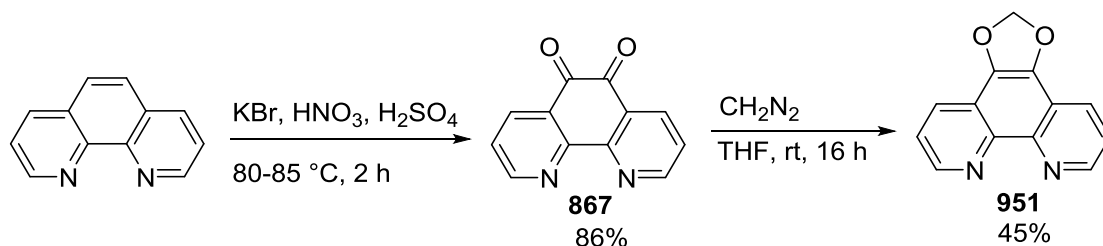
Scheme 198. formation of the 2,3-dicarbonitrilopyrazine[2,3-f]-1,10-phenanthroline **950** described by Si et al.⁸⁷¹

Che et al.⁸³⁴ have proposed to form the pyrazine ring with a hydrothermal synthetic method. Thus, in a stainless-steel autoclave, phendione and the corresponding diamine are put together in a mixture of ethanol and water at 180 °C for one day under autogenous pressure. Even though the conditions are more drastic than the ones described in other articles, the authors

claim that this method allows to obtain directly pure crystals in high yields of the corresponding compounds.

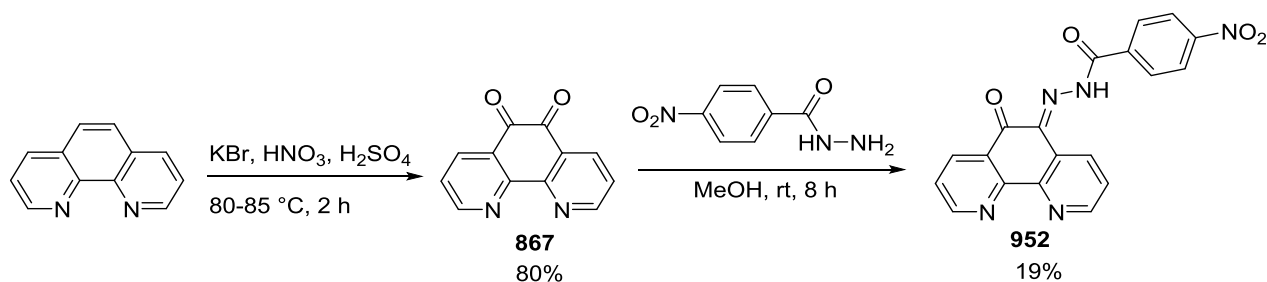
3.4.5.3. Concluding remarks

Other original modifications of the phendione can be found. In particular, although the examples are rare, other nucleophiles than amines have been reacted on phendione. For example, Antkowiak et al.⁸³⁸ have found that the phendione (obtained from Yamada et al.'s procedure) can react easily with diazomethane to form the acetal 5,6-methylenedioxy-1,10-phenanthroline **951** (Scheme 199). Interestingly, the diketone function can be protected using an acetal function too, when refluxing phendione with 2-nitropropane.⁹⁷³ This is particularly useful in the frame of multi-functionalization in different positions, as will be exposed in the next sections.



Scheme 199. Synthesis of 5,6-methylenedioxy-1,10-phenanthroline **951** from **867**⁸³⁸

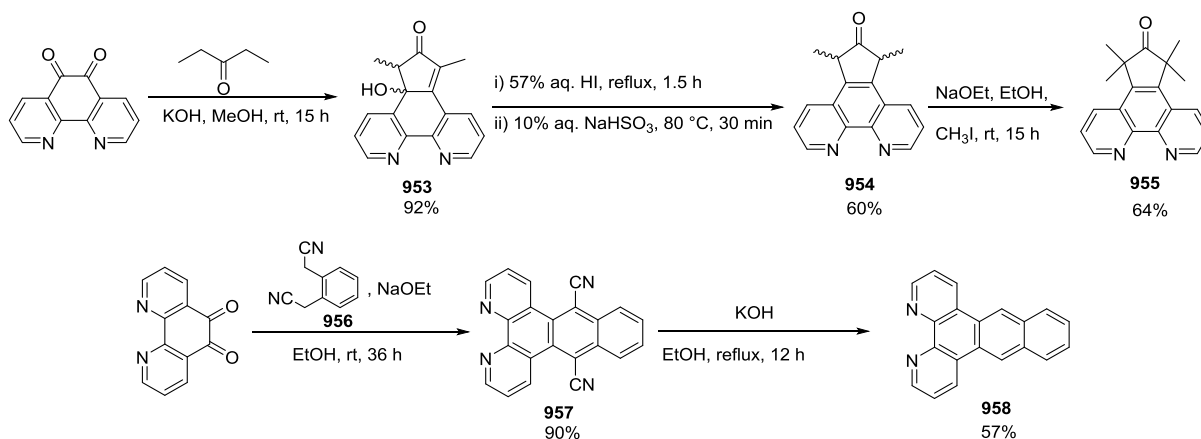
Goswami et al.⁸⁵⁴ have reacted the phendione with an hydrazide reagent to form a colorimetric sensor. In presence of Pb^{2+} , the ligand shifts from the yellow hydrazo form to a deep red diazo form. This molecule proves to be a very interesting colorimetric selective probe for Pb^{2+} . (Scheme 200).



Scheme 200. Colorimetric sensor **952** synthesized from **867** by Goswami et al.⁸⁵⁴

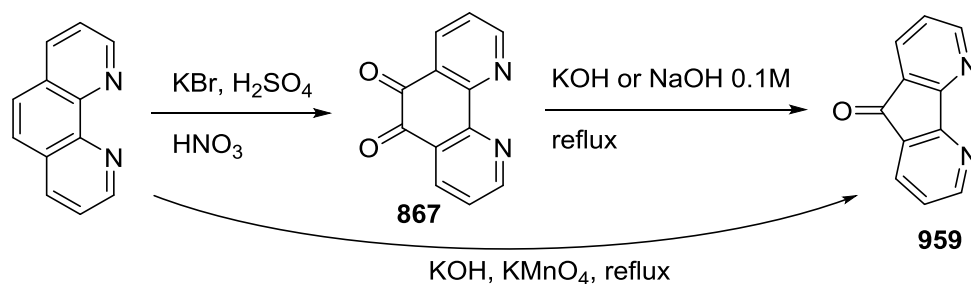
Heinrich et al.⁸³⁰ prepared different 5-hydrazone functionalized phenanthrolines from **867** that were further metallated with Cu(II) ions. It was shown that those copper complexes were active in the oxidative cleavage of DNA and increased the nuclease activity in the presence or absence of reducing agent.

Oh et al.⁷¹¹ reacted the phendione with pentan-3-one in basic solution. The deprotonated pentan-3-one attacks the diketone function of phendione to form a 5-membered ring containing an α -enone (**953**). The latter is rearomatized after dehydration in acidic medium and lastly methylation of the 5-membered ring leads to a new ketone bearing phen ligand **955** (Scheme 201). Belser, Albano and co-workers⁹⁷⁴ have reported a similar strategy to prepare ligand NP, a dppz-like ligand where a naphthalene segment has been fused to phen along the C₅-C₆ bond. The synthesis relies on the attack of phendione by the carbanion of **956** generated by sodium ethanolate. The nitrile groups of **957** are then hydrolyzed, and decarboxylation finally affords ligand **958**. The same ligand has been re-synthesized by Barton and co-workers but with a much lower yield.⁹⁷⁵



Scheme 201. Ligands synthesized from the phendione by nucleophilic attacks by carbanions

It is important to point out that in boiling aqueous basic medium (NaOH or KOH 0.1M), **867** will convert into 4,5-diazafluoren-9-one **959**.^{842,864,932,976} This 4,5-diazafluoren-9-one **959** can be as well obtained directly from the phen using boiling KOH and potassium permanganate (Scheme 202).⁸⁶³ Such side reactions may justify that it can be challenging to perform synthetic work with phendione in basic medium.



Scheme 202. Formation of 4,5-diazafluoren-9-one from the phendione or phen in basic medium

4. Divergent polyfunctionalization

4.1. Synthetic methods for the preparation of phen_{(2,3,8,9)sub} and parent molecules

Several regioisomers will be taken into account: bis-functionalized phen can be substituted in positions 2 and 3 or 2 and 8; ter-functionalized phen can be substituted in positions 2, 3 and 9

or 2, 3 and 8; finally, we will consider the case of tetra-substituted phen where positions 2, 3, 8 and 9 are all occupied by a substituent (Figure 31).

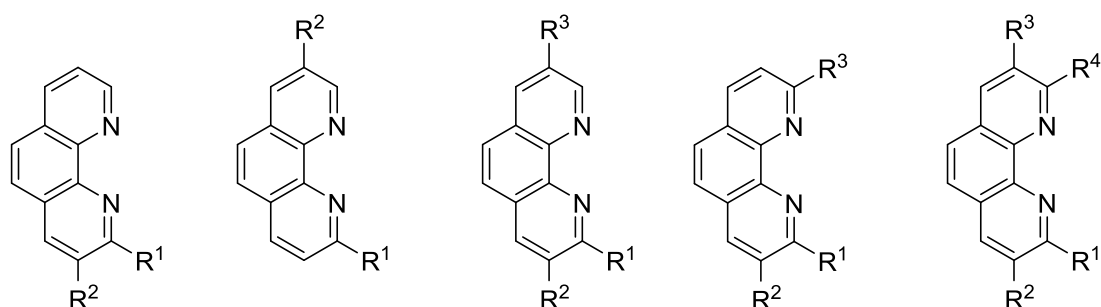


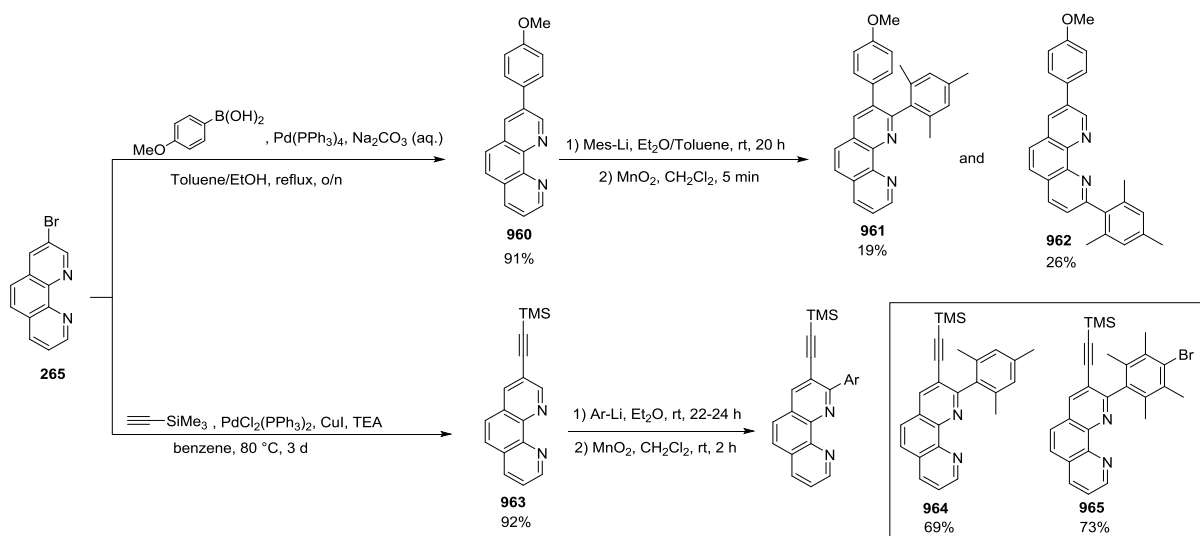
Figure 31. The five different regioisomers available when positions 2, 3, 8 and/or 9 are occupied by a substituent

4.1.1. Bis-functionalization of phen in positions 2,3 or 2,8

The most frequently used methods rely on the decoration of synthon **265** through a palladium cross-coupling reaction, followed by a functionalization reaction in position 2. For example, Sauvage et al. use a Suzuki cross-coupling to graft the 4-anisole moiety on **265**. The resulting compound **960** can then be submitted to a nucleophilic attack by 1.2 equivalent of mesityl-lithium followed by re-aromatization/oxidation in presence of MnO_2 ,^{977,978} following the Dietrich-Buchecker-Sauvage method described in section 3.1.1. Both 2,3- and 2,9-regioisomers **961** and **962** are obtained because positions 2 and 9 are approximately equally reactive vs. mesityl-lithium, at least in the described conditions. The yields for both regioisomers are comparable, with a slight advantage for 2,8 isomer **962**, probably for steric reasons (Scheme 203).

Schmittel developed a similar strategy, coupling **265** with trimethylsilylacetylene in the Sonogashira cross-coupling conditions,⁶⁸⁶ and then performing a nucleophilic attack in α of the nitrogen atom with aryl-lithium reagents.⁹⁷⁹ In contrast to the above observations, the nucleophilic attack is in this case highly regioselective, leading almost exclusively to the 2,3 regioisomers (**964** and **965**) (Scheme 203). One can infer that the electron withdrawing

character of the alkynyl group may contribute activating position 2 towards a nucleophilic attack. In addition, a triple bond is less sterically challenging than an aromatic group (like in the case of **960**). Both features could explain this impressively regioselective addition of organo-lithium reagents on **963**.

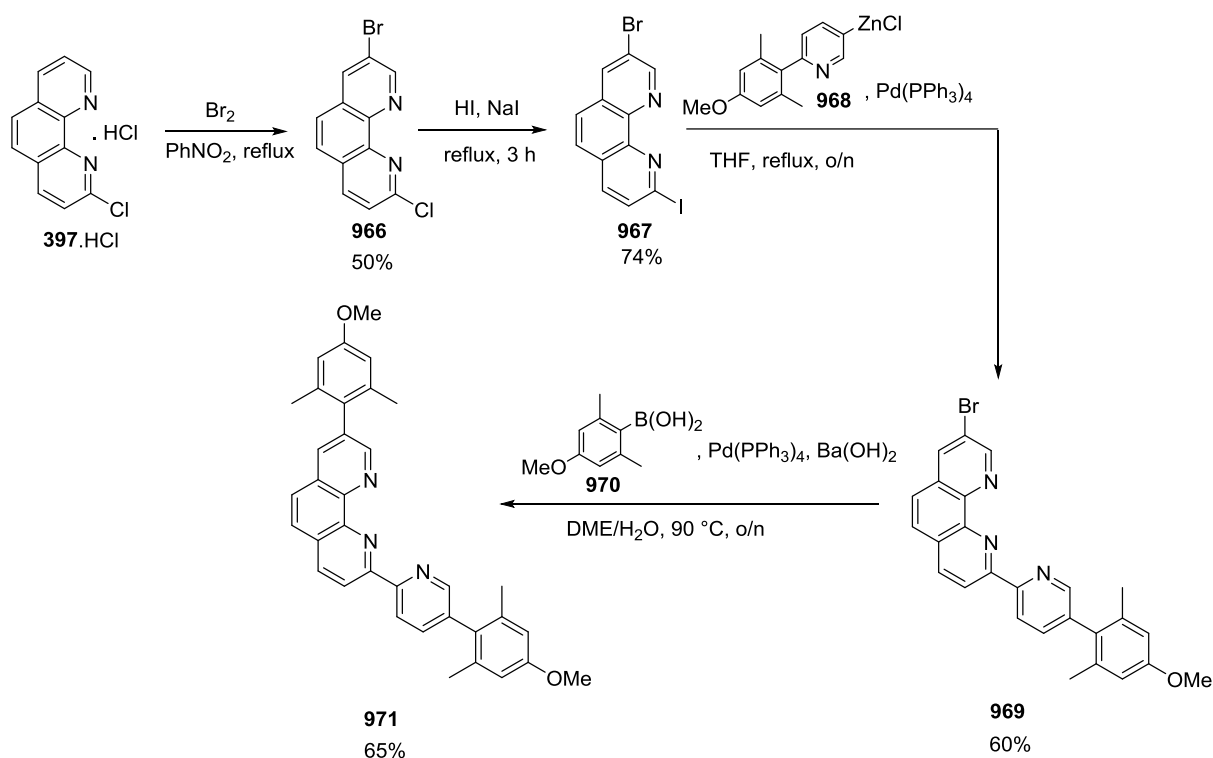


Scheme 203. Examples of bis-functionalization of phen in positions 2 - 3

Siegel and co-workers have developed a resolutely different method to reach efficiently 2,8-regioisomers. Indeed, bromination of the hydrochloride salt **397**.HCl leads to synthon 2-chloro-8-bromo-1,10-phenanthroline **966** in a reasonable yield.⁴²⁰ In order to enhance the reactivity, the Cl atom is selectively replaced by an iodine atom by refluxing **966** in HI, leading to **967**. The C-I and C-Br bonds feature a sufficiently different reactivity vs. pallado-catalyzed cross-couplings to allow the regio-selective functionalization of positions 2 and 8 in a sequential manner. In all accounts, the C-I bond is the first to be involved *via* a Suzuki⁴²⁰ or a Negishi⁹⁸⁰ cross-coupling. Then, the resulting still brominated ligand can be committed in other coupling reactions.^{420,980,981} For example, the Negishi coupling of **967** with freshly prepared organo-zinc reagent **968** affords **969** which is still bearing a free bromine atom. The latter is then committed in a Suzuki-Miyaura cross coupling with **970** to afford **971**⁹⁸⁰ (Scheme 204) or in another Negishi coupling (overall yield of 62%).¹⁹⁵ The disubstituted

compound can be obtained as well by reacting directly an excess of organozinc reagent that lead to the final compound with 67% yield.¹⁹⁵

The ligand **971** in Scheme 204 could coordinate a number of various metal cations, and the resulting complexes have been proven to arrange in self-assembled supramolecular arrays of molecular helices.⁹⁸²

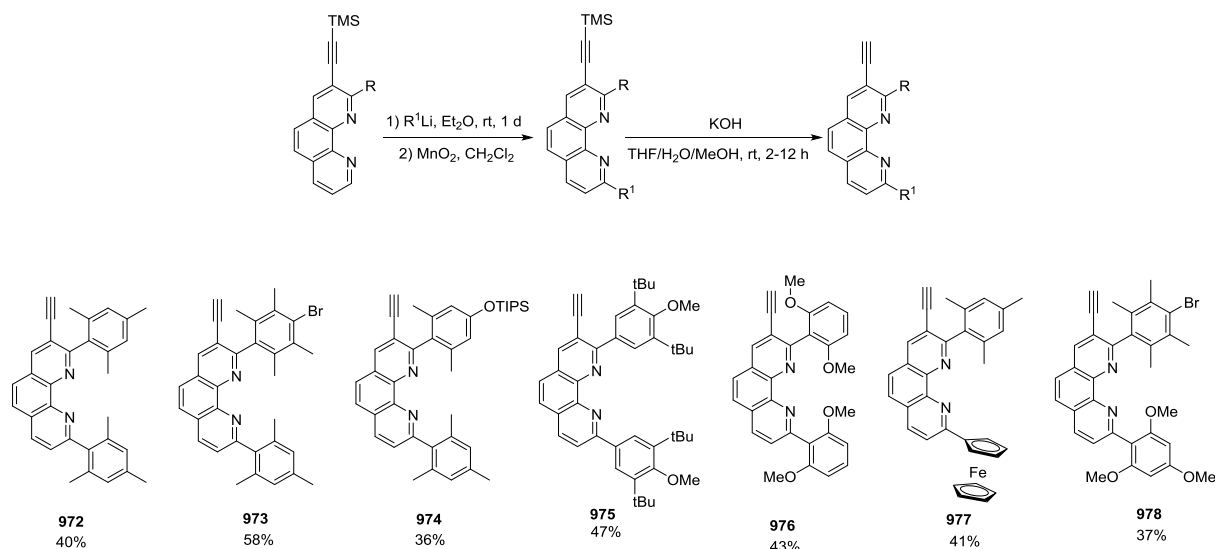


Scheme 204. Negishi coupling followed by a Suzuki coupling on the 3-bromo-9-iodophen **967**⁹⁸⁰

4.1.2. Tris-fonctionnalization of phen in positions 2,3 and 9

The most straightforward manner to reach 2,3,9-trisubstituted phen is to perform nucleophilic additions of organo-lithium reagents on previously described 2,3-disubstituted phen. This method has been developed by M. Schmittel and coworkers,⁹⁷⁹ to prepare a collection of phen ligands diversely substituted in positions 2, 3 and 9 (**972-978**, Scheme 205). Interestingly, better yields have been obtained if the addition of the organo-lithium reagents is performed in a stepwise manner (i.e. nucleophilic addition of one equivalent of R-Li followed by oxidation

with MnO_2 and reiteration of these steps) even if the organo-lithium reagents are identical. The significant size of the organo-lithium reagents that were used in all instances could be responsible for this observation.



Scheme 205. Examples of phen(2,3,9)_{sub} obtained from **265** (yields are given for all steps from 3-ethynyltrimethylsilane-1,10-phenanthroline).

972 to **978** have been used as building blocks to prepare an impressive amount of discrete, extended supramolecular systems: grids,⁹⁷⁹ racks,⁹⁸³⁻⁹⁸⁵ supramolecular ladders¹⁸⁵ and wheels,⁹⁸⁶ nano-boxes,⁹⁷⁹ prisms,^{984,987-989} triangles of different shape,⁹⁹⁰⁻⁹⁹² trapezoids,^{992,993} pentagons.⁹⁹⁴

All those intricate arrays have been obtained from mixtures of all molecular protagonists, which self-assemble in a organized manner based on well-defined affinities between ions and ligands and the maximum occupancy condition. In some cases, those large supramolecular structures have been used as nanoswitches⁹⁹⁵⁻⁹⁹⁹ and catalysts.^{1000,1001}

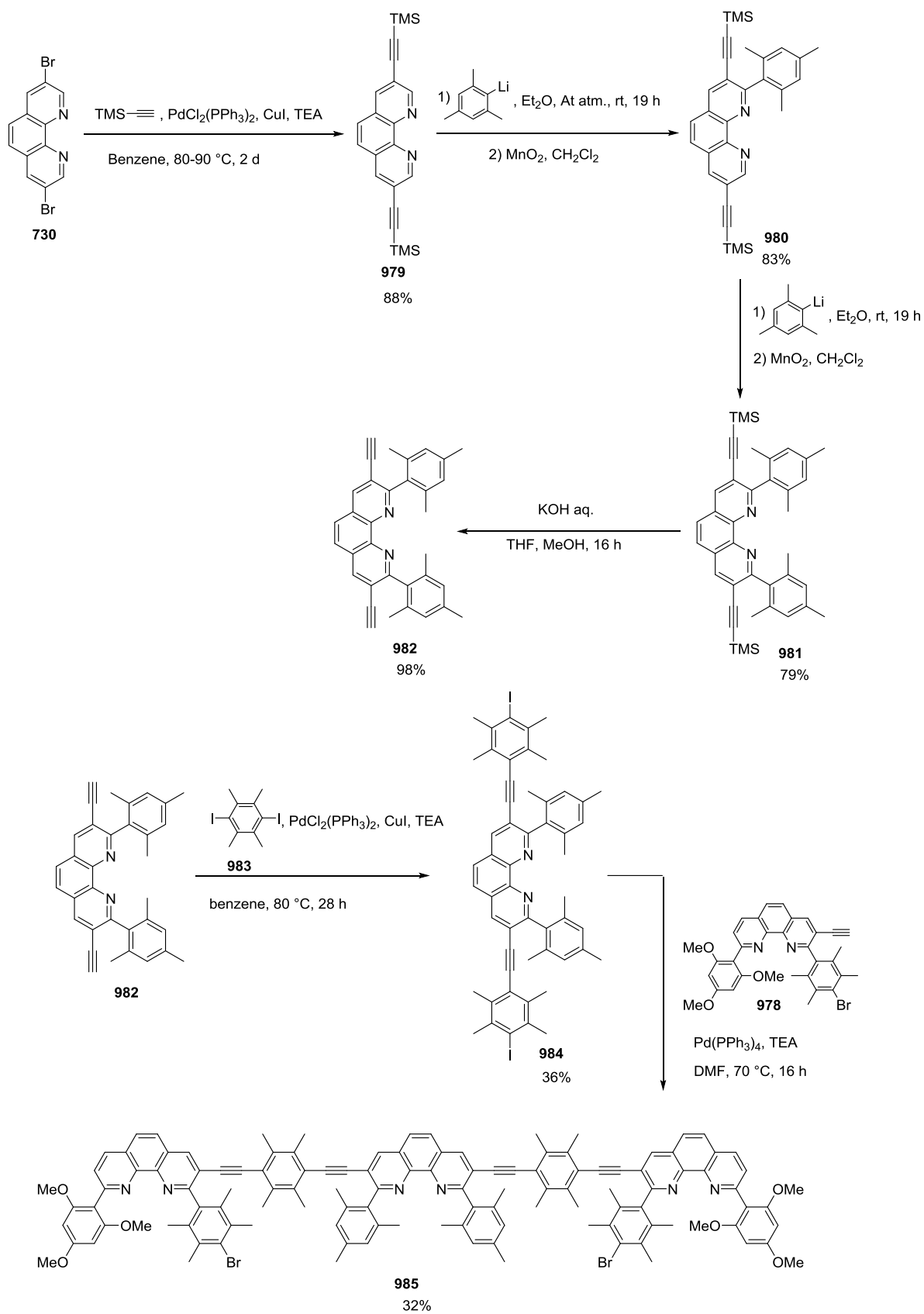
4.1.3. Tris-functionalization of phen in positions 2, 3 and 8 and tetra-functionalization of phen in positions 2, 3, 8 and 9.

Most methods developed so far to prepare phen_(2,3,8) and phen_(2,3,8,9) ligands are significantly similar, and they will thus be treated simultaneously to avoid unconstructive repetitions.

The most obvious method that can be used to prepare phen_(2,3,8) and phen_(2,3,8,9) is to apply the strategy described above with **265** (section 4.1.2) on 3,8-dibromo-1,10-phenanthroline **730** instead: namely functionalizing positions 3 and 8 with substituents which are compatible with organo-lithium reagents R-Li using well-known cross-coupling reactions, and reacting the resulting phen_(3,8) with one or two equivalents of R-Li, followed by re-aromatization with MnO₂.

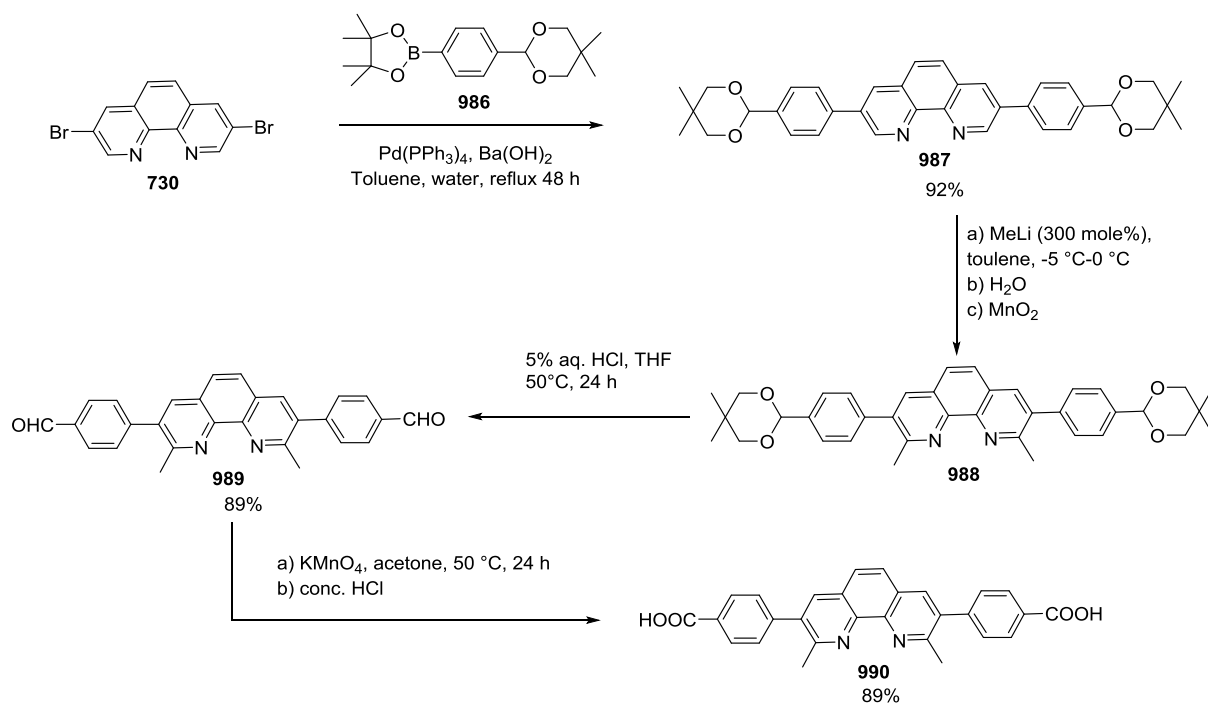
Thus, **730** has been functionalized with various alkynes and aryles, using Sonogashira,^{1002,1003} Suzuki^{189,1004–1007} or Negishi¹⁰⁰⁸ cross-coupling conditions. The resulting compounds are compatible with organo-lithium reagents R-Li. By controlling the amount of added R-Li, it is possible to graft one R group in position 2 or two R groups on positions 2 and 9. Again, reactions with organo-lithium reagents are always realized in a stepwise manner, even if positions 2 and 9 are substituted by the same group.¹⁰⁰³ Authors report that such precautions allow to isolate the tetra-substituted compounds in higher yields.

Examples are given in Scheme 206. Schmittel has used this strategy to isolate **982** as versatile synthon for the elaboration of rod-like ligands such as **985**, which can notably be used to prepare an impressive C-shaped porphyrin/metal complex polyfunctional supramolecular array.



Scheme 206. Example of synthetic strategy leading to elaborate phen_(2,3,8,9)sub

Sauvage and coworkers have proposed the synthesis of bis-carboxylated synthon **990** using a similar strategy: positions 3 and 8 of **730** are first functionalized with boronic ester **986** in traditional Suzuki coupling conditions. Then a first methyl group is appended in position 2 by the usual nucleophilic addition of methyllithium/MnO₂ re-aromatization sequence, and a second methyl group is tethered to position 9 following the same sequence. Treatment of **988** with HCl then KMnO₄ leads to bis-carboxylic acid **990** (Scheme 207). The COOH functions have been used for their reactivity in presence of amines¹⁰⁰⁹ or for their coordinating ability (preparation of a metal-organic framework incorporating a rotaxane).¹⁰¹⁰

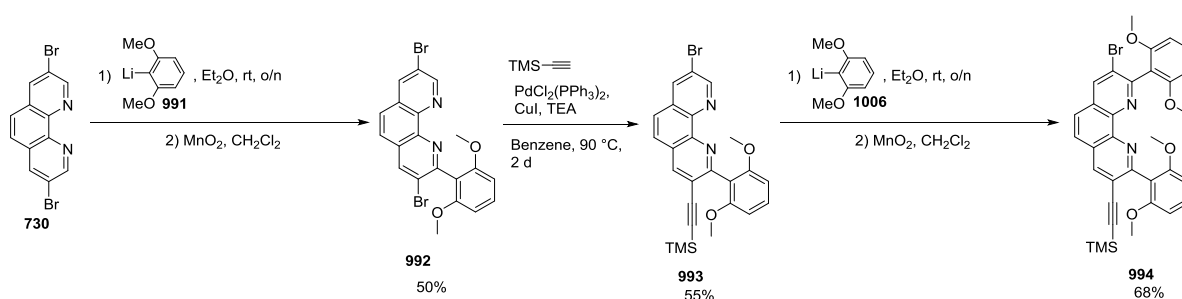


Scheme 207. Synthesis of COOH-bearing phen_{(2,3,8,9)sub} ligand **990**

In all the above cases, the steric hindrance imposed by substituents in positions 2 and 9 is necessary to force a tetrahedral geometry for the corresponding molecular metal (especially Cu(I)) complexes.

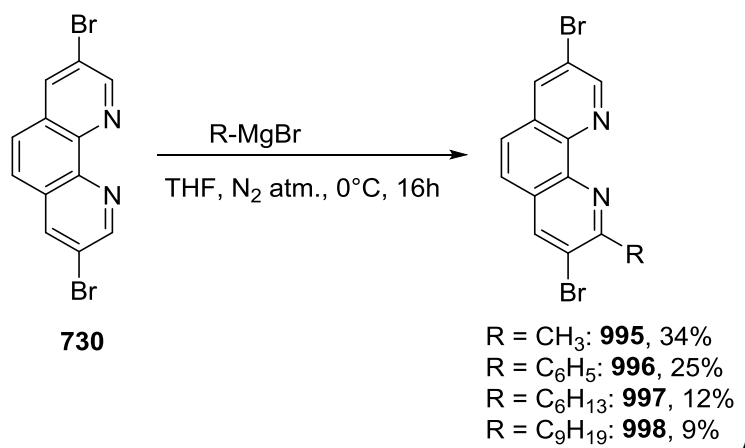
In those strategies, pre-functionalization of **730** is performed to avoid undesired side reactions with organo lithium reagents (such as halogen/lithium exchange). However, there exists one

reported case where organo lithium reagent **991** has been successfully added on position 2 of **730** leaving Br atoms untouched.¹⁰¹¹ The coupling of one equivalent of trimethylsilylacetylene on **992** in usual Sonogashira coupling conditions yielded exclusively one regio-isomer **993**. This could be due to the formation of a favorable intermediate involving Pd complexation by the oxygen atoms of the 1,3-dimethoxyphenyl group. In presence of another equivalent of organo-lithium compound **991**, the tetrasubstituted ligand **994** is obtained, bearing no less than three different functional groups and an available Br atom for further functionalization (Scheme 208).



Scheme 208. Action of organolithium reagent on **730** with no significant impact on the C_{3,8}-Br bonds.

To the best of our knowledge, this is the only reported case where **730** is successfully functionalized in positions 2 and 9 by organo lithium reagents. This strategy is likely to depend strongly on the nature of the organo lithium reagent. As a matter of fact, Yamamoto has reported that complex mixtures of unidentified compounds were obtained when **730** was mixed with R-Li reactants^{1012,1013} (resulting from the reaction of R-Li with C_{3,8}-Br bonds or in positions 2 and 9. No detail is given on the identity of R-Li). Using softer Grignard reagents R-MgBr (R = CH₃, C₆H₅, C₆H₁₃ and C₉H₁₉), a more selective nucleophilic addition is observed (Scheme 209). Addition of a second group in position 9 is reported in the same article, although the final compound could not be isolated because it was polluted with mono-functionalized compounds **995-998** which could not be removed by chromatography.



Scheme 209. Action of Grignard reagents on brominated **730** leading to phen_{(2,3,8)sub}

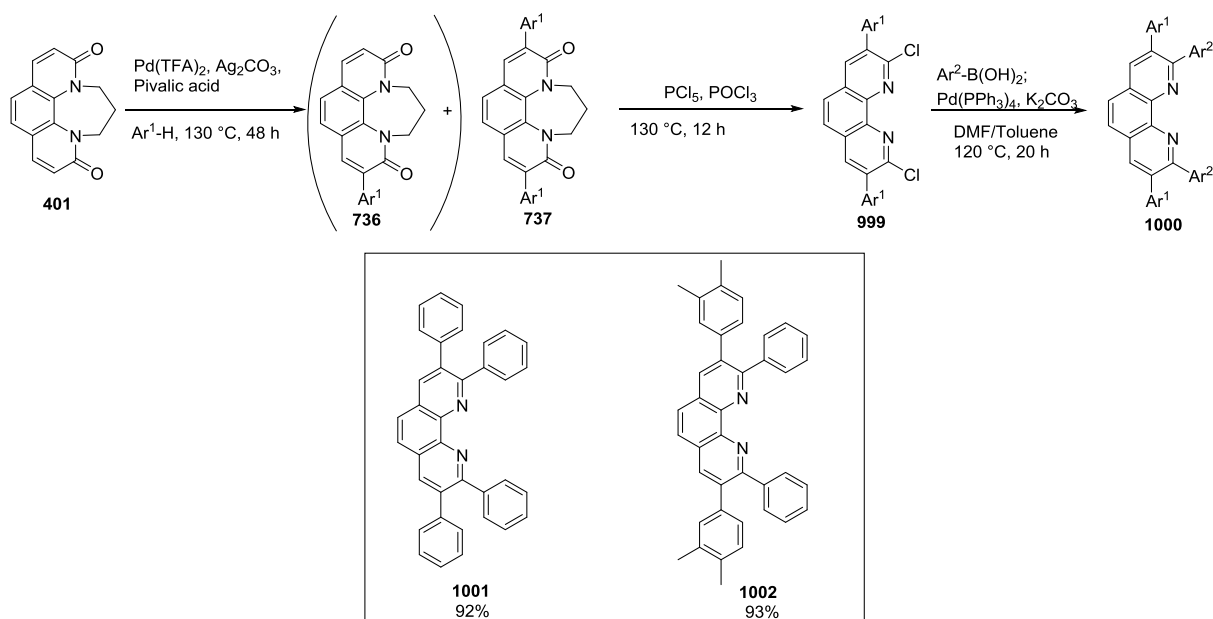
This approach is interesting in that ligands **995-998** feature reactive C_{3,8}-Br bonds; in presence of nickel(0) catalysts, homocoupling of **995**, **997** and **998** leads to linear coordinating polymers.¹⁰¹³

Curiously, bromination of a phen_{(2,9)sub} has never been reported. As previously mentioned (section 3.2.1), the required conditions are quite harsh and it is likely that aromatic or aliphatic pending groups in positions 2 and/or 9 would be damaged during the process.

4.1.4. Miscellaneous and concluding remarks

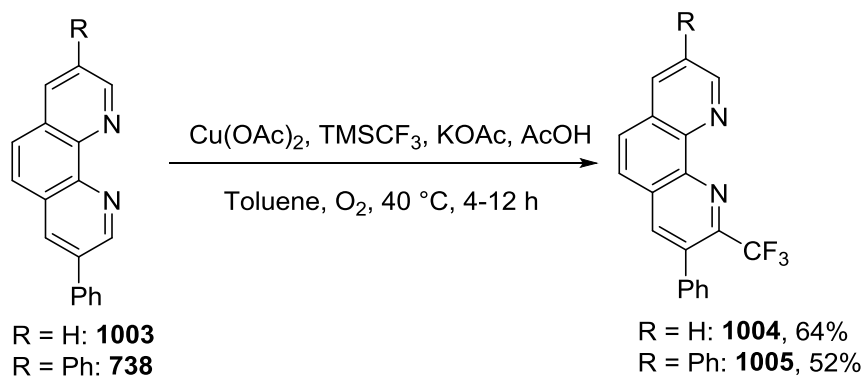
A few rare and original functionalization methods can be found in the literature to access tris- and tetra-functionalized phen ligands in positions 2, 3, 8 and 9.

For example, direct C-H/C-H arylation of N,N'-annelated-diketone **401** with non-functionalized arenes Ar₁-H in positions 3 and 8 has been reported (Scheme 210).¹⁰¹⁴ Both mono and bis-functionalized derivatives **736** and **737** form during the synthesis, but are easily separated by chromatography techniques. Treatment of **736** or **737** (and **1000**) with PCl₅ leads as already presented before to **999** which can be protonated in positions 2 and 9 as previously demonstrated, or which can subsequently be functionalized the same way than **396**, e.g. *via* a Suzuki coupling (Scheme 210).



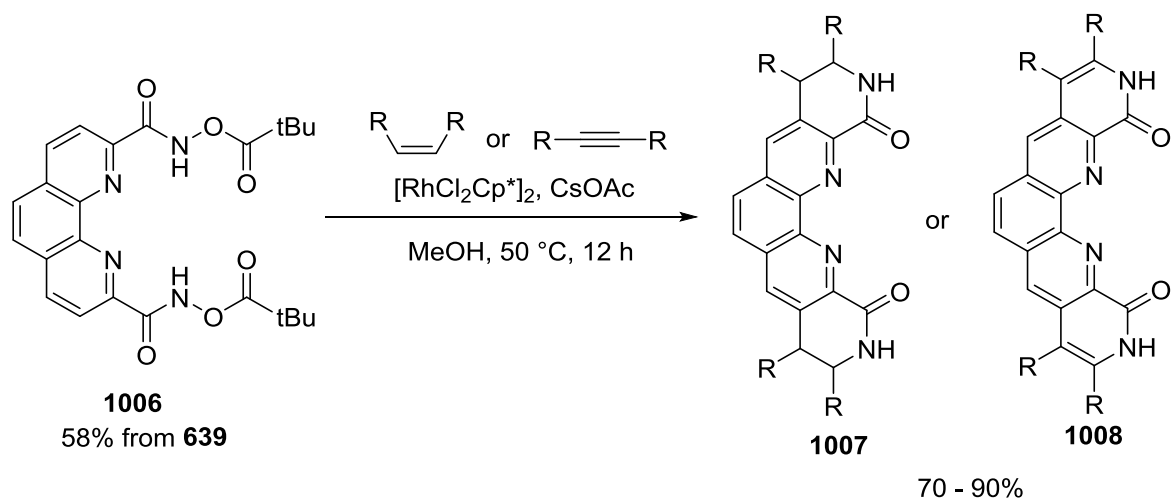
Scheme 210. Synthesis of phen_{(2,3,8,9)sub} through C-H arylation of **401**. Yields are given from **999**.

Earlier in this review, a copper-catalyzed addition of a CF₃ moiety in position 2 of phen has been mentioned (Scheme 65). This method can be easily extended to phen_{(3)sub} and phen_{(3,8)sub} ligands as exemplified in Scheme 211⁴⁰⁴. The phenyl groups appended in positions 3 and 8 are not harmed in those conditions. Interestingly, the trifluoromethylation of **738** or **1003** occurs regioselectively in position 2 (**1004** and **1005**).



Scheme 211. Copper-catalyzed trifluoromethylation of phen_{(3)sub} and phen_{(3,8)sub}.

A peculiar method to reach phen_(2,3,8,9) ligands consists in performing cycloadditions. For example, the Rh-catalysed cycloaddition involving hydroxamic acid reactive pendant groups located at the end of chains attached to positions 2 and 9 in **1006** (obtained from **639**) and alkynes or alkenes lead to phen_(2,3,8,9) where positions 2(9) and 3(8) are connected within a 6-membered ring (Scheme 212).¹⁰¹⁵



Scheme 212. Example of a Rh-catalysed cycloaddition reaction leading to a phen_(2,3,8,9) ligand

Conclusively, the methods to prepare phen_(2,3,8,9) ligands are rather scarce, and that is certainly due to the lack of methods available to prepare phen_(3,8) molecules since, conversely, there are many different methods to prepare phen_(2,9). Many reactions such as oxidation of methyl groups in positions 2 and 9 or deprotonation of the latter have never been explored on.

4.2. Synthetic methods for the preparation of phen_(2,4,7,9) and parent molecules

Five kinds of multiply substituted phen in positions 2, 4, 7 and 9 will be considered, the structure patterns are given in Figure 32.

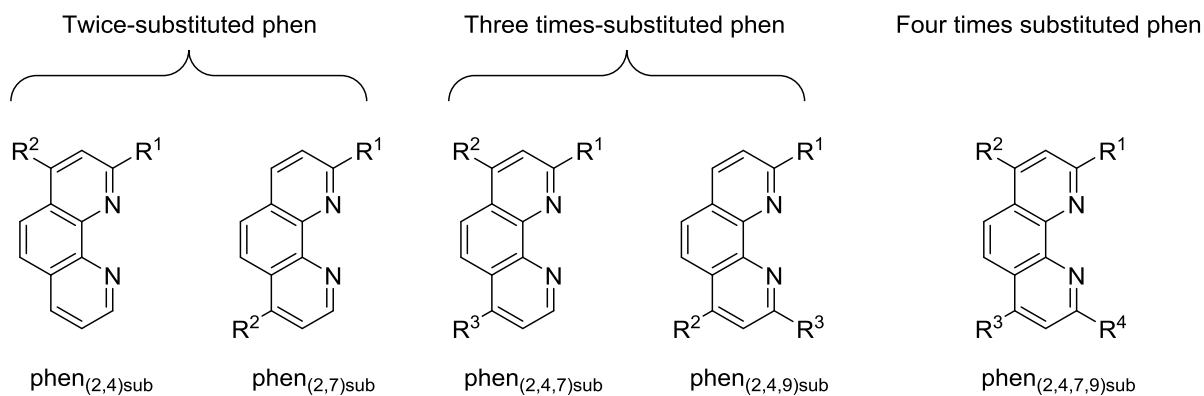


Figure 32. Substitution pattern for twice, three-times and four-times substituted phen in positions 2, 4, 7 and 9. R^n stands for any functional group, R^1 - R^4 can be identical or not.

4.2.1. Considerations about the synthons used to prepare multiple-substituted $\text{phen}_{(2,4,7,9)\text{sub}}$

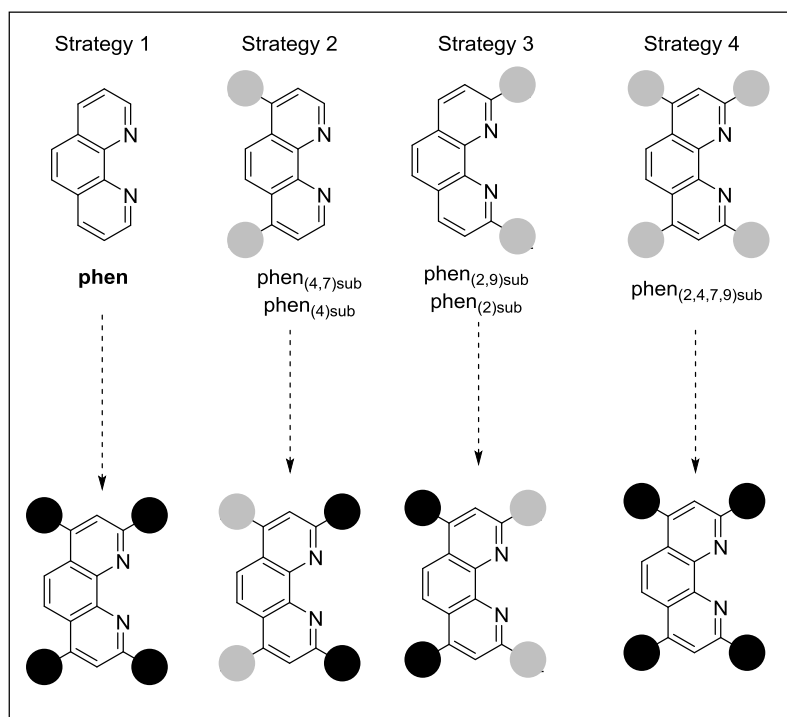


Figure 33. Four different strategies to functionalize phen in positions 2, 4, 7 and/or 9.

There are basically four strategies to prepare $\text{phen}_{(2,4,7,9)\text{sub}}$ phen with divergent methods (Figure 33). Although naked phen can be multiply substituted in positions 2, 4, 7 and 9 in one step (strategy 1) the most often encountered methods rely on the stepwise modification of an

already substituted phen. Basically, one can begin with phen_(4,7) or phen₍₄₎ and then follow known procedures described in section 3.1. to functionalize positions 2 and/or 9 (strategy 2). The opposite strategy, reacting phen_(2,9) or phen₍₂₎ to append onto them substituents in position 4 or in positions 4 and 7 is feasible too (Strategy 3) but it is known from section 3.3 (functionalization in position 4 and 7) that passing from phen to phen_(4,7) with divergent methods is particularly difficult. This will be obviously the same case when attempting to pass from phen_(2,9) to phen_(2,4,7,9). Fortunately, there are many different starting phen_(4,7), phen_(2,9) and even phen_(2,4,7,9) which can be further decorated to reach more complex phen ligands (strategy 4). Those previous building blocks are readily available (either by convergent methods or from commercial sources).

4.2.2. Multiple substitution of phen in positions 2,4,7 and/or 9: from naked phen

Although it is very rare, one can find two different examples of one-pot poly-substitutions of phen in positions 2, 4, 7 and 9.

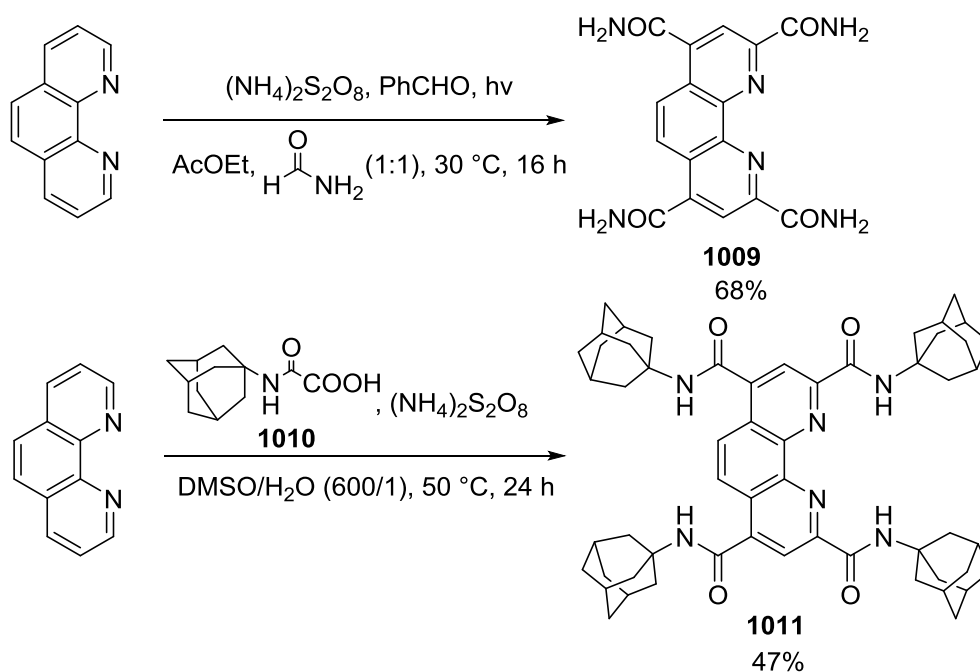
4.2.2.1. Trifluoromethylation of phen in positions 2, 4, 7 and 9.

Heating phen in presence of CF₃I, at high temperature in a sealed autoclave, allows to append trifluoromethyl groups to phen in various positions.⁵²⁵ Different regio-isomers are obtained and can be separated by HPLC, affording for instance 2,4,7,9-tetra(trifluoromethyl)-1,10-phenanthroline in 0.5 % yield (mg scale). This method is quite simple but suffers from the difficulty to handle gaseous CF₃I, drastic conditions (330 °C for 10 hours) and above all low selectivity (mixture of regio-isomers) and low yield.

4.2.2.2. Functionalization of phen using radical species

As mentioned in the introduction, the Minisci reaction consists in reacting radical nucleophiles on protonated azines to generate C-C bonds in positions α and γ with a high

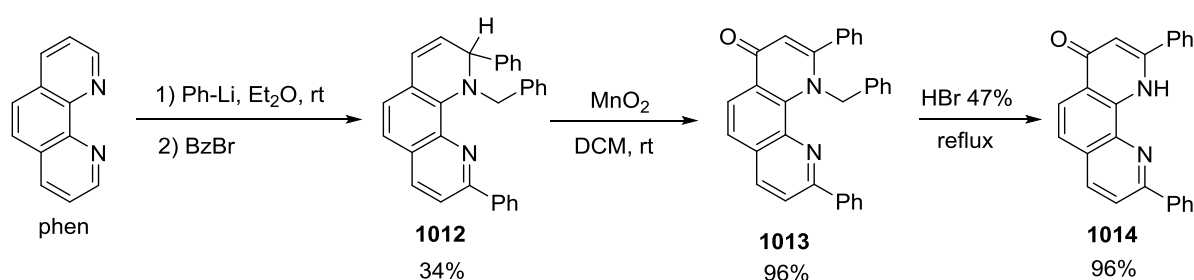
regioselectivity. This method has been successfully applied to the functionalization of phen in positions 2 and 9 (section 3.1.3) and can be extended here to positions 2, 9, 4 and 7. Harwood and co-workers brightly exemplified the relevance of Minisci reaction applied to phen by achieving in one step the tetracarbamoylation of the ligand (**1009**).⁷³⁴ Briefly, the carbamoyl radicals were generated on formamide by H abstraction by $\text{SO}_4^{\cdot-}$ radical, the latter being photogenerated from $(\text{NH}_4)_2\text{S}_2\text{O}_8$ in presence of benzaldehyde as photosensitizer¹⁰¹⁶ (Scheme 213). This reaction was re-explored a few years later by Lee and coworkers who extended the scope of the reaction to secondary and tertiary amides (e.g. **1011**) using oxamic acids such as **1010** as carbamoyl radical donors.¹⁰¹⁷ Importantly, the carbamoyl radicals were still generated by H abstraction by $\text{SO}_4^{\cdot-}$ radicals, but this time the latter were generated by thermal degradation of $(\text{NH}_4)_2\text{S}_2\text{O}_8$ in DMSO/water mixtures, a particularly favourable environment for such reaction. It is remarkable that such advanced functionalization reactions can be achieved in absence of light and costly metal catalysts (Scheme 213).



Scheme 213. Radical addition (Minisci's reaction) on phen affording phen_(2,4,7,9)sub ligands in one pot.

4.2.2.3. Formation of phen_{(2,4,9)sub} precursor through the organolithium reaction pathway

As mentioned in the introduction, all extended (aromatic-ring fused) phen and reduced non-conjugated phen structures have been voluntarily excluded from the review. We wish however to make here an exception and report on an article by Nierengarten and wo-workers where an original precursor of phen_{(2,4,9)sub} is obtained in mild conditions which may interest the reader (Scheme 214).¹⁰¹⁸ After addition of an organolithium reagent onto phen, an anionic de-aromatized substituted phen is obtained: while the latter is usually treated with water, quenching by another electrophile such as benzyl bromide is possible. This results in the formation of tertiary amine **1012** which, upon oxidation by MnO₂, affords ketone **1013**. Treatment of the latter by HBr yields almost quantitatively **1014**, as a very useful precursor of several relevant phen_{(2,4,9)sub}.



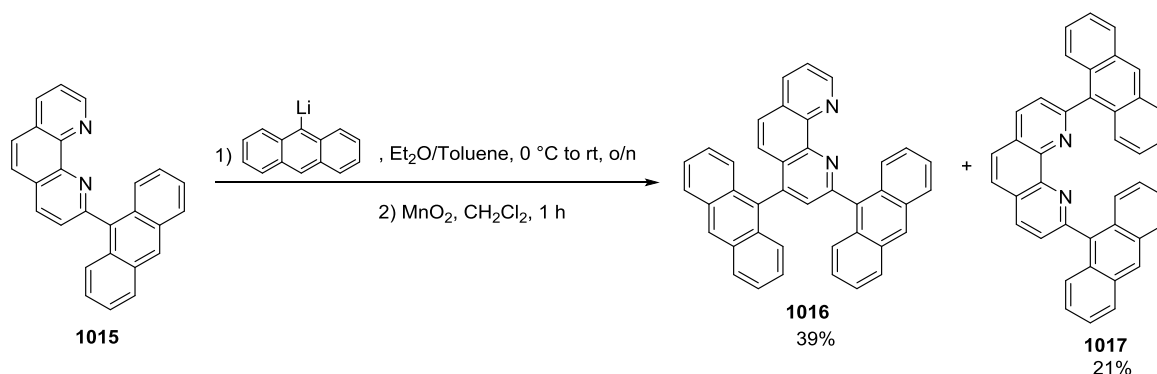
Scheme 214. Synthesis of **1014** phen_{(2,4,9)sub} precursor

4.2.3. Multiple substitutions of phen in positions 2,4,7 and/or 9: from phen_{(2)sub} or phen_{(2,9)sub}.

4.2.3.1. Action of organolithium reagents on phen_{(2)sub}

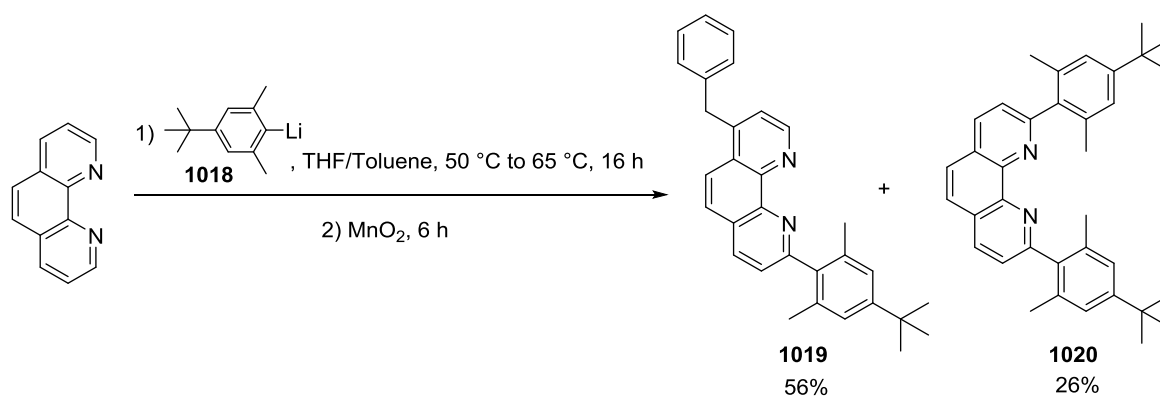
In most cases, the action of organolithium reagents RLi on phen leads to 2,9-R₂-1,10-phenanthroline molecules but a few rare cases have been reported where other substitution patterns are observed instead. In 2001, while aiming at preparing phenanthrenyl-phen derivative **1017**, Schmittl et al. have reported the unexpected synthesis of **1016** as main product while adding phenanthrene-lithium on mono-functionalized **1015**,¹⁰¹⁹ because the steric hindrance of the phenanthrenyl moiety precluded the “regular” addition in position 9

(Scheme 215). Similar observations were made on pyridine when put in presence of Grignard reagents¹⁰²⁰ of various sizes. Overall this demonstrates that position 4 (and 7) of phen, like positions 2 and 9, are both activated towards nucleophilic attacks, as expected from the orbital patterns.⁷⁵⁹



Scheme 215. Unexpected synthesis of a phen_{(2,4)sub} ligand with organolithium reagents

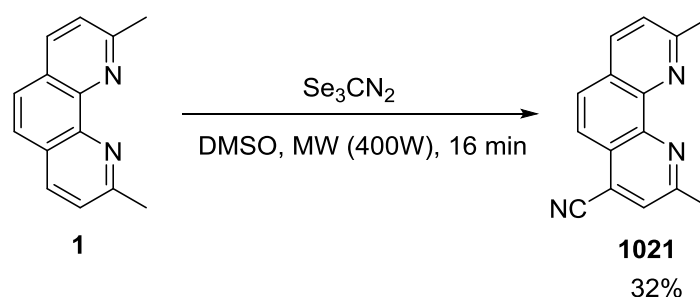
More recently, Ruppert et al.¹⁰²¹ have published the unexpected synthesis of **1019** (Scheme 216) and highlighted the impact of the source of lithium on the outcome of the functionalization reaction. Indeed, organo lithium reagent 2-lithium-5-(tert-butyl)-1,3-dimethylbenzene **1018** is prepared from 2-bromo-5-(tert-butyl)-1,3-dimethylbenzene by a lithium-halogen exchange, in presence of a lithiating agent. When *tert*-butyllithium is used to prepare **1018** the latter is efficiently generated together with significant amounts of tolyl-lithium (toluene being the co-solvent of the reaction). **1018** is probably the first reagent to attack phen in position 2 while, unexpectedly, tolyl-lithium preferably reacts in position 7. The authors have attempted a rationalization of this observation by proposing the formation of a phen-lithium complex, where Li⁺ is coordinated by the mono-substituted phen, and prevents further nucleophilic attack in position 9 because of steric hindrance. The peculiar regioselectivity of the reaction in position 7 and not position 4 is however not discussed and interestingly opposes to the one observed by Schmittel and co-workers (Scheme 215).



Scheme 216. Unexpected synthesis of a phen_{(2,7)sub} ligand with organolithium reagents

4.2.3.2. Selective cyanation of neocuproine by Se₃CN₂

Cyanation of halo-aromatics is well-known and proceeds by substitution of the halide leaving group by CN⁻ using cyanide sources such as TMSCN, or Zn(CN)₂. Using Se₃CN₂ as cyanide source under micro-wave irradiation has allowed the group of Maity to perform the cyanation of a number of aromatic compounds by direct hydrogen substitution, including neocuproine (Scheme 217).¹⁰²² Compound **1021** was thus obtained easily in a modest yield, but in remarkably simple conditions.

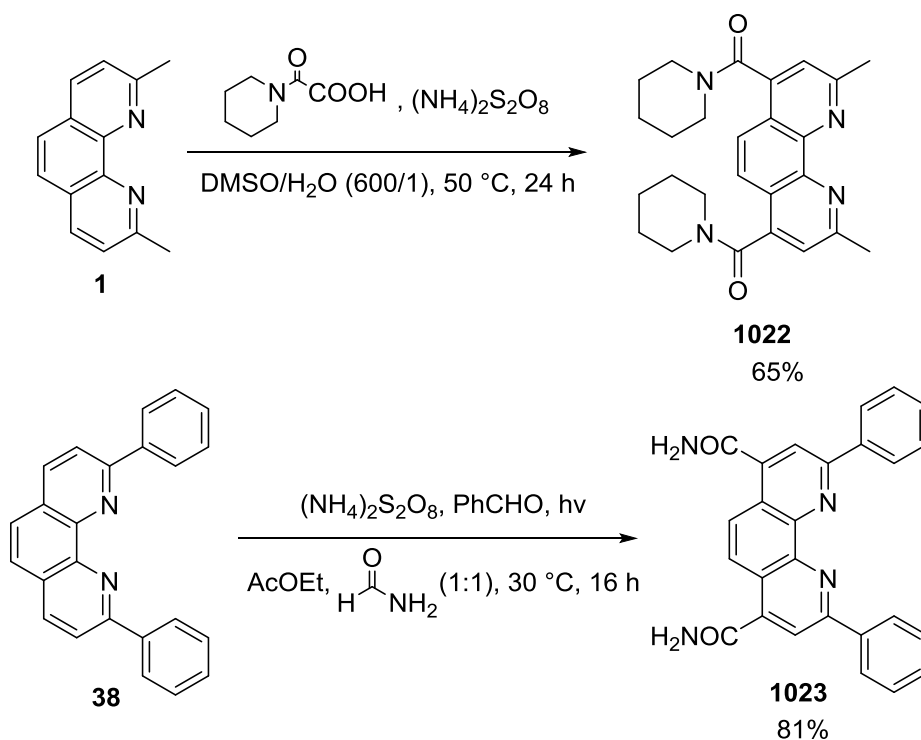


Scheme 217. Regioselective cyanation of neocuproine **1** in position 4 by Se₃CN₂

4.2.3.3. Minisci reactions

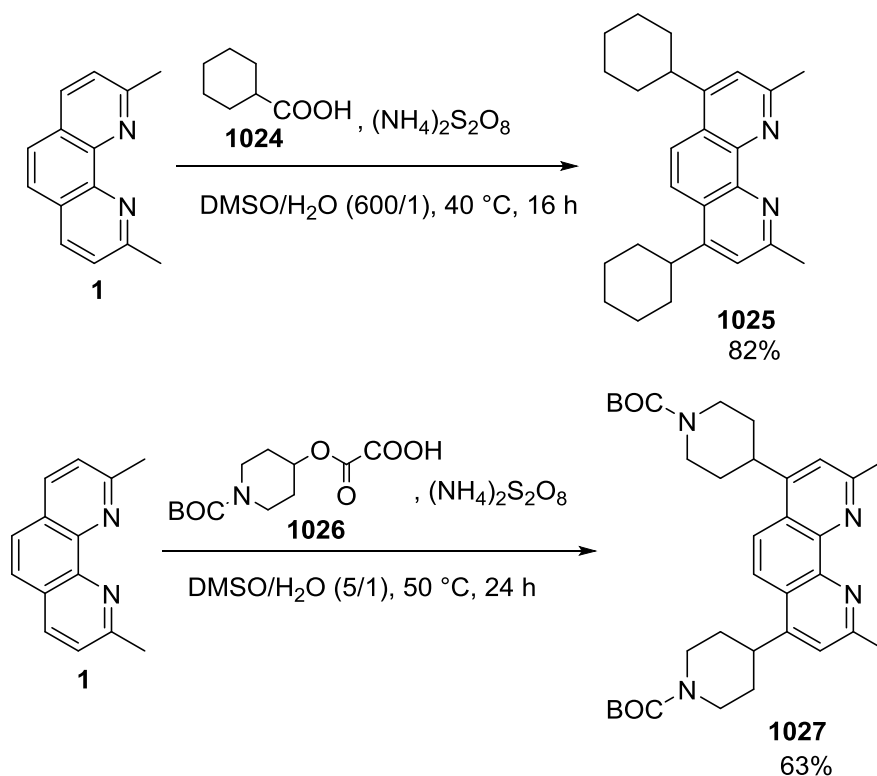
When positions 2 and 9 of phen are already functionalized, radical nucleophiles attack regioselectively positions 4 and 7 with high efficiency. The same conditions than presented above (Scheme 213) can naturally be applied to 2,9-diphenyl-1,10-phenanthroline **38**⁷³⁴ or

neocuproine **1**^{1017,1023} with similar efficiency, leading to corresponding bis-carbamoylated phen in positions 4 and 7 (Scheme 218).



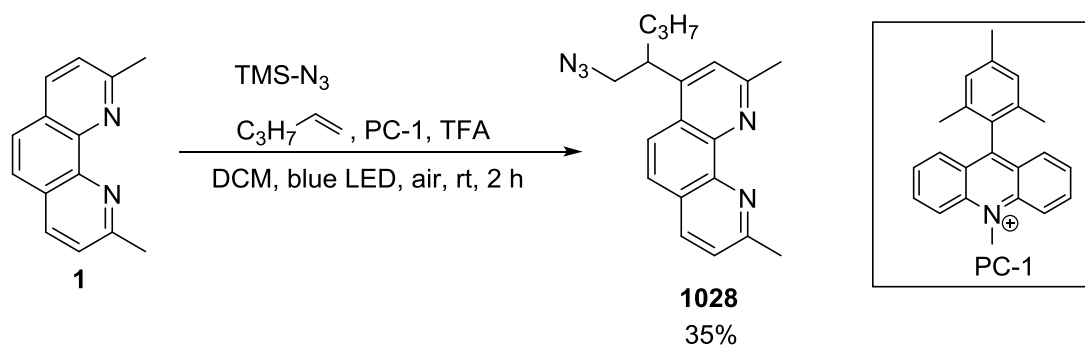
Scheme 218. Minisci reactions allowing the carbamoylation of phen_{(2,9)sub} **1** and **38** into phen_{(2,4,7,9)sub} **1036** and **1037**, respectively.

Other reactive species than carbamoyl radicals have been used to functionalize positions 4 and 7 of phen_{(2,9)sub}. For example, carboxylic acids R-COOH¹⁰²⁴ (e.g. **1024**) and oxalic esters R-OC(O)-COOH (easily obtained by reaction of alcohols with oxalylchloride, see for instance **1026**)¹⁰²⁵ are convenient R[•] sources. In those reactions, SO₄^{•-} radicals are first generated by thermal activation of $(\text{NH}_4)_2\text{S}_2\text{O}_8$ in similar conditions than above. SO₄^{•-} then promotes the decarboxylation of **1024** or **1026** into nucleophile alkyl radicals R[•] which attack both positions 4 and 7 of phen_{(2,9)sub} leading to **1025** and **1027** in average to good yields (Scheme 219).



Scheme 219. Minisci reactions allowing the alkylation of phen_(2,9)sub **1** into phen_(2,4,7,9)sub **1025** and **1027**

A last example describes a photo-initiated cascade radical reaction, where trimethylsilyl azide TMS-N₃ is photo-oxidized by acridinium dye PC-1 leading to the N₃[•] radical.¹⁰²⁶ The latter then reacts on olefin derivatives such as pent-1-ene affording secondary carbon radical, which finally attacks neocuproine on the free position 4 (Scheme 220).



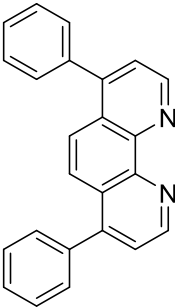
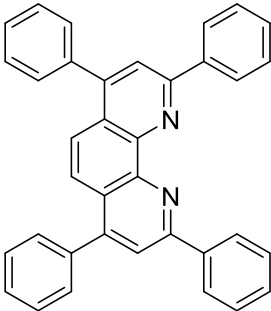
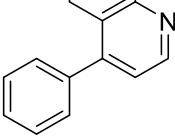
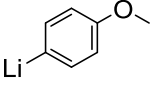
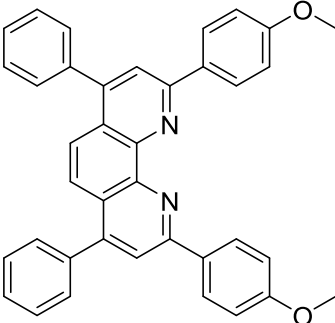
Scheme 220. N₃[•] assisted radical addition of pent-1-ene on neocuproine **1**

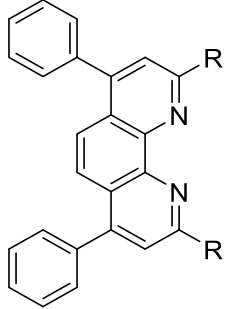
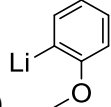
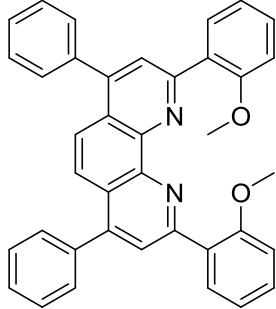
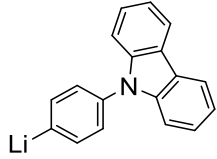
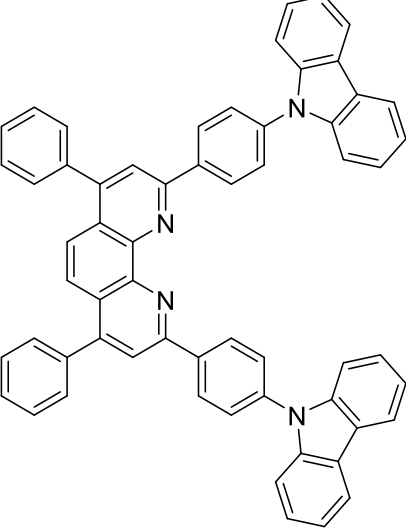
4.2.4. Multiple substitution of phen in positions 2,4,7 and/or 9: from phen_{(4)sub} and phen_{(4,7)sub}

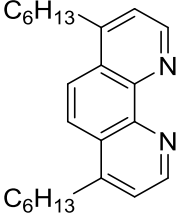
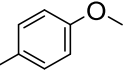
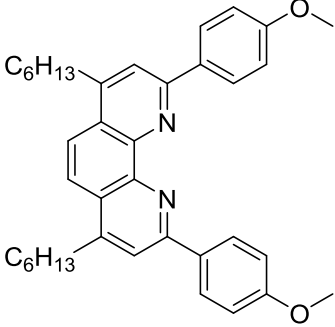
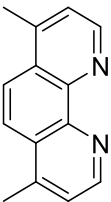
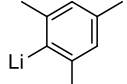
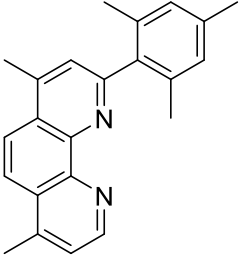
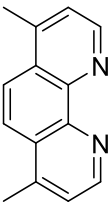
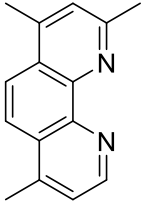
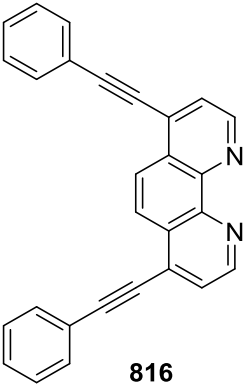
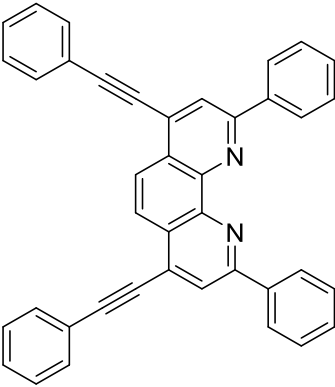
4.2.4.1. Action of organolithium reagents

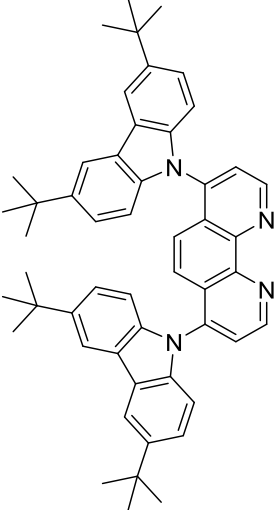
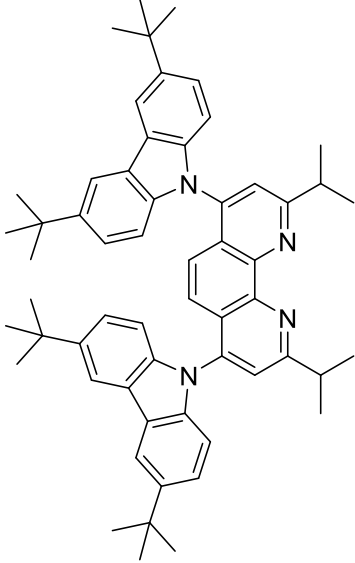
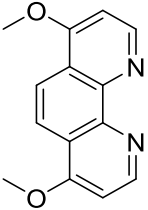
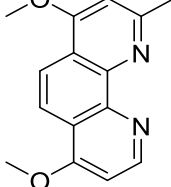
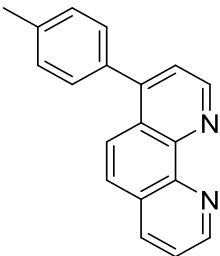
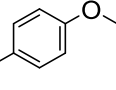
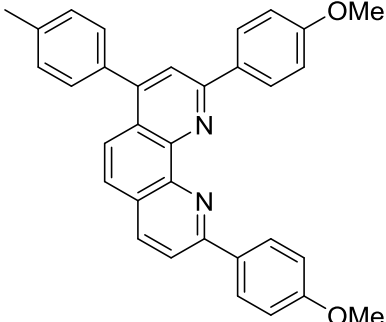
Many strategies developed to functionalize phen in positions 2 and 9 are perfectly adaptable to phen_{(4)sub} and phen_{(4,7)sub} molecules obtained by convergent methods. For example, action of organolithium reagents on phen_{(4)sub} and phen_{(4,7)sub} (followed by a re-aromatization step in oxidizing medium) is certainly the most abundantly used methodology to append alkyl and aryl substituents of all sorts in positions 2 and/or 9. A collection of tris- and tetra-substituted phen has been synthesized for various applications and is presented in Table 18.

Table 18. Reactants, conditions and products with yields for the transformation of (phen_{(4)sub}) phen_{(4,7)sub} into (phen_{(2,4,9)sub}) phen_{(2,4,7,9)sub} by organolithium reagents

Entry	Starting material	conditions	obtained compound (yield)	Ref
1		1) PhLi, Toluene, rt 2) MnO ₂	 1029(80%)	335
2	 30	1)  , toluene/Et ₂ O, rt 2) MnO ₂	 1030 (80%)	1027

3		<p>1) RLi (R = <i>n</i>-Butyl, <i>sec</i>-Butyl, <i>tert</i>-butyl, <i>n</i>-Octyl)</p> <p>2) MnO₂</p>	 <p>R = <i>n</i>-Butyl: 1031 (85%)</p> <p>R = <i>sec</i>-Butyl: 1032 (72%)</p> <p>R = <i>tert</i>-butyl: 1033 (68%)</p> <p>R = <i>n</i>-Octyl: 1034 (42%)</p>	338
4		 <p>1)</p> <p>toluene, 0 °C to reflux, 24 h</p> <p>2) MnO₂</p>	 <p>1035 (51%)</p>	62
5		 <p>1036</p> <p>Et₂O / toluene, reflux 24 h</p> <p>2) MnO₂</p>	 <p>1037 (52%)</p>	

6	 <p>1038</p>	<p>1) ,</p> <p>toluene/Et₂O, rt</p> <p>2) MnO₂</p>	 <p>1039 (31%)</p>	90
7	 <p>3</p>	<p>1) ,</p> <p>toluene, 0 °C to rt, 20 h</p> <p>2) MnO₂</p>	 <p>1040 (70%)</p>	1028
8	 <p>3</p>	<p>1) CH₃Li (1 eq), THF/Et₂O, 0 °C to rt, 16 h</p> <p>2) MnO₂</p>	 <p>1041 (47%)</p>	1029
9	 <p>816</p>	<p>1) PhLi, Et₂O / cyclohexane, -20 °C, 2 h</p> <p>2) MnO₂, CH₂Cl₂</p>	 <p>1042 (39% - two steps)</p>	137

10	 <p style="text-align: center;">845</p>	<p>iPrLi, Et₂O, 0 °C</p> <p>to rt, 24 h</p>	 <p style="text-align: center;">1043 (36%)</p>	751
11	 <p style="text-align: center;">827</p>	<p>1) CH₃Li (1 eq), THF/Et₂O, 0 °C</p> <p>to rt, 16 h</p> <p>2) MnO₂</p>	 <p style="text-align: center;">1044 (18%)</p>	1029
12	 <p style="text-align: center;">1045</p>	<p>1) , toluene/Et₂O, rt</p> <p>2) MnO₂</p>	 <p style="text-align: center;">1046 (65%)</p>	1030

Additions of one (entries 7, 8, 11) or two groups (entries 1-6, 9 and 10) in α of the nitrogen atoms on phen_{(4,7)sub} have thus been reported. The presence of groups in positions 4 and 7 often improves the solubility of the starting phen material,^{90,1031} which likely facilitates the reactivity with RLi. One notices on the other hand that the steric bulk of the organolithium reagent has an impact on the yields of the target compound (entry 3). Using RLi on

monosubstituted phen(4)_{sub} is working equally well; a possible attack of RLi in position 7, while possible (Schemes 205 and 206) has not been mentioned (entry 12).

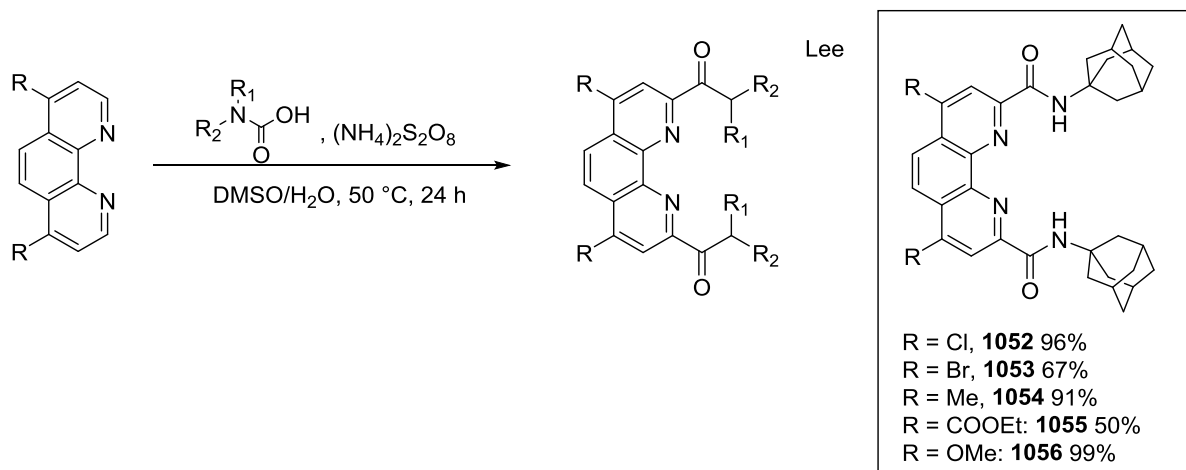
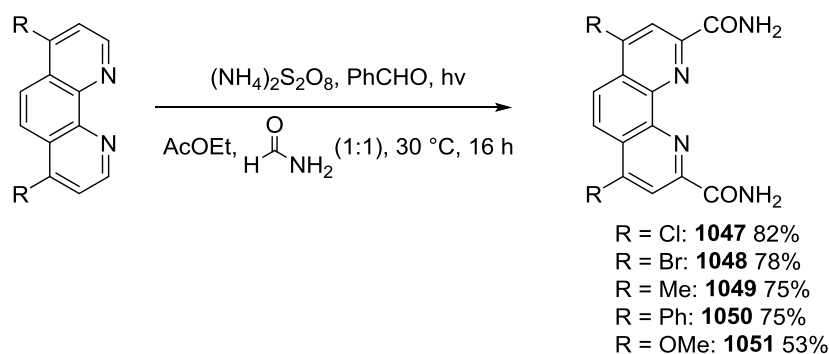
Different groups in positions 4 and 7 are tolerant to the presence of organolithium reagents: alkyl and aryl of course, tertiary amines (entry 10) and ethers too (entry 11).

There is no report of the reaction of organolithium reagents with phen(4,7)_{sub} bearing halides in positions 4 and 7, likely because of the risk of halogen-lithium exchange leading to undesired side-products. It is therefore more relevant to first exploit the reactivity of the halides, by performing aromatic nucleophilic substitutions,^{751,1029} or pallado-catalyzed cross coupling reactions,⁷³⁷ and then use organolithium reagents to functionalize positions 2 and 9.

4.2.4.2. Minisci reactions

We have already mentioned that the Minisci reaction, and related processes, are very efficient in functionalizing positions 4 and 7 of phen(2,9)_{sub} (Section 4.2.3.3). The same conditions can be implemented to tether substituents in positions 2 and 9 of diversely functionalized phen(4,7)_{sub}.

Harwood and co-workers⁷³⁴ have already used formamide as carbamoyl radical source on phen and phen(2,9)_{sub} (Scheme 218). Similarly, the bis-carbamoylated phen derivatives **1047-1051** have thus been obtained in one step from the corresponding phen(4,7)_{sub} (Scheme 221). Lee and co-workers¹⁰¹⁷ applied their own previously described protocol (Scheme 213) using oxamic acids as substrates to form phen(2,4,7,9)_{sub} derivatives **1052-1056** (Scheme 221). Interestingly, those conditions are tolerant to a significant number of substituents in positions 4 and 7: aliphatic chains or aromatic rings, halogen atoms, etheroxides alcohols and esters (Scheme 221). It is interesting to notice that carbamoylation in Harwood's conditions worked less efficiently on electron enriched phen (**1051**) although it was unaffected in Lee's conditions (**1056**).

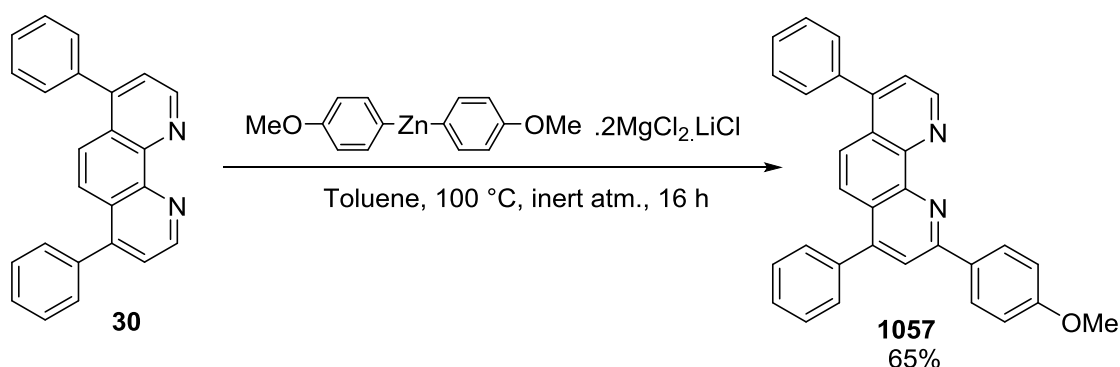


Scheme 221. Functionalization in positions 2 and 9 of phen_{(4,7)sub} by radical nucleophiles

In addition to Harwood and Lee's studies, other Minisci reactions allowing to functionalize phen_{(4,7)sub} have been published. The reactions can be thermally,^{1017,1023–1025,1032} electrochemically,¹⁰³³ photochemically^{409,734,1034–1036} or photo-electrochemically^{1037,1038} driven, using a wide range of radical precursors: alkyl iodide,¹⁰³³ oxalic acid derivatives^{1025,1036,1037} or cyclopropanol derivatives,¹⁰³² boronic acids,¹⁰³⁴ alkyltrifluoroborates⁴⁰⁹ (leading to alkylations) and α -keto acids^{1023,1035} (leading to acylation). Functionalization of phen_{(4,7)sub} usually occurs in both positions 2 and 9 or in position 2 only.^{1033,1034,1037} The reactions can be scaled up¹⁰²³ (gram scale) showing the relevance of the Minisci reactions to easily functionalize phen_{(4,7)sub}.

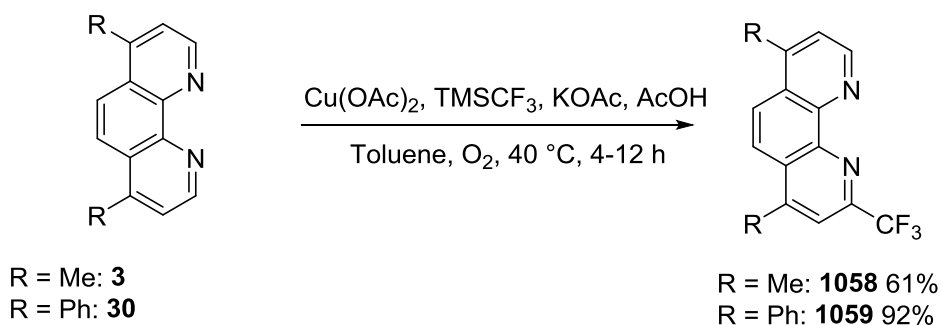
4.2.4.3. Miscellaneous

Apart from organolithium reagents, direct C-H arylation of bathophenanthroline can be performed using a diaryl-zinc compound in straightforward conditions (Scheme 222).¹⁰³⁹ This alternative method to the organolithium strategy can be practical when an organolithium reagent is not available. However, no double functionalization in positions 2 and 9 is yet reported.



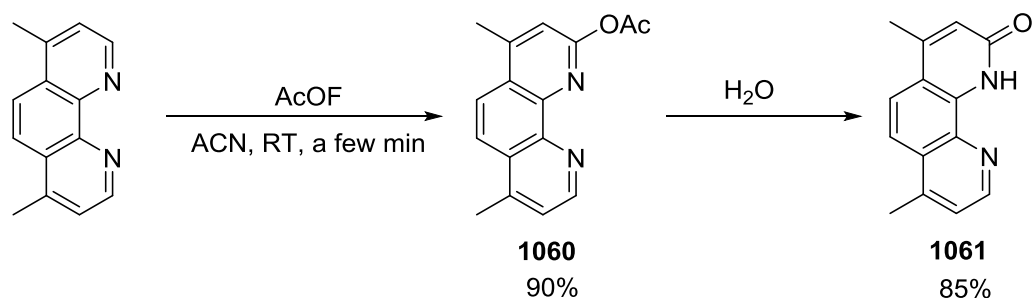
Scheme 222. Negishi cross-coupling on bathophenanthroline **30**

Coordination of metal cations by $\text{phen}_{(4,7)\text{sub}}$ has been reported to activate the C=N bond of the phen cavity towards nucleophilic addition, just as observed for naked phen (Scheme 65). For example, trifluoromethylation of 4,7-diphenyl-phen **30** or 4,7-dimethyl-phen **3** in position 2 has been reported, using TMSCF_3 in presence of sub-stoichiometric amounts of copper(II) acetate (Scheme 223).⁴⁰⁴ It is hypothesized that a copper complex intermediate forms, where both CF_3 and phen are bound to Cu(II); then CF_3^- attacks coordinated phen which evolves in presence of oxygen into **1058** or **1059**. A similar approach, using stoichiometric amounts of Ag(I) instead of Cu(II) and TMSCF_2H instead of TMSCF_3 has been published too.⁴⁰⁵ Those methods are very versatile and highly selective of position 2, and can be applied to several different phen substituted in other positions (*vide infra*).



Scheme 223. Copper-assisted trifluoromethylation of phen_{(4,7)sub} in position 2

Acetyl hypofluorite AcOF (AcOF is a very efficient oxidant, easily prepared from F₂ and sodium acetate in acetonitrile at low temperature. It is stable and easier to handle than very noxious gaseous F₂ alone) was used to efficiently oxygenate polypyridines on the carbon in α of the nitrogen atoms.¹⁰⁴⁰ In the case of **3**, the reaction is successful and yields compound **1060** in 90% yield (Scheme 224). This acetoxylation is based on the formation of a key intermediate, where an N-F bond is formed between 4,7-dimethyl-phen and electrophilic fluorine from AcOF. This strongly activates the C=N bond towards nucleophilic attack by the acetate anion. After hydrolysis, the 4,7-dimethyl-1,10-phenanthrolin-2(1H)-one **1061** is formed because of its more favourable conjugation pattern compared to the imino-alcohol tautomer.



Scheme 224. Functionalization of phen_{(4,7)sub} by efficient oxygenation in position 2

4.2.5. Decoration of pivotal phen_{(2,4,7,9)sub} synthons

In this section, we will give examples associated to strategy 4 exposed in Figure 33. There is mainly one important building block we will consider (Figure 34), namely neocuproine derivatives where substituents have been tethered in positions 4 and 7. Similarly to our notation for phen, those molecules will be designated **1**_{(4,7)sub}. **1**_{(4,7)sub} derives from neocuproine and bears therefore two methyl groups in positions 2 and 9. Many **1**_{(4,7)sub} are commercially available (e.g. famous 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline **22**, best known as bathoneocuproine) or synthesized by convergent synthetic methods. **1**_{(4,7)sub} potentially exhibits the reactivity of neocuproine **1** (section 3.1.4.2) and of course the reactivity of groups R attached in positions 4 and 7. All those reactivities have been only partially explored for the decoration of phen_{(2,4,7,9)sub}.

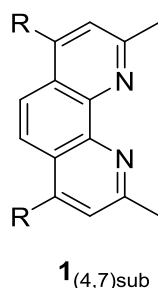


Figure 34. Key phen_{(2,4,7,9)sub} synthons used for the decoration of phen in positions 2, 4, 7 and 9.

4.2.5.1. Decoration of the methyl groups of neocuproine derivatives functionalized in positions 4 and 7 (**1**_{(4,7)sub})

Most of the methods developed to alter the methyl groups of plain neocuproine **1** can be adapted to the parent molecules where additional substituents have been grafted to positions 4 and 7. Since those methods are extensively described in the previous sections, they will be only briefly overviewed here.

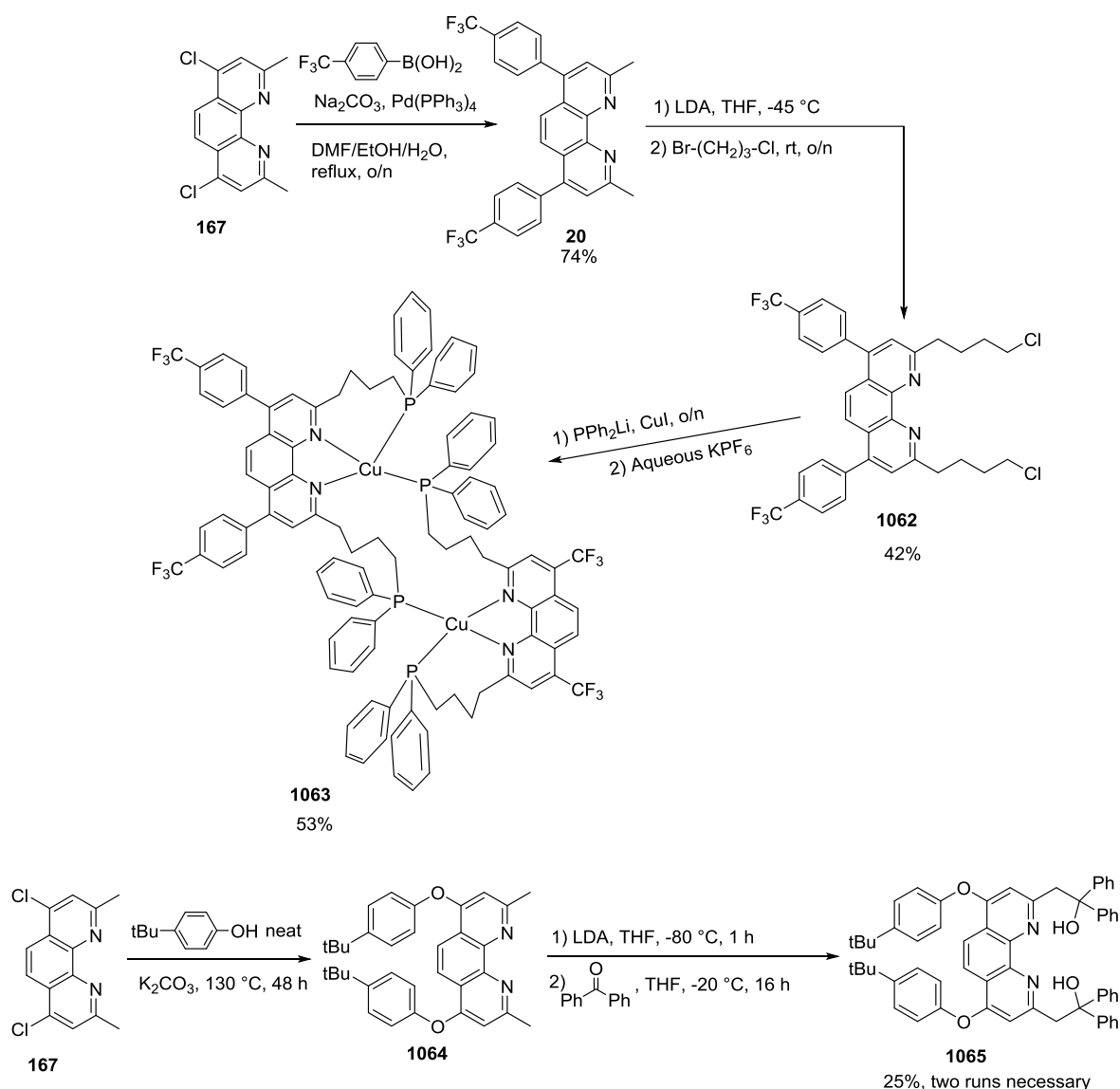
Deprotonation of the methyl groups of **1**_{(4,7)sub}

The methyl groups in positions 2 and 9 of **1**_{(4,7)sub} can be deprotonated by a strong base such as LDA. The resulting di-carbanion is a strong nucleophile whose reactivity can be exploited to design extended coordinating arrays.

For example, Ishitani and co-workers have used this method to prepare **1062** among other similar derivatives from **167** (Scheme 225).¹⁰⁴¹ **167** is first reacted with boronic acid affording **20**. The pendant chlorine atoms in **1062** are next substituted by diphenylphosphine-lithium in presence of CuI, and the product self-assembles to lead to stable and efficient copper(I) dimers photocatalysts **1063**.

The LDA strategy is tolerant to alkoxy groups as demonstrated by Karlov and co-workers¹⁰⁴² who have prepared **1065** by reacting the deprotonated **1064** (obtained from **167** *via* aromatic nucleophilic substitution) with electrophilic benzophenone (the reaction was performed in a stepwise manner, appending one diphenylalcohol fragment at a time). The obtained diol is a tetradentate ligand able to coordinate Ge and Sn for the design of complexes able to catalyse the ring opening polymerization of cyclic esters.

Importantly, the LDA strategy is never performed directly on **167**. The latter is systematically reacted first (aromatic nucleophilic substitutions or metal catalysed cross-couplings), maybe because because the carbanions can react on the chlorinated positions.

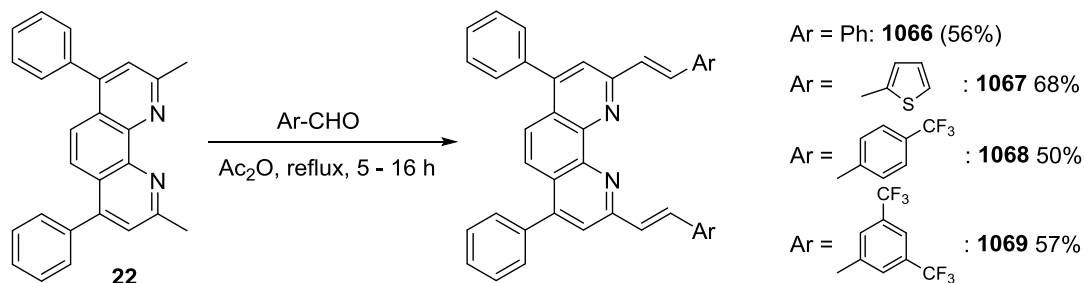


Scheme 225. Exploitation of the reactivity of the methyl groups in α of the chelating nitrogen atoms to decorate phen_{(2,4,7,9)sub}

Action of aldehydes on 1_{(4,7)sub} in presence of acetic anhydride

The reaction of aldehydes with neocuproine in acetic anhydride has already been presented (Scheme 93) and can be transposed to neocuproine derivatives bearing substituents in positions 4 and 7. For example, **22** leads to arylvinyl phen derivatives **1066-1069** in presence of catalytic amounts of acetic anhydride, as reported by Beller and co-workers¹⁰⁴³. The simplicity of the reaction conditions contrasts with the significant complexity of the obtained

molecules. A few examples are given in Scheme 226, those ligands were designed for structure-reactivity relationship studies of the corresponding heteroleptic copper(I) complexes photocatalysts in the frame of H₂ photoproduction.

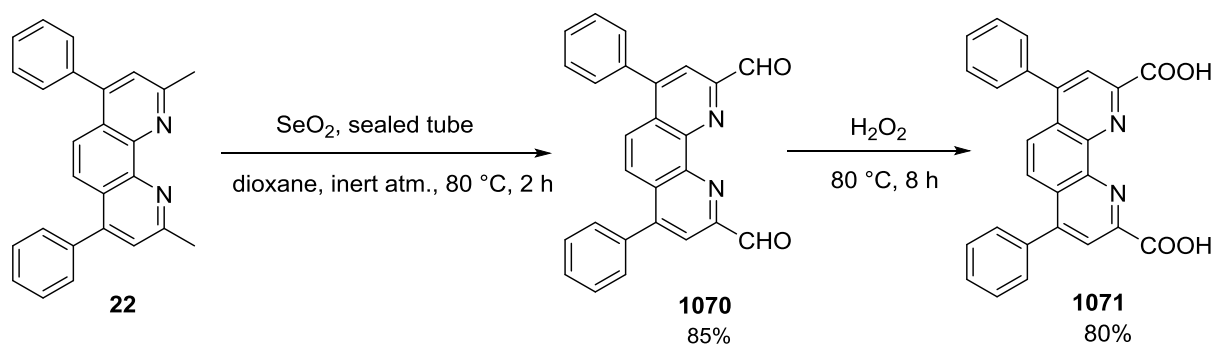


Scheme 226. Example of condensation reaction between **22** and aromatic aldehydes

SeO₂-oxidation of the methyl groups on **1**_{(4,7)sub} into aldehyde functions and reactivity of the obtained synthons

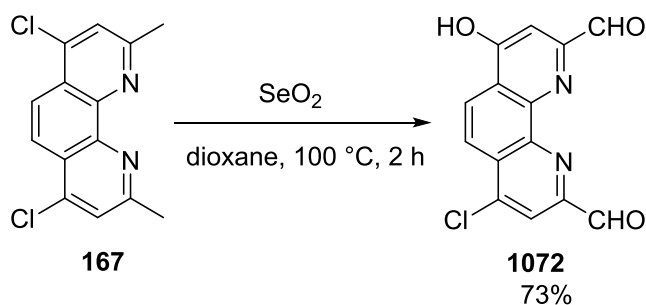
This method has been abundantly used on **1**, and is well adapted to **1**_{(4,7)sub} derivatives, in order to oxidize methyl groups into aldehyde functions. As a matter of fact, the presence of additional substituents in positions 4 and/or 7 improves the solubility of the target compound, which is a salient issue for the synthesis of **565** (Scheme 96). The SeO₂ oxidation of the methyl groups in positions 2 and 9 is tolerant to aromatic groups^{1043,1044} and alkoxy chains^{1044,1045} tethered in positions 4 and 7 on **1**_{(4,7)sub}. Curiously, there is no report in the literature of any SeO₂ oxidation of a **1**_{(4,7)sub} derivative bearing alkyl chains in positions 4 and 7. Accordingly, parasitic oxidation reactions between SeO₂ and those alkyl chains is a potential risk.

For example, **1070** was obtained in 85% yield by Beller and co-workers.¹⁰⁴³ It was further oxidized by H₂O₂ to afford **1071**. Treatment of **1070** by HNO₃ at reflux lead to **1071** too (Scheme 227).¹⁰⁴⁴



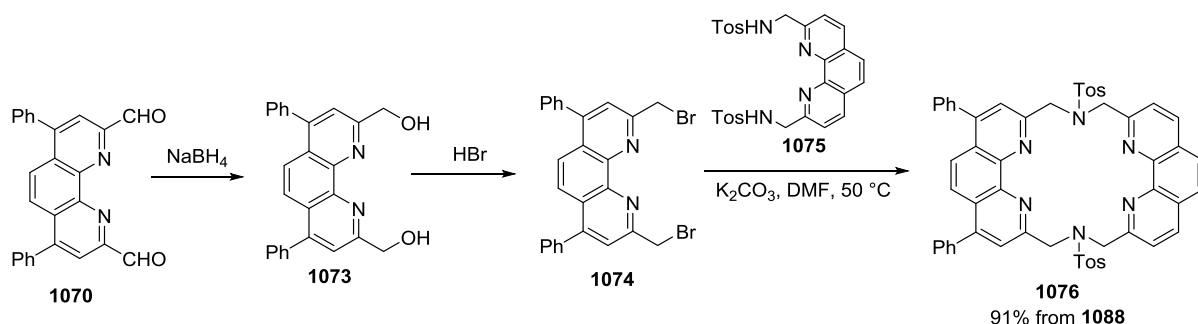
Scheme 227. Oxidation of the methyl groups of **22** by SeO_2 leading to bis-aldehyde and bis-carboxylic acid synthons **1070** and **1071**

However, the SeO_2 oxidation of **167** leads to **1072** as main compound, resulting from the oxygenation of one chloro position (Scheme 228).²⁶⁶



Scheme 228. Special case of the SeO_2 oxidation of **167**

There are surprisingly few reactions involving $\text{phen}_{(2,4,7,9)\text{sub}}$ molecules where positions 2 and 9 are occupied by aldehyde functions.^{1043,1046} For example, Sasamoto and co-workers have adapted the famous strategy developed by Chandler et al.⁵¹⁵ to **1070**, affording bis-brominated derivative **1074** in two steps. This intermediate was reacted with **1075** obtained by tosylation reaction of **565** to generate the non-symmetrical macrocycle **1076** (Scheme 229).

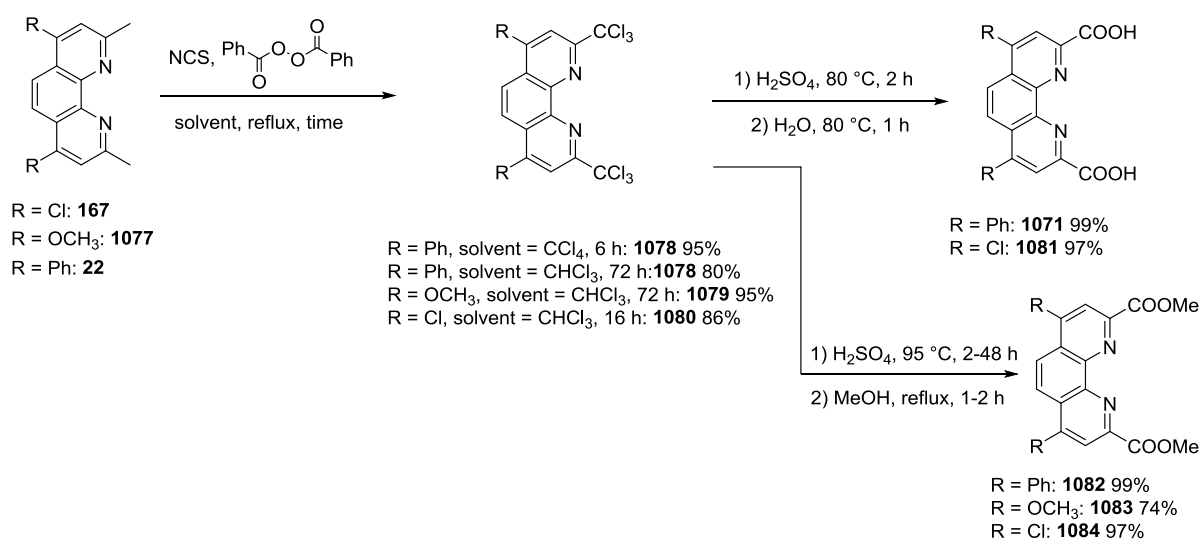


Scheme 229. Formation of macrocycle **1076**. N.B. The conditions and yields for the reactions from **1070** to **1074** are not reported.

Reaction of $1_{(4,7)\text{sub}}$ with NCS and NBS

NBS has been rarely used as reagent with $1_{(4,7)\text{sub}}$ (to the best of our knowledge, there is only one article reporting on the reaction of NBS on 4,7-dimethoxy-neocuproine **1077**, allowing to prepare a brominated compound).¹⁰⁴⁷

On the other hand, the reaction of neocuproine with NCS in presence of benzoyl peroxide leads to 2,9-bis(trichloromethyl)-phen, an emblematic key intermediate in phenanthroline chemistry. This reaction has been adapted to $1_{(4,7)\text{sub}}$ as demonstrated by Diamandis and co-workers. (Scheme 230)¹⁰⁴⁸ In this seminal report, the solvent is CCl_4 . The latter is toxic and environmentally unfriendly, and has been advantageously replaced by CHCl_3 .²⁶⁹



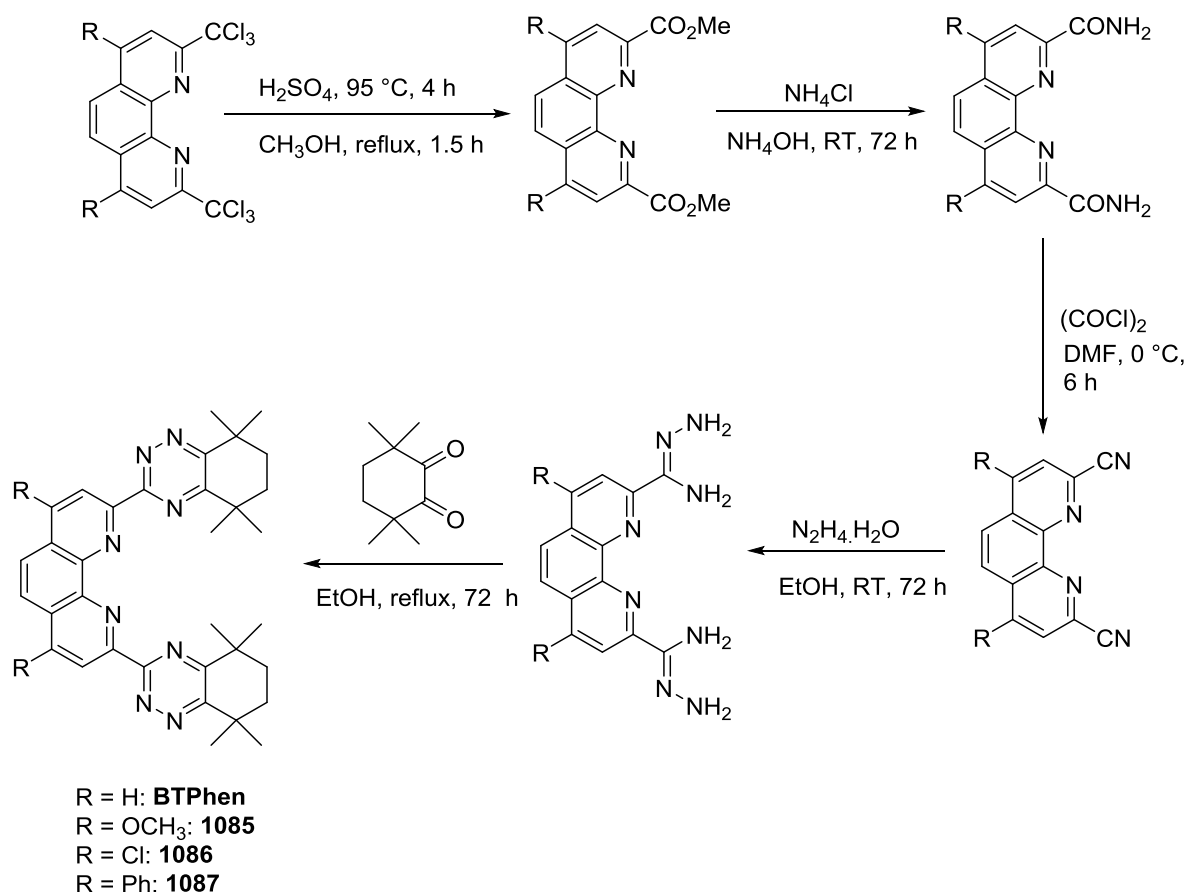
Scheme 230. Formation of phen_{(2,4,7,9)sub} synthons bearing CCl₃ and COOH reactive groups in positions 2 and 9.

This strategy shows tolerance to various functional R groups located in positions 4 and 7, including alkoxy groups (**1079**)²⁶⁹ and even chlorine atoms (**1080**).^{266,269,276,530}

The most relevant use of **1078-1080** is to be converted into COOH-bearing **1071** and **1081** when heated in sulfuric acid and subsequent treatment in hot water (Scheme 230). The resulting diacids are pivotal building blocks for a number of phen-based arrays, a few examples will be given below. The H₂SO₄/H₂O treatment is compatible with aromatic groups¹⁰⁴⁸ and chlorine as R.²⁶⁶ It is reported that the ester **1082-1084** can be obtained if the hot H₂O treatment is replaced by a reflux in alcohol.^{269,1049} This proves important as the diesterd are easier to purify than the dicarboxylic acids for solubility reasons.¹⁰⁴⁸ As can be seen from Schemes 227 and 230, **1071** can be obtained in two different ways, either from **1070** or **1078**.

Overall, there is an obvious parallel between the reactivities of **44** and all phen_{(2,4,7,9)sub} derivatives bearing COOH groups in positions 2 and 9, like **1071** or **1081**. Formations of esters or amides are reported, in conditions which are compatible with R = phenyl,^{269,1048} alkoxy groups^{269,1044,1045} or chlorine (where R refers to the substituents in positions 4 and 7, Scheme 230).^{266,269,276,530}

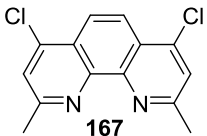
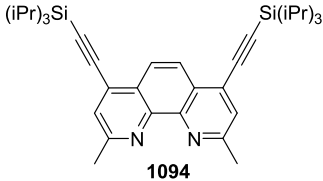
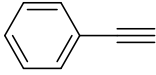
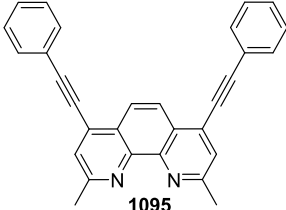
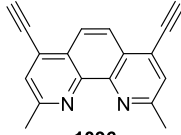
In addition, a comprehensive article has been published by Harwood and co-workers showing too that reactions developed on **567** are effective with phen_{(2,4,7,9)sub} derivatives bearing CN groups in positions 2 and 9 and R groups in positions 4 and 7, regardless the nature of the R groups (**1085** to **1087**, Scheme 231).²⁶⁹ The obtained molecule are used for actinides selective complexation and the study of the influence of groups ni positions 4 and 7 on the efficacy of the complexation.



Scheme 231. Synthesis of phen_{(2,4,7,9)sub} ligands for actinides separation starting from **1078**, **1079** or **1080**

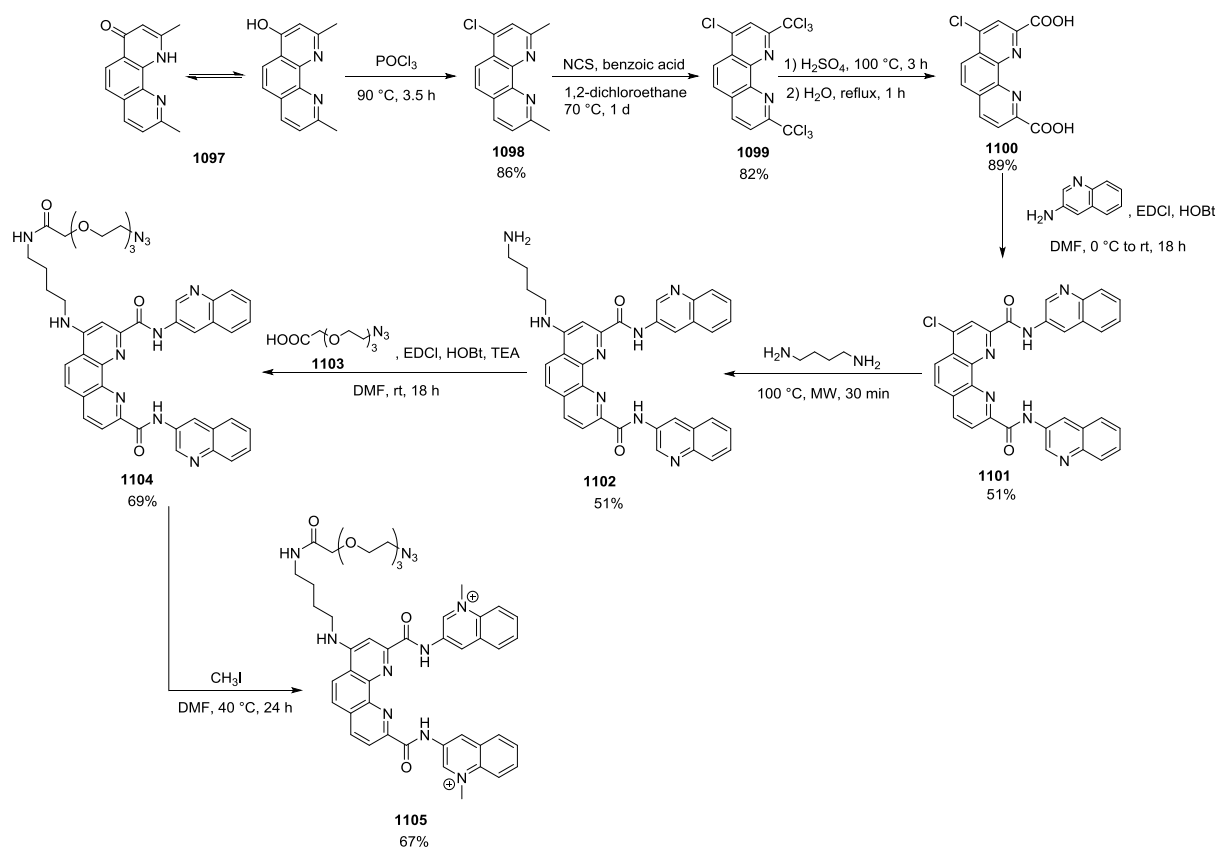
Activation of 1_{(4,7)sub} by formation of N-oxide

Activation of neocuproine by H₂O₂ yields the N-oxide and allows to selectively functionalize only one methyl group by one OH function in mild conditions (Scheme 99). The same protocol has been adapted to 4,7-diphenyl-neocuproine **22** (Scheme 232).⁵⁷ This strategy has allowed to prepare a cyclam-phen adduct. The cyclam moiety coordinates lanthanides ions while the 4,7-diphenyl-phen moiety serves as light collecting antenna, funnelling photonic energy to the lanthanide complex which is a poor light absorber. Here, the presence of the methyl groups in positions 2 and 9 and phenyl groups in positions 4 and 7 allows to red-shift the absorption and emission properties compared to naked phen.

 167	$\equiv\text{Si}(\text{iPr})_3$, Pd(dppf) Cl ₂ , CuI, Et ₃ N, Benzene, 80 °C, 72 h	 1094	30%	735,73 6
	 , Pd(dppf) Cl ₂ , CuI, DIPA, THF, rt, 72 h	 1095	75%	735,73 6
	\equiv , Pd(dppf) Cl ₂ , CuI, Et ₃ N, Benzene, 80 °C, 72 h	 1096	91%	735,73 6

The following example is an interesting summary of the present section in that the reactivities of both the methyl groups in positions 2 and 9 and a halogen atom in positions 4 are exploited. We remind that **34** is a very good DNA and RNA G4 quadruplex ligand as previously described in this review (Figure 8). It has been turned into a strong luminescent probe by clicking a fluorescent dye on its molecular structure.²⁷⁶ In order to do this, an additional function has been appended in position 4 of previously described **34** and this has required to re-think the whole synthesis (Scheme 233). The synthesis starts with **1097** obtained by a convergent method. Chlorination of the latter affords **1098** which is the parent mono-functionalized version of **167**. The methyl groups of **1098** are oxidized in presence of NCS in 1,2-dichloroethane, another interesting alternative to CCl₄. Acidic hydrolysis as previously

described (Scheme 230) affords **1100**. The authors then prepared the bis-amide **1101**, and finally substituted the chlorine atom in position 4 by 1,4-diaminobutane (aromatic nucleophilic substitution). The resulting **1102** species is functionalized by carboxylic acid **1103** through EDCI/HOBT assisted peptide bond coupling, allowing to endow the molecule with a reactive azide function. A final methylation by CH₃I of the quinoline fragments afford the target quadruplex ligand with an azide pendant function, ready for copper-catalysed Huisgen dipolar addition with alkyne-bearing fluorescent cyanine dyes.



Scheme 233. Example of multi-step synthesis of phen_(2,4,9)sub ligand from synthon **1098**

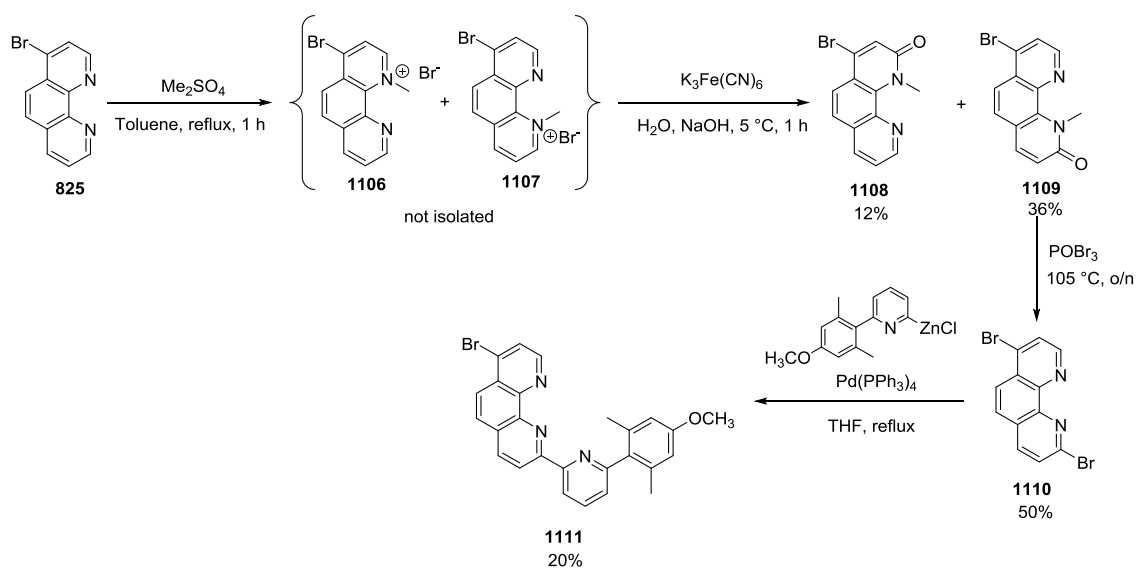
4.2.6. Miscellaneous and concluding remarks

No brand-new method has been exposed in this section because all the synthetic strategies have already been described to prepare phen_(2,9)sub or phen_(4,7)sub. However, a few very

efficient strategies developed in previous sections are curiously not very well represented here, for no specific reason. For example, the halogenation reaction of phen(4,7)sub or phen(4)sub in position 2 or in positions 2 and 9 has been scarcely studied.¹⁰⁵⁴

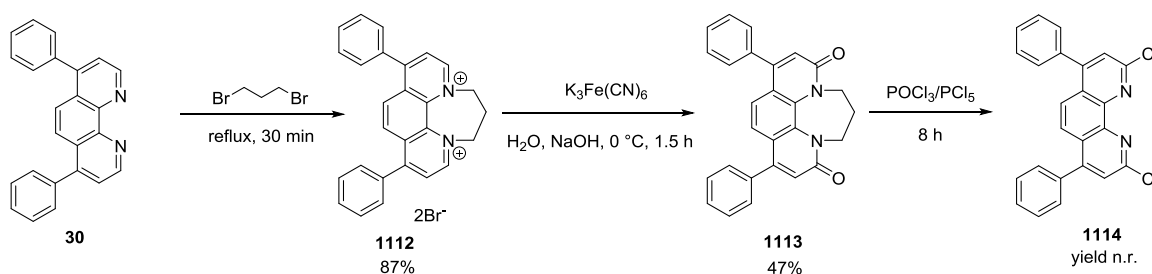
Siegel has reported a very interesting functionalization of **825** by another bromine atom in α of the nitrogen atom, affording the original synthon 2,7-dibromo-phen **1110** (Scheme 234).⁹⁸⁰

The strategy relies on the methylation of one nitrogen atom of **825**, thus activating the position in α towards oxidation in mild usual conditions. The methylation step is not regioselective and both methylated ammoniums **1106** and **1107** have been obtained. This mixture of regioisomers has been treated in alkaline aqueous medium by $K_3Fe(CN)_6$ to yield ketones **1108** and **1109** which were then separated by chromatography. Refluxing pure regioisomer **1109** in $POBr_3$ affords **1110** in 18% yield from **825**. Negishi cross-coupling⁹⁸⁰ on **1120** affords the terpy analogue **1125**. The use of the Negishi conditions here is strategic, because the obtained terpy analogue coordinates the zinc ions and precipitate in the mixture allowing to easily retrieve the pure target compound. This particularly important in this case because both bromine atoms feature similar reactivities, thus leading to mixtures of regioisomers (hence the low yield of 20%).



Scheme 234. Synthesis of original synthon (2,7)-dibromo-1,10-phenanthroline **1110**

The method reported by Yamada to functionalize naked phen in positions 2 and 9 by chlorine atoms (Scheme 70) has been successfully adapted to **30** (Scheme 235).¹⁰⁵⁴ Briefly, the latter is first quaternized by 1,3-dibromopropane and the resulting dication **1112** is oxidized into diketone **1113** by $K_3Fe(CN)_6$ in alkaline medium at low temperature. Finally, refluxing **1113** in $POCl_3$ with PCl_5 leads to **1114**. The brominated parent molecule is known but its synthesis is not documented in literature written in English.



Scheme 235. Synthesis of dihalogenated synthon “batho-(2,9)-dichlorophenanthroline” **1114**

The halogenated (either chlorinated or brominated) compound **1114** can be involved in palladium catalysed Suzuki cross coupling reactions but there are only a limited number of examples.^{1055,1056}

4.3. Synthetic methods for the construction of $phen_{(2,5,6,9)sub}$

$Phen_{(2,5,6,9)sub}$ are molecules which have a finely tuned coordination cavity (by sterically straining the environment around the metal center) and additional tuning can be performed by grafting substituents in positions 5 and 6, which can transmit electronic effects to the $\widehat{N-N}$ cavity.^{81,82,159} In addition, other functional groups can be advantageously grafted in positions 5 and 6 because they are diametrically opposed to the coordinating cavity (e.g. electron

acceptor groups for the design of extended dyads aiming at limiting charge recombination).¹⁰⁵⁷

4.3.1. Considerations about the synthons used to prepare multiply-substituted phen_{(2,5,6,9)sub}

Functionalization of phen in positions 2 and/or 9 on one hand, and positions 5 and/or 6 in the other are among the most documented as can be seen from sections 3.1 and 3.4. Many of the previously exposed strategies can be used. Essentially, methods to prepare phen_{(5,6)sub} from phen will work to prepare phen_{(2,5,6,9)sub} from phen_{(2,9)sub}. Conversely, methods to prepare phen_{(2,9)sub} from phen may be used to prepare phen_{(2,5,6,9)sub} from phen_{(5,6)sub}. However, the incompatibility of certain reagents with given functional groups has to be considered and we will show the strategies developed to circumvent these issues. We will split this chapter into three sections: functionalization of naked phen, functionalization of phen_{(5,6)sub} and finally functionalization of phen_{(2,9)sub} into phen_{(2,5,6,9)sub} (strategies 1-3, Figure 35). All along, we will present synthons obtained by those methods and explore their reactivity (strategy 4, Figure 35).

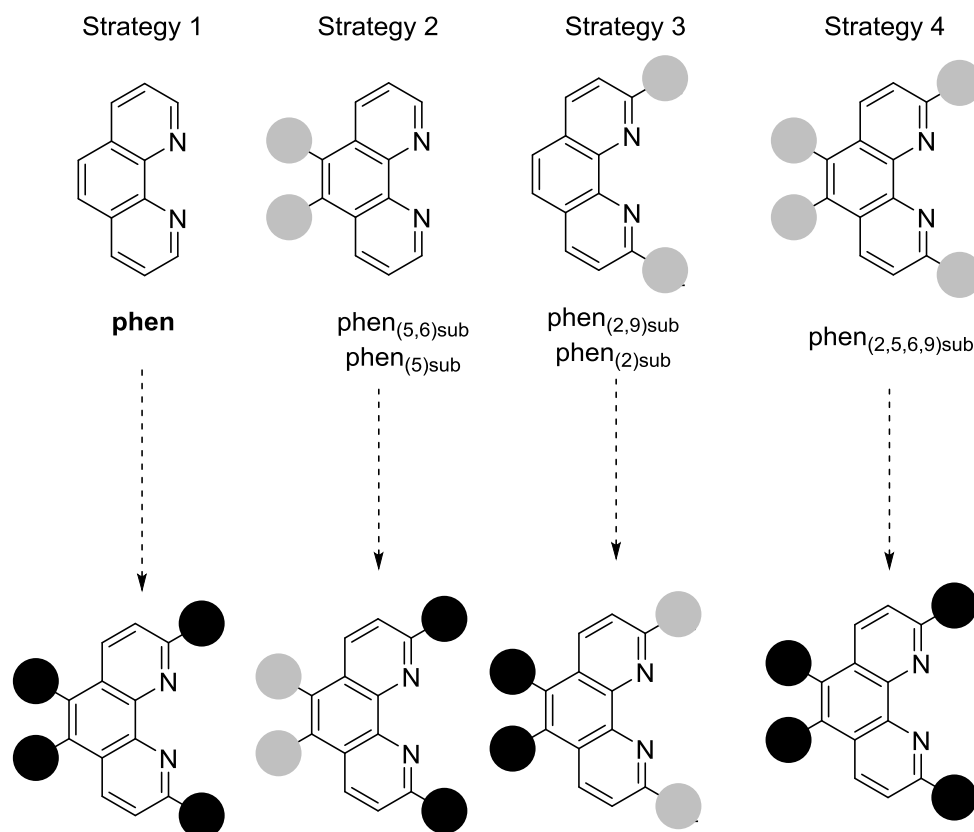


Figure 35. Four different strategies to functionalize phen in positions 2, 5, 6 and 9.

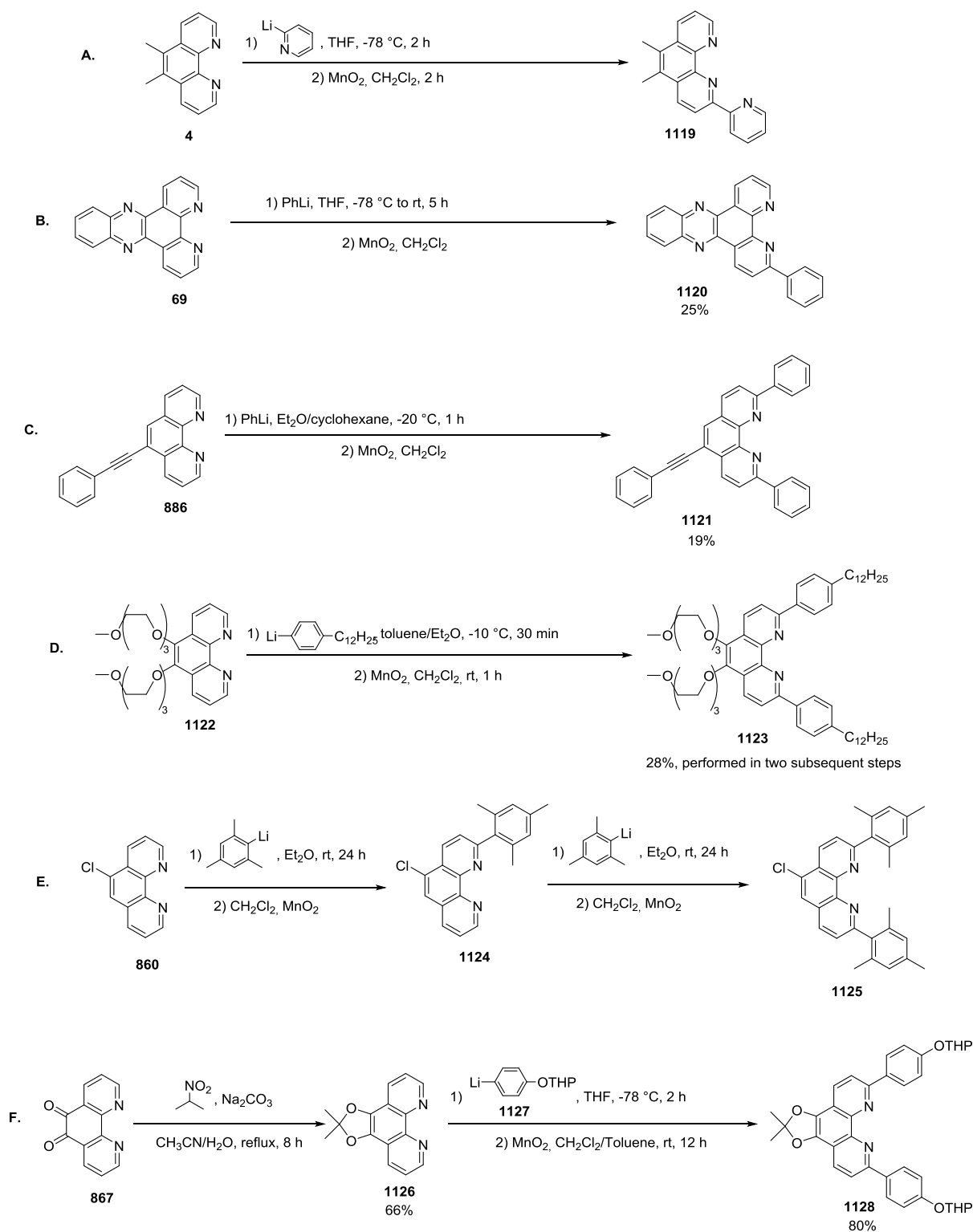
4.3.2. Multiple substitution of phen in positions 2, 5, 6 and/or 9: from naked phen

To the best of our knowledge, there are only two reported cases where naked phen is decorated in positions 2, 5, 6 and 9 in one step. First, reacting phen and CF_3I at high temperature in sealed tubes leads to a mixture of trifluoromethylated phen in different positions in very low yields (section 4.2.2.1), including 2,5,9-trifluoromethyl-1,10-phenanthroline (0.16% yield) which was separated from other regioisomers by chromatography.

The second case is probably a fortuitous discovery. The oxidation of phen in positions 5 and 6 has been extensively studied, leading to pivotal building block phendione **867** or epoxide **865**. Using bleach HClO as oxidant, and varying the pH, Antkowiak and co-workers¹⁰⁵⁸ have found that, at $\text{pH} < 7$, a peculiar intermediate **1115** could be obtained, in addition to **1116** and

readily commercially available RLi (and their price in some cases) and the fact that RLi reagents are dangerous and very reactive nucleophiles which are incompatible with many organic functional groups. This being said, a significant number of phen_{(5,6)sub} (obtained *via* convergent or divergent methods) are fully compatible with RLi and were used to synthesize phen_{(2,5,6,9)sub} (Scheme 237). For example, phen ligands functionalized in positions 5 or 5 and 6 by alkyl groups^{152,1059} or aromatic rings^{108,1003,1060,1061} were successfully functionalized in positions 2 and 9 by RLi reagents. Following this strategy, an additional coordinating pyridine ring was added on **4** (using 2-pyridinelithium) to generate the rigid terpy analogue **1119** (Scheme 237A)¹⁵² and a phenyl group was appended to famous dppz **69** to afford **1120** (Scheme 237B).¹⁰⁶⁰ Both ligands were used to prepare stable luminescent platinum complexes. Importantly, the supplementary methyl groups in positions 5 and 6 in **1119** impact the orbital contributions to the luminescent excited state of the corresponding Pt complex, hereby significantly affecting their photophysical properties. Conversely, Karpishin and Miller have reported that the electronic properties of complex [Cu(**1119**)₂]⁺ were little affected by the presence of the phenylethynyl spacer in position 5 of phen (Scheme 237C).¹⁰⁰³ As noticed in the introduction, it is highly difficult to rationalize in one simple rule how impactful can be the substituents tethered on positions 5 and 6 on the electronic properties of the final ligand and associated complex.

Etheroxides (and thioethers)¹⁰⁶² in positions 5 and 6 are compatible with RLi reagents too,^{921,1063} as exemplified with the functionalization of **1122** by 4'-dodecylphenyl groups (Scheme 237D).⁹²¹ The obtained amphiphilic ligand **1123** has been used to prepare carbo-metallated NNC palladium complexes which self-assembled into vesicles when dissolved in water. These vesicles exhibited interesting catalytic properties in aqueous medium.



Scheme 237. Direct functionalization of phen_{(5,6)sub} by organolithium reagents

It has been recently demonstrated that reacting mesityllithium is compatible with 5-chlorophen, leading to **1124** in one step or **1125** in two (Scheme 237E).¹⁰⁶⁴ The anticipated

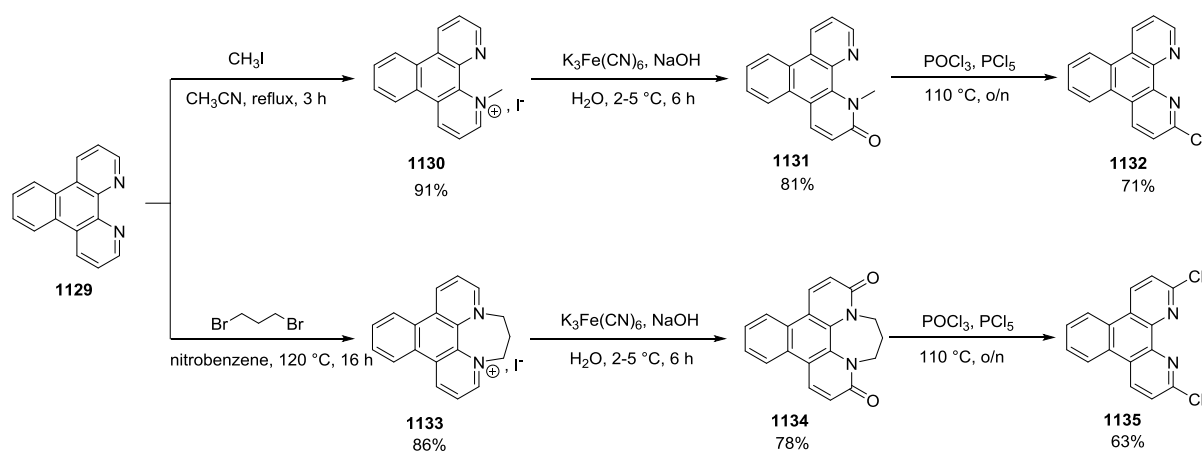
halogen-metal exchange surprisingly does not occur, possibly because of the high stability of the C-Cl bond and/or because mesityllithium is not as reactive (i.e. bulkier) as other organolithium reagents. Incidentally, the authors underline that the preparation of the mesityllithium reagent (mesityl bromide added to butyllithium) must be carefully realized in order to avoid the presence of excess butyllithium which may interfere with the desired synthesis, maybe by reacting on 5-chlorophen. Interestingly, the regio-isomer 2-mesityl-5-chloro-1,10-phenanthroline **1124** is very much dominant over 2-mesityl-6-chloro-1,10-phenanthroline but no information related to this experimental fact is given.

Direct functionalization of phen_{(5,6)sub} by RLi reagents is not systematically feasible. For example, the strongly electrophilic diketone motif of pivotal synthon phendione **867** is not compatible with strong nucleophiles RLi. To address this issue, Sauvage and co-workers have proposed to protect the diketone function of **867** with an acetal group,⁹⁷³ adapting a procedure published by Ohshiro and co-workers.¹⁰⁶⁵ Addition of 2-nitropropane on **867** in basic medium lead to **1126**, and nucleophilic addition of organolithium reagent **1127** afforded **1128** (the reaction was iterated twice to reach a higher yield). The diketone function can be recovered when **1128** is treated in aqueous TFA.

4.3.3.2. Halogenation of phen_{(5,6)sub} in positions 2 and 9

This halogenation of positions 2 and 9 of phen is particularly well documented (section 3.1.4.1) but has been scarcely reported in the case of phen_{(5,6)sub}. For example, Yen and co-workers¹⁰⁶⁶ have reported the mono- and bis-chlorination of benzo[f]-(1,10)-phenanthroline **1129** (Scheme 238) using similar protocols than with naked phen. **1129** is N-methylated using methyl iodide and the resulting ammonium **1130** is selectively oxidized by K₃Fe(CN)₆ in alkaline medium into **1131**. The latter is then chlorinated in POCl₃ in presence of PCl₅ to afford **1132**. Likewise, bis-chlorination (from **1129** to **1135**) proceeds smoothly following

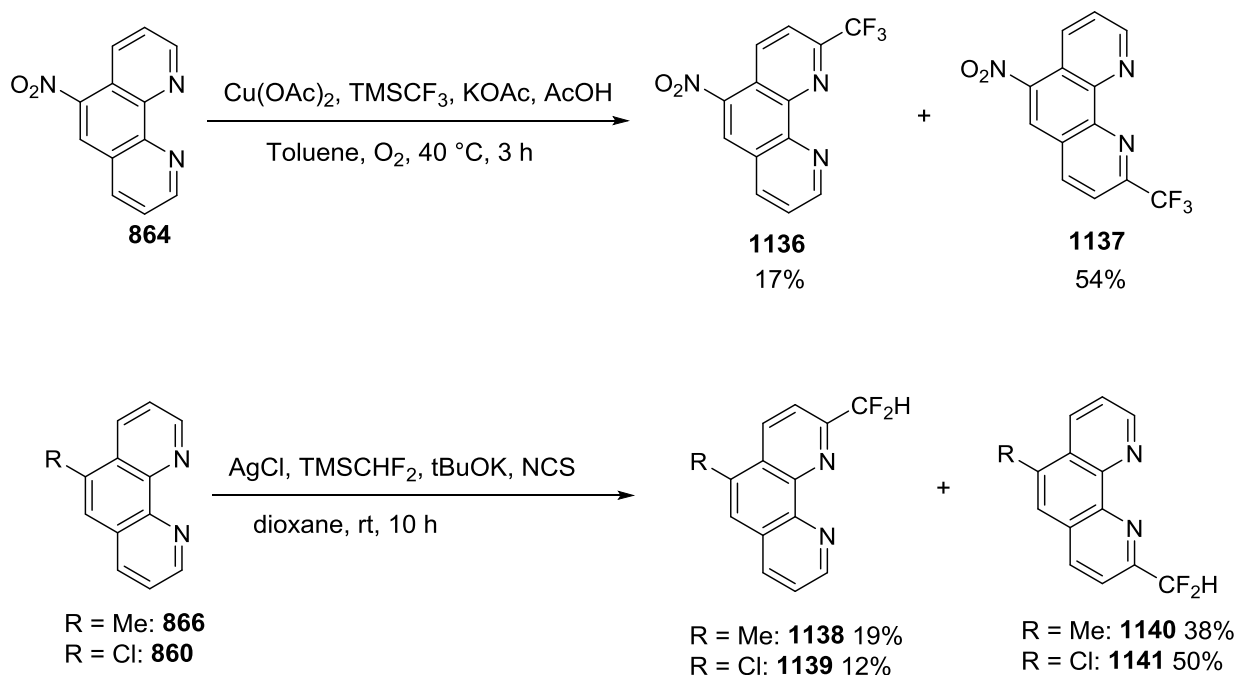
Yamada's protocol (Scheme 238).⁴¹⁵ The overall yields are better than those obtained for naked phen, due to a much more efficient oxidation step (formation of **1131** or **1134**). However, it is noteworthy to mention that **1133-1135** were not characterized. The chlorinated compounds **1132** and **1135** were used as building blocks to design large conjugated arrays (through multiple Suzuki couplings) for OLED applications.



Scheme 238. Synthetic pathways for the chlorination of positions 2 or positions 2 and 9 of $\text{phen}_{(5,6)\text{sub}}$ **1129**.

4.3.3.3. Functionalization of $\text{phen}_{(5,6)\text{sub}}$ in positions 2 and 9 through activation by metal coordination

Positions 2 and 9 of phen can be activated towards nucleophilic additions by metalation of the coordinating cavity, as exposed in Schemes 63-65, in the case of naked phen. The protocols described in scheme 64 can be directly applied to $\text{phen}_{(5)\text{sub}}$ (Scheme 239) using either copper(I) or silver(I) to respectively achieve trifluoromethylation and difluoromethylation of 5-nitro-1,10-phenanthroline **864**, 5-chloro-1,10-phenanthroline **860** and 5-methyl-1,10-phenanthroline **866** in positions 2 or 9. Mixtures of regioisomers were obtained, the $\text{phen}_{(2,6)\text{sub}}$ regioisomers (**1137**, **1140** and **1141**) being always preponderant over the $\text{phen}_{(2,5)\text{sub}}$ regioisomers, maybe for steric reasons.



Scheme 239. Examples of functionalization of phen_{(5,6)sub} in positions 2 and 9 through activation by metal coordination

4.3.4. Multiple substitution of phen in positions 2, 5, 6 and 9: from phen_{(2)sub} and phen_{(2,9)sub} to phen_{(2,5,6,9)sub}

There are three types of pivotal phen_{(2,5,6,9)sub} synthons which can be obtained from different phen_{(2,9)sub}, their generic structures (and nomenclatures) are given in Figure 36, and their synthesis will be presented in what follows.

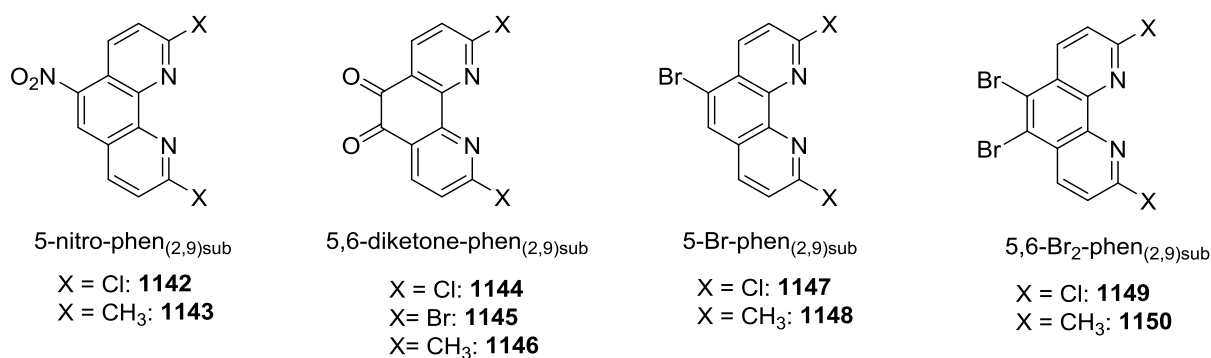


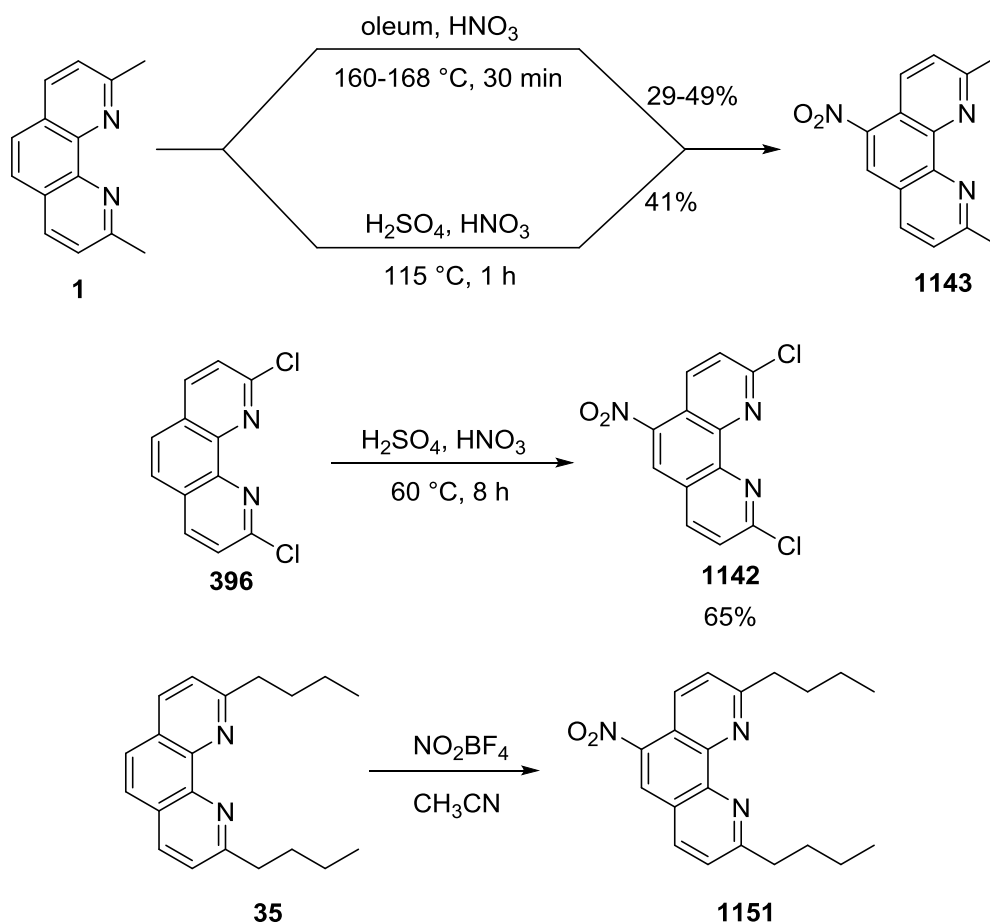
Figure 36. Pivotal synthons substituted in positions 2, 5, 6 and 9

4.3.4.1. Nitration of $phen_{(2,9)sub}$

Protocol and scope

The nitration of $phen_{(2,9)sub}$ in position 5 is usually performed in harsh conditions (oleum and concentrated nitric acid, high temperature) which may be incompatible with a number of functional groups appended in positions 2 and 9.¹⁰⁶⁷ Nevertheless, nitration of neocuproine is performed in those conditions during a limited period of time, affording **1143** in moderate yields.^{1068–1070} During this reaction, numerous side products are formed which complicates the purification step, and no other $phen_{(2,9)sub}$ has ever been nitrated in these conditions.

Slightly less aggressive methods have thus been published. For example, replacing oleum by 98% H_2SO_4 and decreasing the temperature has allowed to perform nitration in position 5 of neocuproine¹⁰⁷¹ and 2,9-dichlorophen **396** (leading to **1142**)¹⁰⁷² in respectable yields. Let us highlight that the use of fuming nitric acid has been reported in one case.¹⁰⁷³ There is one additional (unfortunately little detailed) report concerning the nitration of 2,9-di-*n*-butyl-1,10-phenanthroline **35** into **1151** with nitronium tetrafluoroborate NO_2BF_4 (Scheme 240).¹⁰⁶⁷



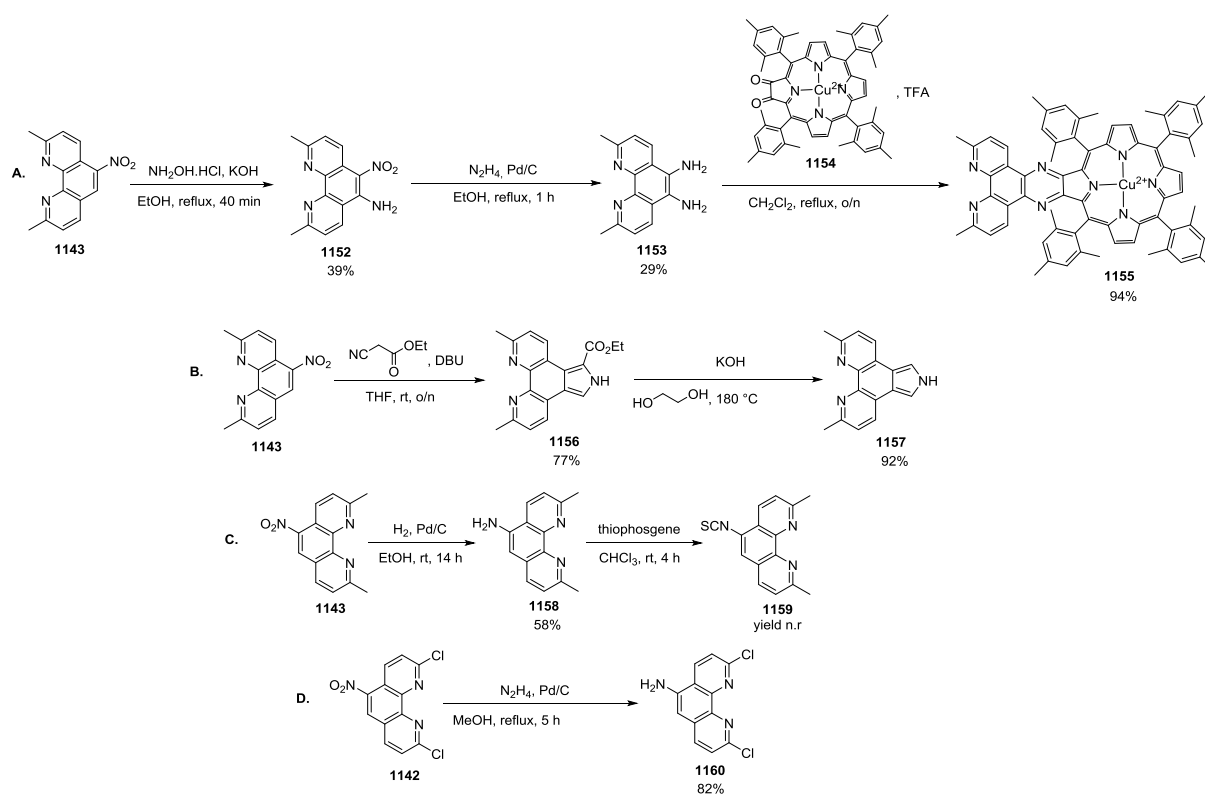
Scheme 240. Examples of nitration of different phen_{(2,9)sub} in position 5

Exploiting the reactivity of the nitro groups in 1142 and 1143

Karpishin and co-workers have shown that refluxing **1143** with hydroxylamine hydrochloride in ethanol allows to functionalize the latter in position 6 with an amino group (**1152**, Scheme 241A).¹⁰⁶⁸ The symmetric diamine **1153** is obtained by reduction in presence of hydrazine and palladium on carbon. Another protocol to obtain the same molecule will be presented later in this section. The condensation of **1153** on copper-porphyrin diketone **1154** yielded **1155** in very good yields.

Otherwise, a pyrrole cycle can be fused to **1143** in only one step, using a method developed by Barton and Zard.^{1074,1075} It is interesting to notice that this method was initially demonstrated on nitroalkenes, showing that the C₅=C₆ double bond of phen exhibits indeed a strong olefin character. Applied to **1143**, the fused pyrrol-phen adduct **1157** is obtained in two

steps and further engaged as building block in the synthesis of phen-porphyrin precursor (Scheme 241B).²⁰⁵



Scheme 241. Reactivity of the nitro group of synthons **1142** and **1143**

The nitrated phen_(2,9)sub can naturally be reduced in amines such as **1158** or **1160**, proving in the latter case that the reduction conditions are compatible with the presence of chlorine in positions 2 and 9 (Scheme 241C). Those amino-phen synthons can be used as such, e.g. for ion sensing.¹⁰⁶⁷ Otherwise, the amino group features the same reactivity than 5-aminophen **888** as previously described. For example, **1158** has been used as nucleophile to generate extended functional coordinating arrays.¹⁰⁵⁷ Interestingly, **1158** is efficiently converted into thiocyanate derivatives **1159** by thiophosgene; the resulting compound reacts efficiently with amino groups pending from biomaterials,¹⁰⁷³ allowing to conjugate the phenanthroline coordinating cavity to oligonucleotides,¹⁰⁶⁹ antibodies¹⁰⁷¹ etc.

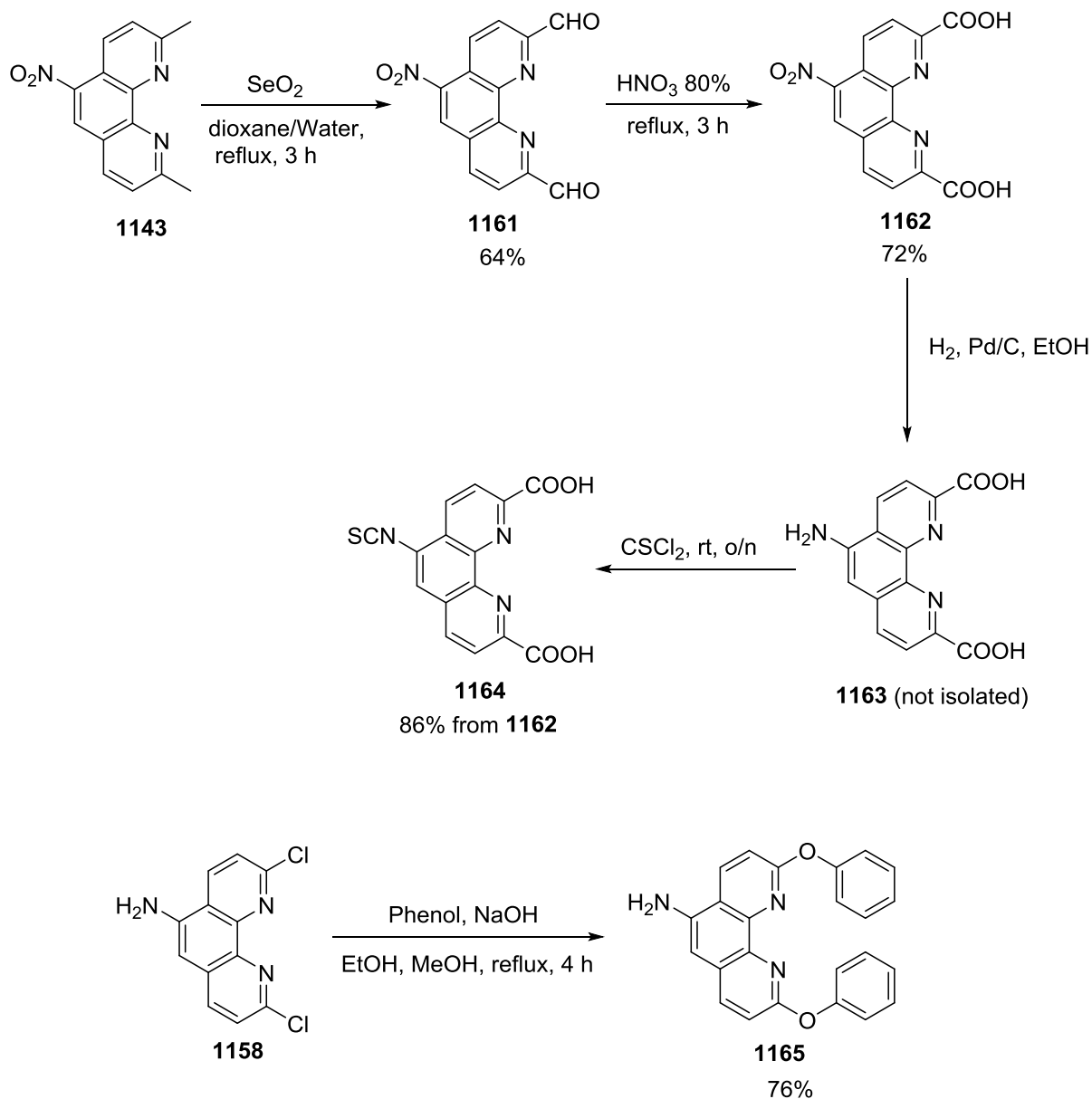
Finally, reduction of the nitro group of **1142** into **1160** in presence of hydrazine and Pd/C is feasible (Scheme 241D). It is interesting to notice that hydrazine does not interfere at the level of the halogen atoms, despite the known possible nucleophilic substitution.

Other reactivity of **1142**, **1143** and **1158** involving substituents in positions 2 and 9

1142 and **1143** are very robust molecules and the nitro group does not interfere with the reactivity of CH₃ or halogens in positions 2 and 9. For example, **1143** can be oxidized in classical conditions by SeO₂ into bis-aldehyde **1161** (Scheme 242).¹⁰⁷¹ Further oxidation in boiling HNO₃ leads to **1162** and the nitro group in position 5 can then be reduced in the corresponding amine **1163**. This compound is however unstable and has to be engaged immediately in the last functionalization step by thiophosgene, leading to stable compound **1164**. The latter can efficiently react with amines pendant groups via the NCS function.

1158 exhibits the usual reactivity of **396** as demonstrated in Scheme 231. where the chlorine atoms in positions 2 and 9 are efficiently substituted by phenolates to form **1165**.¹⁰⁷² The added phenoxy groups are known to improve the affinity of phen for Bi(III) ions. **1165** is easily grafted on porous silica, preparatorily treated with (γ -chloropropyl)triethoxysilane thus affording a solid state “Bi(III) ions sponge” for decontamination of copper(II) crude extraction solutions.

Curiously, no functionalization of **1142** or **1158** through metal catalysed cross-coupling reactions has ever been published so far, apart from one patent¹⁰⁷⁶ claiming the feasibility of a Sonogashira coupling on the BOC protected 5-amino-2-chloro-1,10-phenanthroline (the latter being obtained from **397** in similar conditions to **1142**).



Scheme 242. Reactivity of synthons **1143** and **1158** in positions 2 and 9

4.3.4.2. Oxidation of $\text{phen}_{(2,9)\text{sub}}$ into 5,6-diketone- $\text{phen}_{(2,9)\text{sub}}$

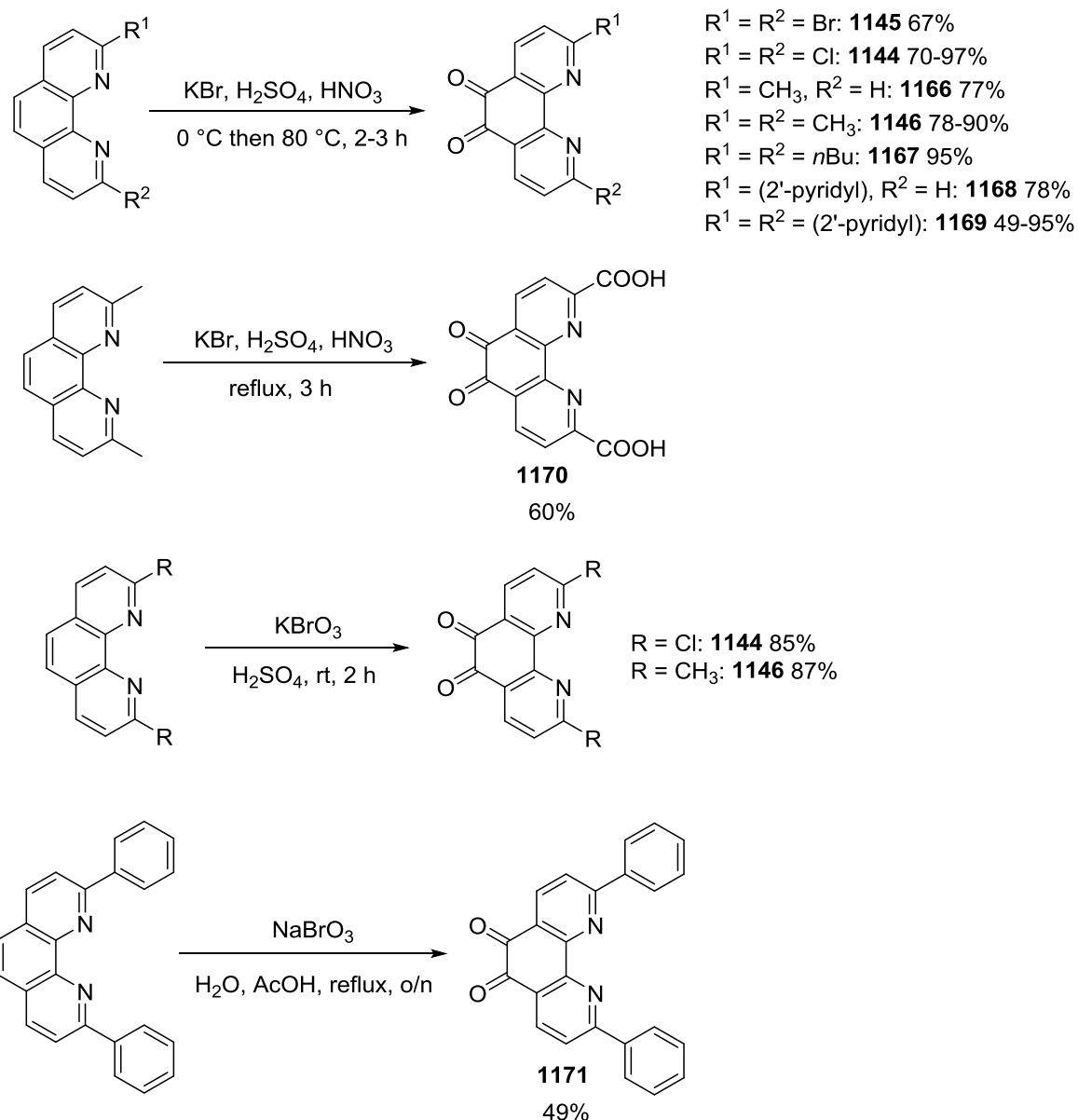
Protocol and scope

Phenanthroline-5,6-dione derivatives are among the most versatile and easy-to-use building blocks in phenanthroline chemistry. Their syntheses, like the above described nitration, usually require harsh conditions, which however seem to be compatible with the usual substituents tethered to positions 2 and 9 of phen. Indeed, **1**, **35**, **39**, **43**, **108**, **396**, **405** can all

be oxidized into the corresponding diketone in very similar conditions (Scheme 243). Briefly, the phen_{(2)sub} or phen_{(2,9)sub} are mixed with KBr and heated in strongly acidic medium (concentrated H₂SO₄ and HNO₃) for a few hours. In many instances, the authors point out the importance of the sequential, careful addition of sulfuric acid first, followed by nitric acid, at low temperature in order to ensure a reasonable yield for the reaction. Interestingly, Sigurdsson et al. have reported that neocuproine could be oxidized directly into **1170** with an acceptable yield,¹⁰⁷⁷ in presence of KBr in a refluxing mixture of sulfuric and nitric acids. **1170** is a probable impurity accumulating in the refluxing mixture.

Importantly, those conditions proved incompatible with phenyl groups attached in positions 2 and 9 of phen.^{88,1078} Indeed, undesired oxidation of the latter aromatic rings have been monitored. Interestingly, milder conditions have been developed to synthesize **1144** and **1146** in good yields (Scheme 232)⁸⁶² using potassium bromate in 60% sulfuric acid. This protocol was further softened, replacing H₂SO₄ by acetic acid, and allowed the formation of **1171** from **38** with a reasonable yield of 49%.¹⁰⁷⁸

It is very interesting to remark that when a pyridyl substituent is linked to position 2 or to positions 2 and 9 of phen, the traditional protocol (refluxing mixture of concentrated H₂SO₄ and HNO₃) is still valid to obtain diketones **1168** and **1169** (albeit with little reproducibility, yields varying between 49% and 95%).

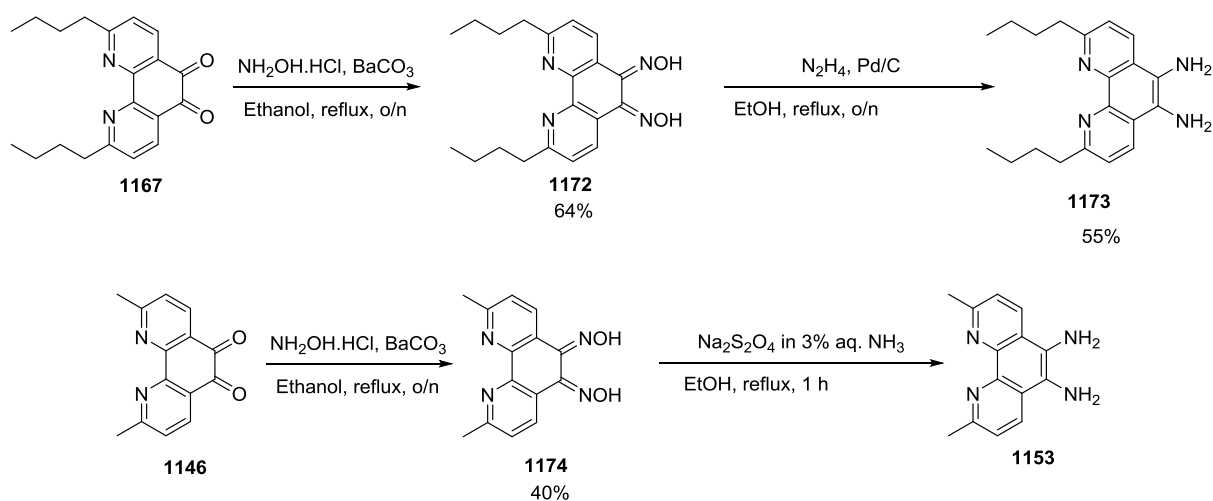


Scheme 243. Synthesis of 5,6-diketones-phen_{(2,9)sub} from phen_{(2,9)sub}

Further reactivity of the synthons 5,6-diketone-phen_{(2,9)sub} in positions 5 and 6

Unsurprisingly 5,6-diketone-phen_{(2,9)sub} can be converted into imines when put in presence of aliphatic or aromatic amines. Among the numerous possibilities, the condensation of **1146** or **1167** with hydroxylamine hydrochloride yields dioximes **1174** and **1172** respectively. Incidentally, proton NMR spectra of such molecules can be difficult to read because of the existence of several isomers involving cis or trans configurations of the imine bonds. The main interest of **1172** and **1174** is that their reduction yields the corresponding precious

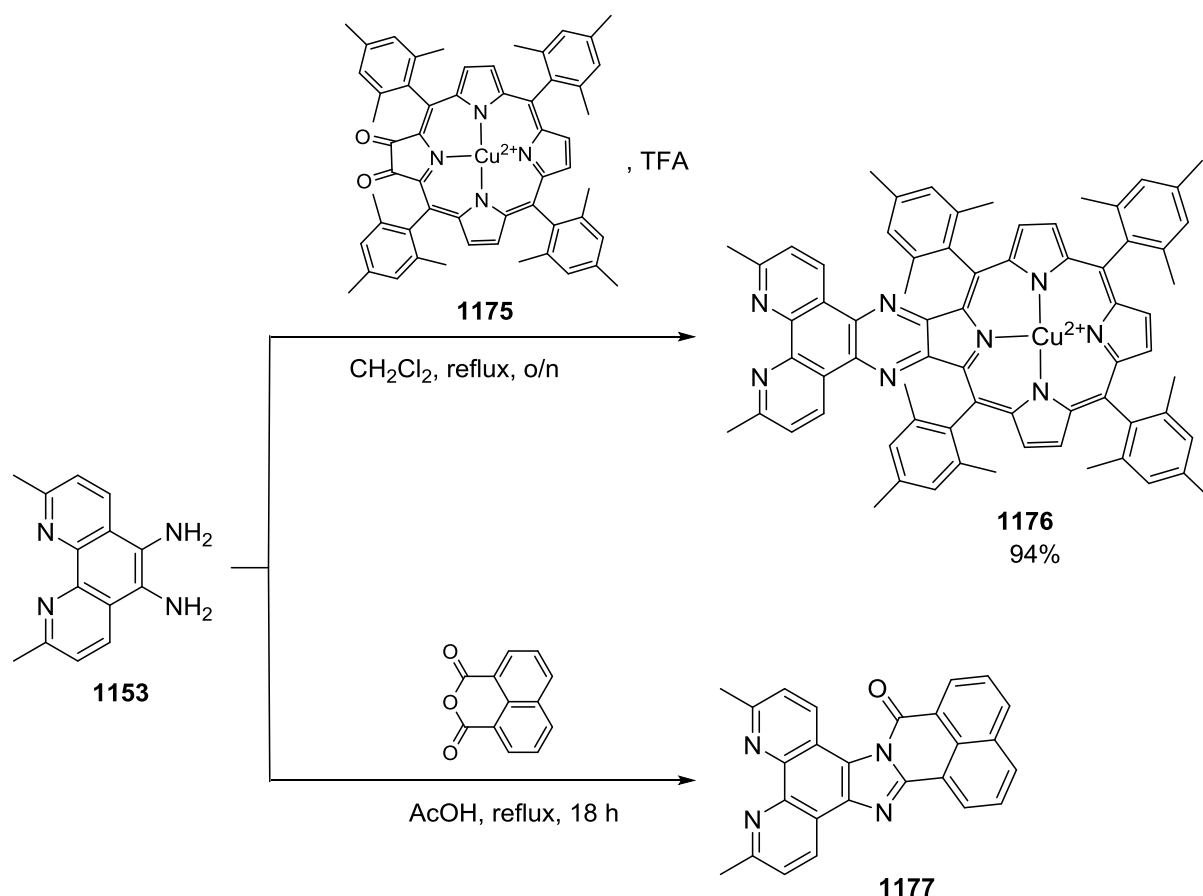
building blocks **1173** and **1153** respectively. Either hydrazine⁸⁸ or dithionite¹⁰⁷⁹ can be used as reductants (Scheme 244).



Scheme 244. Synthesis of pivotal building blocks **1173** and **1153**

Those building blocks feature improved solubility in organic media thanks to the presence of solubilizing substituents in positions 2 and 9, which improved the work-up procedures.

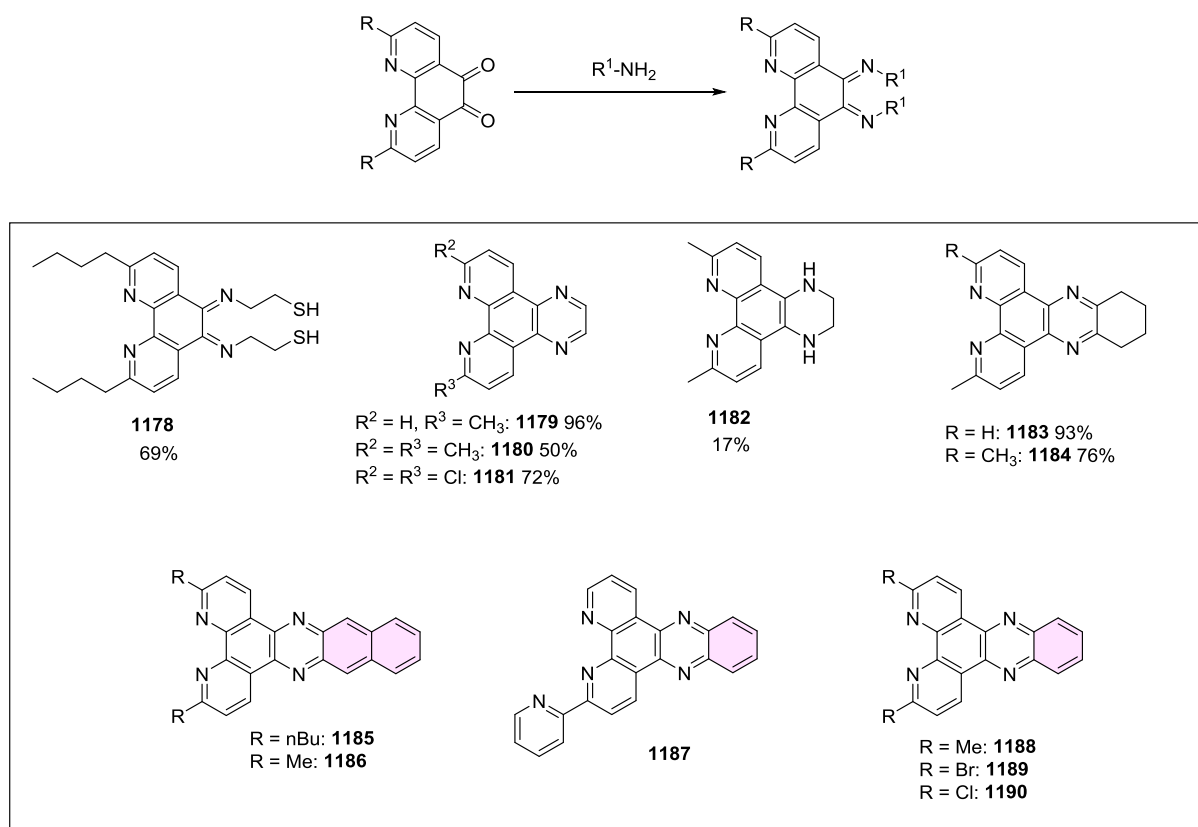
The reactivity of **1173** and **1153** is similar to the one of **914** as briefly exemplified in Schemes 241 and 245. For example, **1173** has been reacted with diketones to prepare conjugated phen adducts with much improved solubility in organic medium.⁸⁸ Similar conditions have been applied by Karpishin and co-workers to **1153** to prepare a phen-porphyrin hybrid system **1176** (Scheme 245). As a last example, **1153** can be condensed with naphthalic anhydride in refluxing acetic acid and lead to a peculiar conjugated ligand **1177** (Scheme 245) which allowed to design copper(I) complexes with improved excited state lifetimes.¹⁰⁷⁹



Scheme 245. Examples of reactions involving building block **1153**.

The condensation of other aliphatic amines and diamines on (5,6)-diketone-phen_(2,9)sub proceeds smoothly in refluxing ethanol or THF, affording imines with various structures (Scheme 246).^{1080–1082} For example, **1178** has been designed in order to self-assemble at the surface of gold nanoparticles through formation of the favourable S-Au bond.¹⁰⁸³ The obtained nanomaterial has been studied as a lithium ion sensor.

One notices that when 1,2-diaminoethane is reacted with diketones **1141**, **1146** or **1166**, the oxidized compounds **1179**, **1180** and **1181** are obtained, probably because re-aromatization occurs spontaneously in presence of O₂ at refluxing temperature. Nevertheless, Vagg and co-workers have reported that, when the reaction is performed in milder conditions (50 °C in ethanol for 16 h), a substantial quantity of the reduced compound **1182** could be isolated.¹⁰⁸²

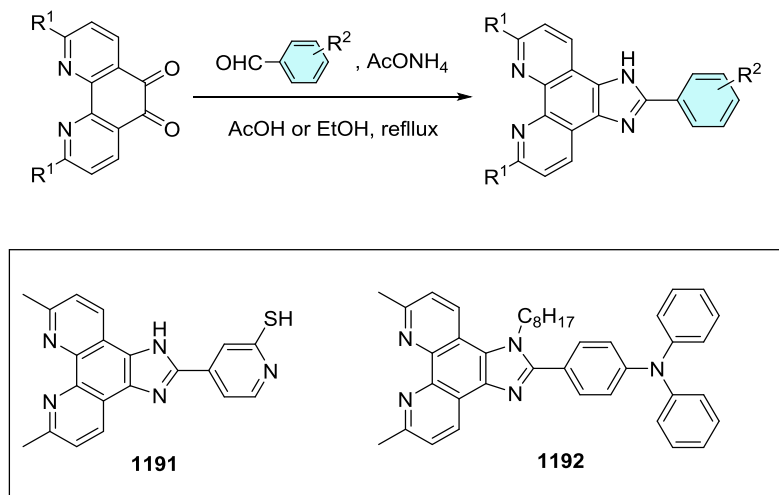


Scheme 246. Synthesis of imine-functionalized phen from (5,6)-diketone-(2,9)-phen and aliphatic or aromatic amines.

In the case of aromatic (α,β)-diamines, the condensation leads to dppz derivatives^{904,915,1082–1086} functionalized in α of the chelating nitrogen atoms. **1186** for example has been used as organophosphorus pesticides luminescent sensor; importantly, the presence of the methyl groups in α of the nitrogen atoms was shown to significantly modify the interactions between three different pesticides and **1186** compared to plain dppz, resulting in a much-improved selectivity of **1186** as sensor.⁹⁰⁴ In another example, the methyl groups in the case of **1188** fragilize the coordination sphere of the corresponding ruthenium complex because of the steric strain. This promoted the photo-induced (UV light) decoordination of ligand **1188**.^{1084,1085}

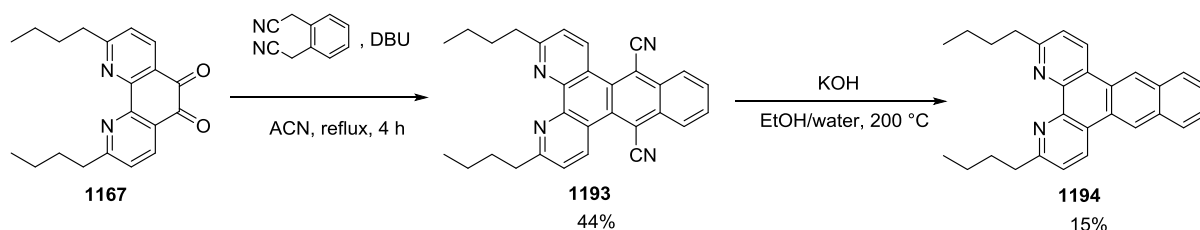
Another convenient way to decorate 5,6-diketone-phen_{(2,9)sub} in positions 5 and 6 relies on the condensation of aldehydes Ar-CHO in presence of ammonium acetate, usually in refluxing

acetic acid^{1057,1087-1089} or ethanol and leading to the concatenation of Ar to phen through a fused imidazole ring (Scheme 247). The mechanism and conditions are identical to those described before from phendione and will therefore not be further described here.



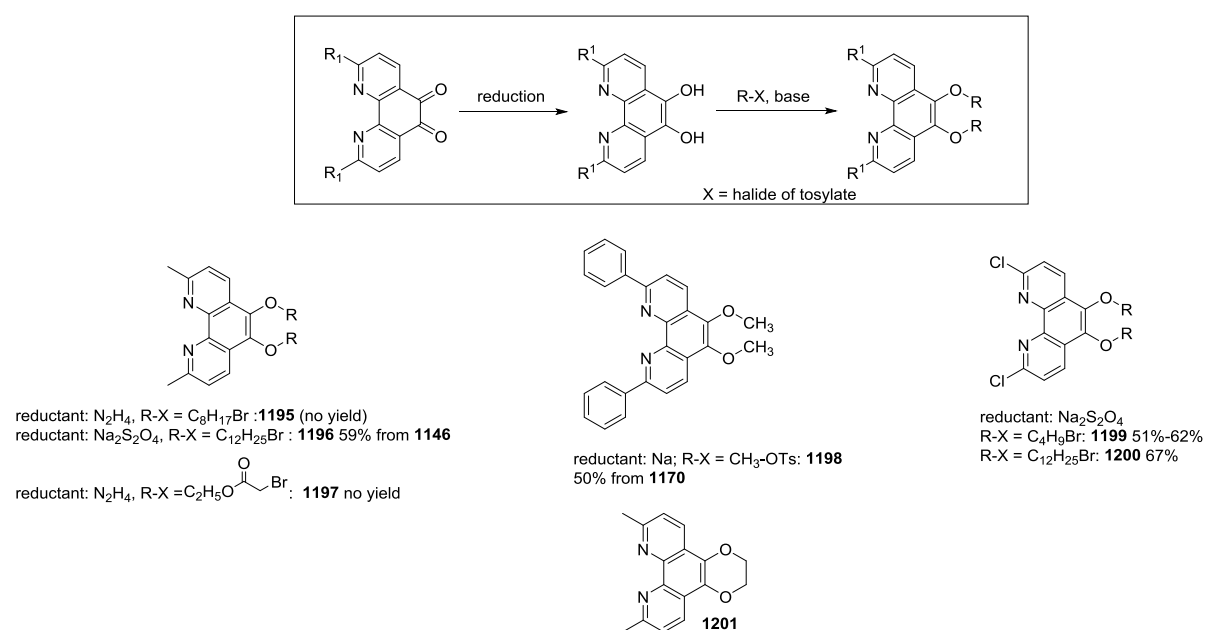
Scheme 247. General synthetic pathway to synthesize phenimidazole phen_(2,5,6,9)sub derivatives

The condensation of carbanions on the diketone function of 5,6-diketone-phen_(2,9)sub has been reported only once, adapting a procedure known on phendione.^{974,975,1090} The protons on the methylene groups of 1,2-diacetonitile benzene can be deprotonated by DBU, forming the corresponding carbanion which attacks the strongly electrophilic positions on **1167** leading to **1193** (Scheme 248). The latter can be de-cyanated following the previously described method (Scheme 201) leading to polyaromatic phen derivative **1194**, albeit with a very poor yield as previously observed for similar reactions.^{974,975} This ligand has been used to prepare copper(I) complexes with improved absorption properties.¹⁰⁹⁰



Scheme 248. Example of condensation of carbanions on **1167**.

The reductive di-alkylations of the diketone functions of 5,6-diketone-phen_(2,9)sub or phendione **897** are comparable. First, the reduction of the diketone in the corresponding diol is performed. Several reductants have been used to achieve this reaction (dithionite in THF/Water mixture,^{1091–1095} sodium in DMF¹⁰⁹⁶ or hydrazine sulfate in water¹⁰⁹⁷). Save the latter case, the diol is usually not isolated and reacted directly as nucleophile with alkyl halides or tosylates in presence of a base (Cs₂CO₃ or KOH) to yield the target O-alkylated compound (Scheme 249). This method is compatible with **1144**, **1166** and **1171** too, the presence of the electrophilic sites in positions 2 and 9 not being an issue.



Scheme 249. Synthetic strategy for the O-alkylation of 5,6-diketone-phen_(2,9)sub.

1197, once hydrolysed, has been used as anchoring ligand in the design of copper(I) complexes able to graft onto TiO₂ and act as photosensitizers for dye sensitized solar cells.¹⁰⁹⁷ Ru complexes have been prepared with ligand **1201**, and featured a high cytotoxicity in the dark and under light irradiation for human cancer cells.¹⁰⁹⁵ Moreover, [Ru(bpy)₂(**1196**)]²⁺ has

been used as photoluminescent dopant in a lipid layer surrounding rare-Earth based upconverting nanoparticles for $^1\text{O}_2$ photogeneration.¹⁰⁹⁴

Further reactivity of the synthons 5,6-diketone-phen_{(2,9)sub} in positions 2, 5, 6 and 9

Synthons bearing the diketone function in positions 5 and 6 and methyl groups or halogen atoms in positions 2 and 9 (Figure 37) potentially feature the reactivity of **1** and **396**. However, the diketone is often more reactive than substituents in positions 2 and 9. Thus, strategies to decorate phen in positions 2, 5, 6 and 9 from the diketone synthons usually start with the functionalization of diketone, but not systematically as will be seen below.

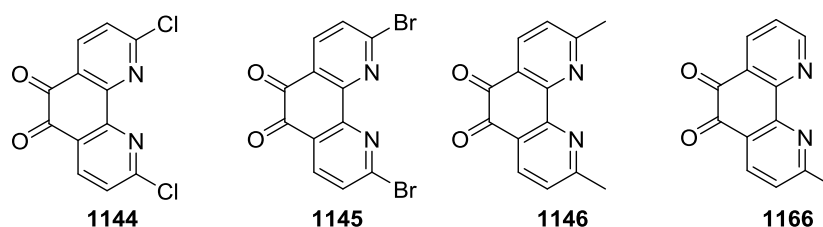
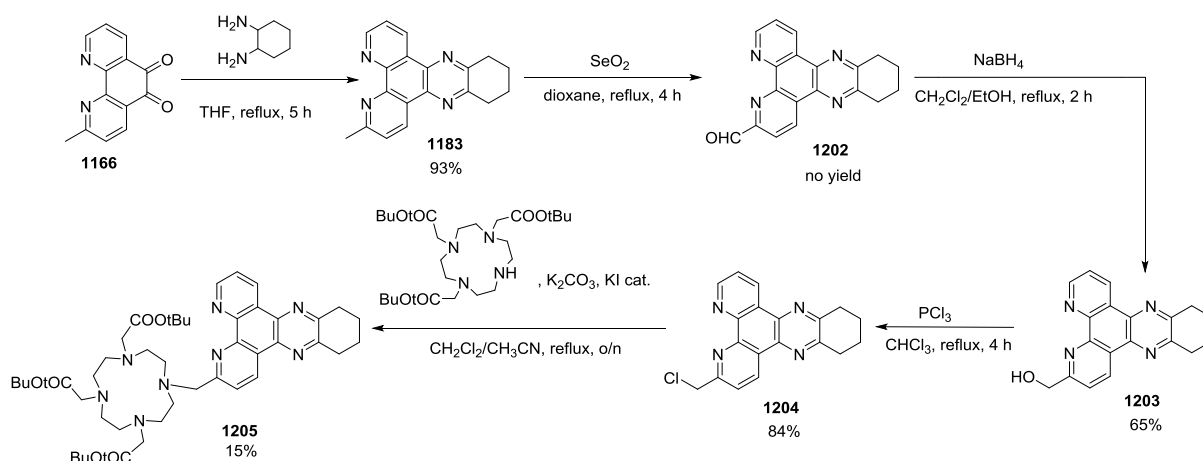


Figure 37. 5,6-diketone-phen_{(2,9)sub} synthons bearing ubiquitous reactivity

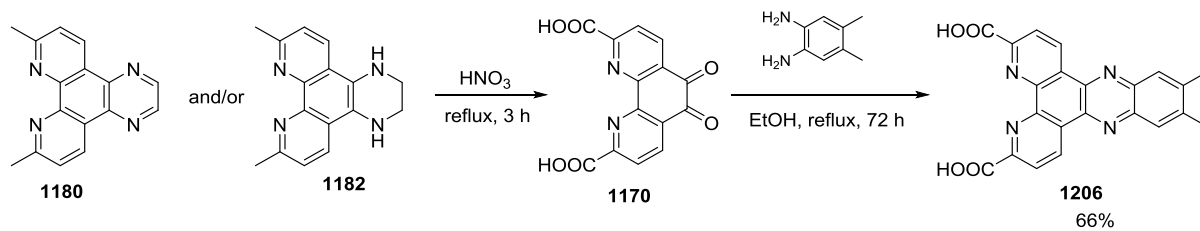
Reactivity of the methyl groups: to the best of our knowledge, there is no reaction in the literature involving the methyl groups in α of the nitrogen atoms of diketones **1146** or **1166**. This is not surprising given that the reactivity of the methyl groups in positions 2 and 9 very often requires nucleophiles or strong bases which are likely to interfere with the diketone function. Thus, in all the cases reported in the literature,^{1080,1082,1098} **1146** is always first condensed on diamines, affording stable compounds where the methyl groups are next functionalized. For example, the methyl group of **1183** can be oxidized by SeO_2 into the corresponding aldehyde **1202**.^{1080,1082} The following steps are very classical in phen chemistry: the aldehyde function in **1202** is reduced in the alcohol **1203**. Then the OH group is substituted by a chlorine atom with PCl_3 . Finally, the leaving group property of the latter allows to tether a cyclam derivative in α of the chelating nitrogen atoms. The resulting

molecule **1205** allows to coordinate efficiently lanthanide ions and the polyaromatic structure acts as light collecting antenna funnelling the photonic energy towards the lanthanide complex and thus increasing significantly the light collecting ability of the latter (Scheme 250).¹⁰⁸⁰



Scheme 250. Synthesis of **1205**

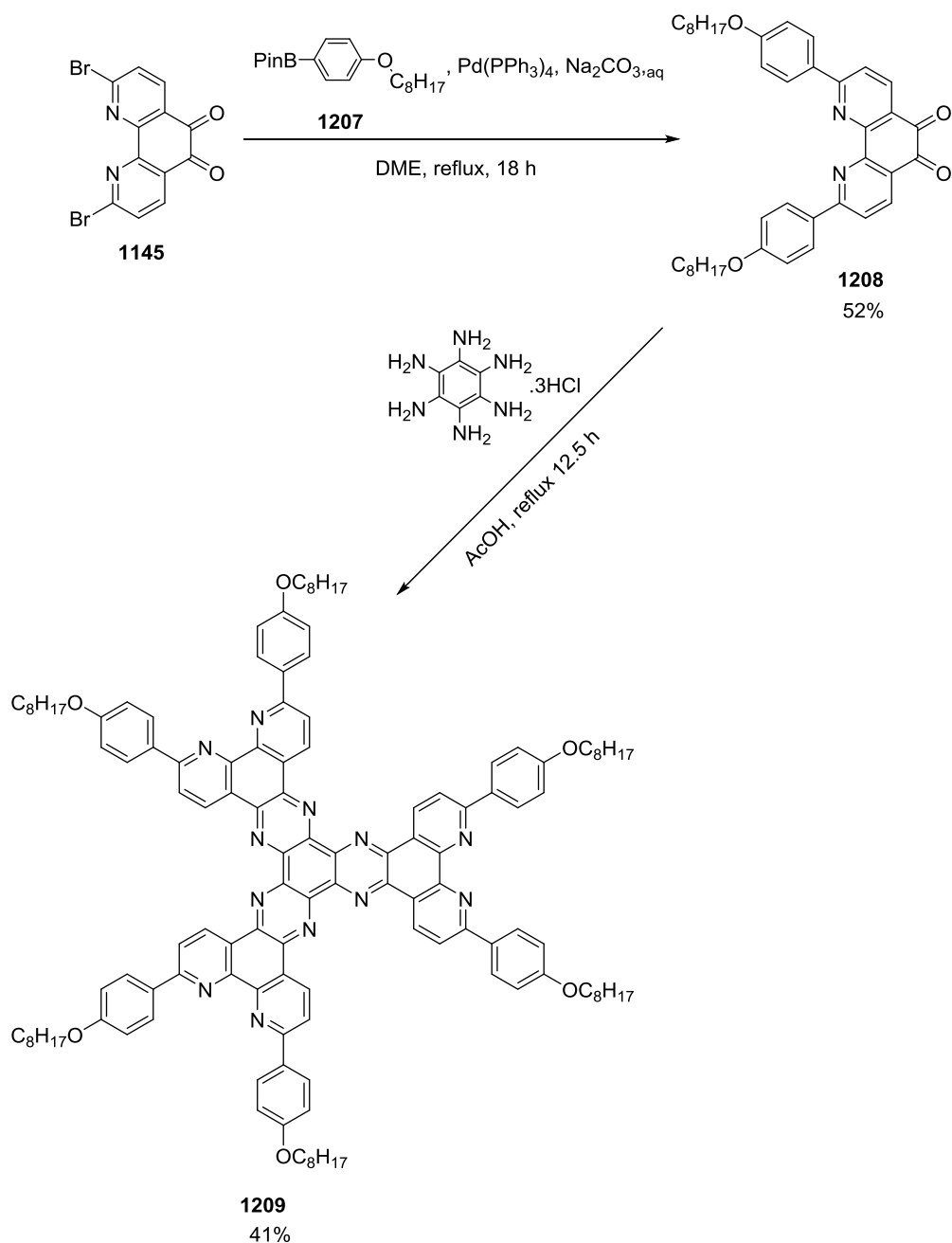
Direct bromination of the methyl group of **1183** by NBS (or NCS) to access the brominated version of **1204** (or **1204** itself) more rapidly was attempted, but perbromination of the molecule was observed.¹⁰⁸⁰ Interestingly, an unexpected reaction involving **1180** and **1182** has been reported by Vagg and co-workers.¹⁰⁸² Indeed, the authors found out that refluxing the latter in boiling HNO₃ for 3 hours lead to compound **1170** with a satisfactory yield of nearly 80%: in short, the imines are hydrolysed and the diketone function is restored, while the methyl groups in α of the nitrogen atoms are directly oxidized into carboxylic groups. This reaction allows to decorate **1180** or **1182** in all four positions 2, 5, 6 and 9 in one easy step. This is all the more interesting as attempts to directly oxidize the methyl groups of neocuproine into COOH usually fail. This original synthon **1170** has been used to design dppz derivatives **1206** bearing useful carboxylic acid functions (Scheme 251).



Scheme 251. Synthesis of **1170** and **1206**

As regards reactions involving the C-halogen bond in **1144**, **1145** and derivatives thereof, to this date, two kinds of reactions have been reported: catalysed cross-coupling reactions^{973,1087,1092,1099} and aromatic nucleophilic substitutions.^{915,1072,1082,1086,1093,1100,1101}

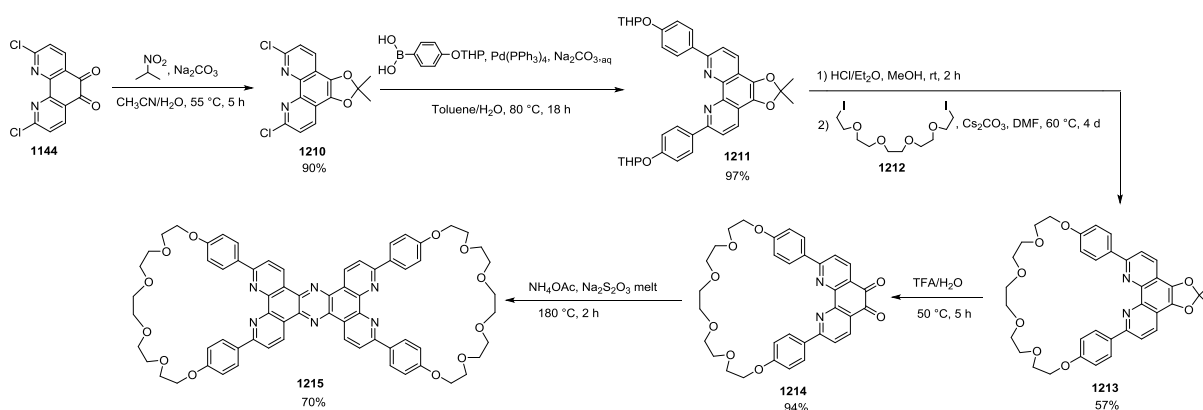
Cross-coupling reactions have rarely been performed directly on **1144** or **1145**. The sole example reported in the literature is depicted in scheme SCH40 and consists in a Suzuki cross-coupling involving **1145** and boronic pinacol ester **1207** in classical conditions.¹⁰⁹⁹ The obtained cross-coupled compound **1208** was condensed on hexaminobenzene leading to star-shaped tris-phen platform **1209** (Scheme 252).



Scheme 252. Unique example of a Suzuki coupling on diketone **1145**, leading to polyaromatic tris-phen **1209**.

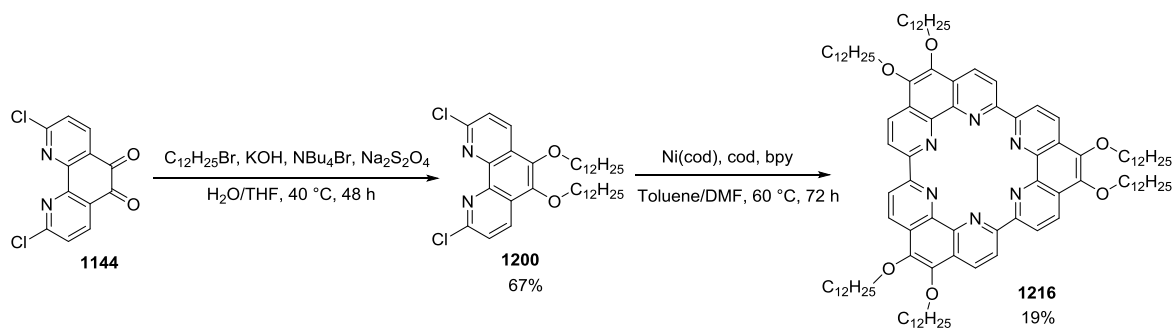
The cross-coupling example presented above is however the sole one reported on a halogenated diketone phen derivative. As regards Suzuki cross-coupling, aqueous basic conditions are often required and phen-diketone derivatives such as **1144**, **1145**, **1146** and **1166** may be unstable in such medium. Indeed, they can quickly turn into the corresponding

fluorenone.¹¹⁰² To circumvent this issue, the protection of the diketone function presented above can be envisioned. Sauvage and collaborators used this method to perform a Suzuki coupling in high yield, as shown on Scheme 253. The coupled compound **1211** is subsequently deprotected from the THP ether, freeing phenol groups onto which **1212** was reacted leading to macrocycle **1213**. Deprotection of the diketone function was finally operated in high yield. Interestingly, **1227** was used to prepare the tpphz derivative **1215** by homo-condensation of **1214** in presence of ammonium acetate. This is a relevant method to synthesize such polycyclic compounds without the need for a diamine.



Scheme 253. Synthetic route for the obtention of ditopic ligand **1215** from **1144**, illustrating the protection-deprotection of the diketone function of **1144**.

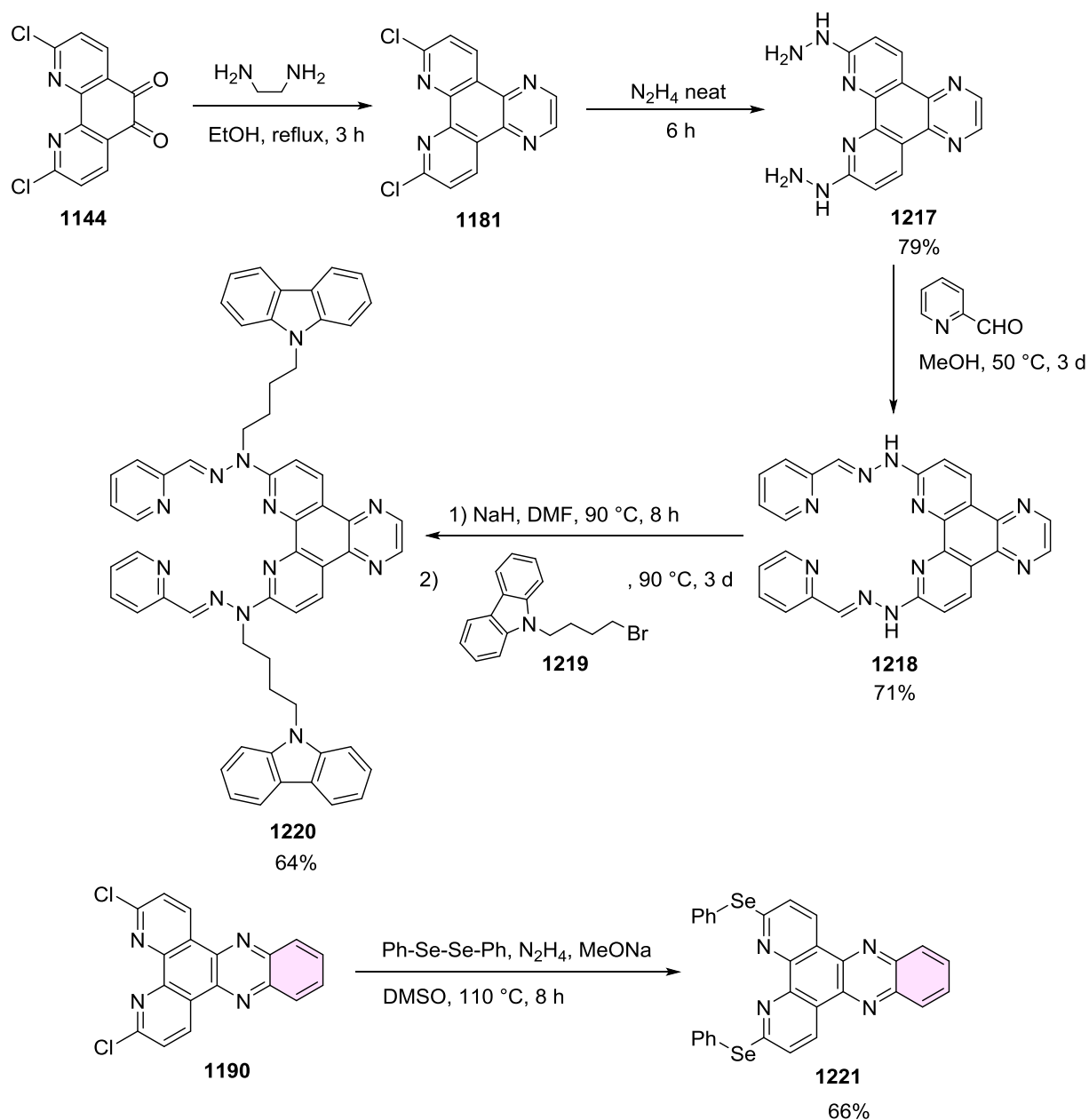
Despite the previous examples, in general, the diketone function of **1144** and **1145** is reacted first, and the cross-coupling reaction is performed in a second step.^{973,1087,1099,1102} For example, **1144** is first submitted to reductive O-dialkylation leading to **1200**, followed by the nickel (0) catalysed homo-coupling of three equivalents of the latter yielding the rigid toroidal hexadentate macrocycle **1216** endowed with interesting sensing properties. Incidentally, the linear and floppy alkoxy chains tethered in positions 5 and 6 conferred a high solubility to this otherwise very insoluble polyaromatic system (Scheme 254).¹⁰⁹²



Scheme 254. Reductive alkylation of **1144** and subsequent homo-coupling leading to **1216**

Other reactions involving C-halogen bonds in **1144** and **1145** (and their derivatives) are aromatic nucleophilic substitution. There is no case reported in the literature where **1144** or **1145** are directly reacted with a nucleophile in order to substitute the halogen atoms in positions 2 and 9. This is likely due to the fact that the diketone is highly electrophilic and would react as well with generating many side products. Thus, nucleophilic substitutions of halogen atoms in positions 2 and 9 are always performed on derivatives of **1144** and **1145** where the diketone function has been first reacted. For example, the reaction of hydrazine on **1181** leads to the bis-hydrazine derivative **1217**.¹⁰⁸² Hydrazone **1218** is then obtained from the reaction of **1217** with 2-pyridinecarboxaldehyde and finally carbazole derivative **1219** is tethered *via* a simple nucleophilic substitution leading to polydentate ligand **1220**.

Likewise, nucleophilic aromatic substitutions can take place with **1190** in presence of nucleophiles, in a similar way to **405** and **396**.^{915,1086,1100} For example, phenylselenide is able to substitute the bromine atoms in **1190** affording **1221** (Scheme 255). The corresponding ruthenium complex exhibits a strong oxophilic behaviour thanks to the two selenium atoms, promoting the cleavage of the O-O bond in molecular oxygen by formation of Ru-O-Se bonds.¹⁰⁸⁶



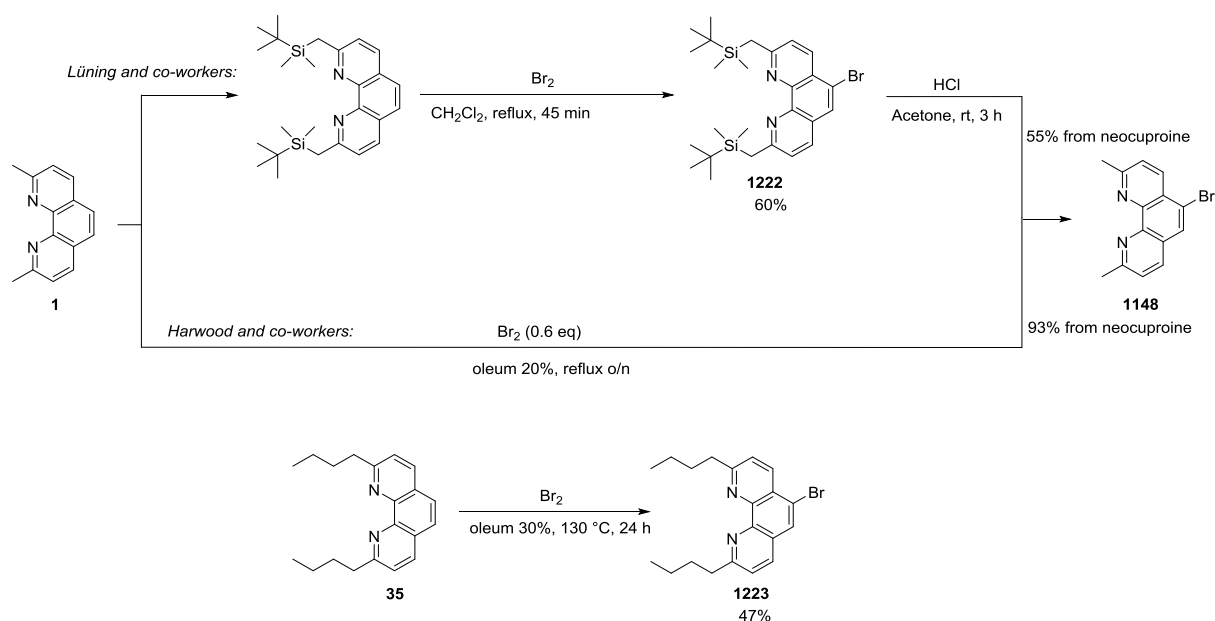
Scheme 255. illustration of the reactivity of the chlorinated positions 2 and 9 of phen.

4.3.4.3. Mono- / bis-Bromination of phen_{(2,9)sub} in position 5 / 5 and 6

Protocol and scope

Tethering one Br atom in position 5 or of two Br atoms in positions 5 and 6 has mostly been reported on neocuproine **1**. The tethering of one Br atom in position 5 of neocuproine is always performed with Br₂ as reagent. The latter is highly reactive and it was anticipated that

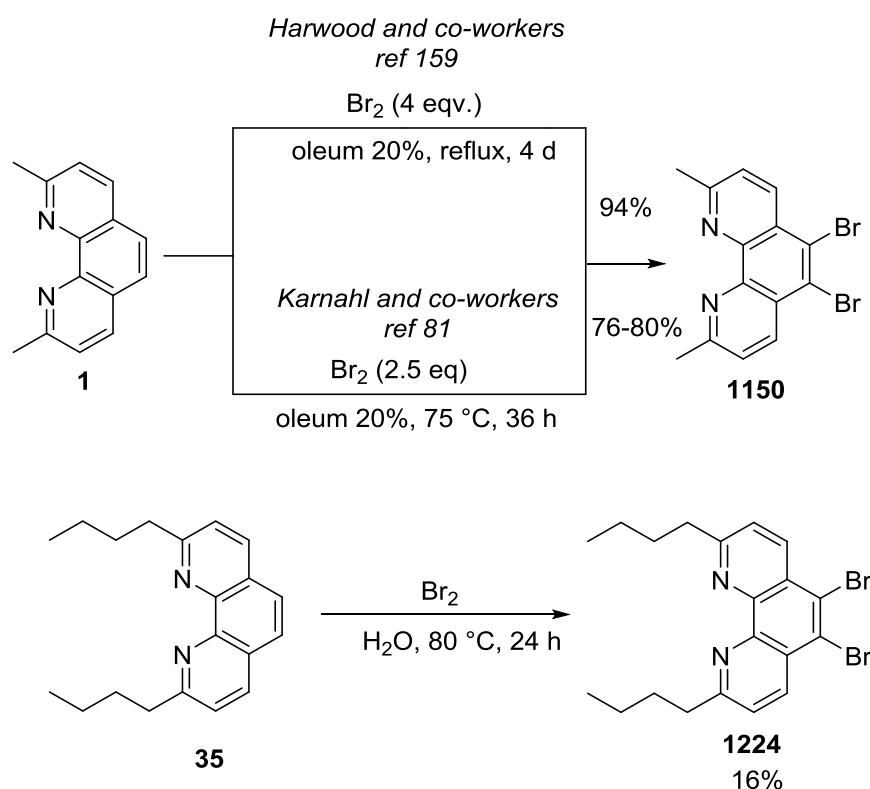
it could react on other reactive positions than 5 and 6, in particular on the methyl groups bound in positions 2 and 9. To circumvent this potential issue, Lüning and co-workers have protected the methyl groups of neocuproine with silyl groups before refluxing resulting **1222** with Br_2 in dichloromethane.^{1103,1104} Subsequent deprotection afforded the target brominated neocuproine **1148** with a reasonable yield. A few years later, Harwood and co-workers developed a more straightforward method where bromination in position 5 proceeded efficiently in one step with Br_2 in oleum at reflux.¹⁵⁹ Similar conditions applied to **35** lead to **1223** with a decent yield,¹¹⁰⁵ demonstrating that the rather harsh bromination conditions are not causing significant damage to the phenanthroline core nor to the alkyl termini (Scheme 256).



Scheme 256. Synthetic pathways for the mono-bromination of position 5 of phen_(2,9)sub.

Interestingly, Harwood et al. have reported that the symmetrical bis-brominated neocuproine derivative **1150** could be obtained in the same conditions than **1148** when excess Br_2 was used and the duration of the reaction was increased (Scheme 257).¹⁵⁹ However, special attention must be paid to the experimental conditions as recently highlighted by Karnahl and co-

workers, who published the most detailed synthetic protocol for the synthesis of **1150**.⁸¹ Notably, the SO₃ concentration in the oleum should not exceed 20% to avoid poly-substitution reactions, and the presence of moisture must be avoided. All those optimizations have been performed on neocuproine as starting material, but there it is not certain that the same conditions can be successfully applied to other 2,9-dialkyl-1,10-phenanthroline. For example, **1224** is obtained from **35** in resolutely different conditions than Karnahl et al's. The reaction is executed in water, without oleum and requires a huge excess of Br₂. Importantly, the yield is very low compared to **1150** (Scheme 257).



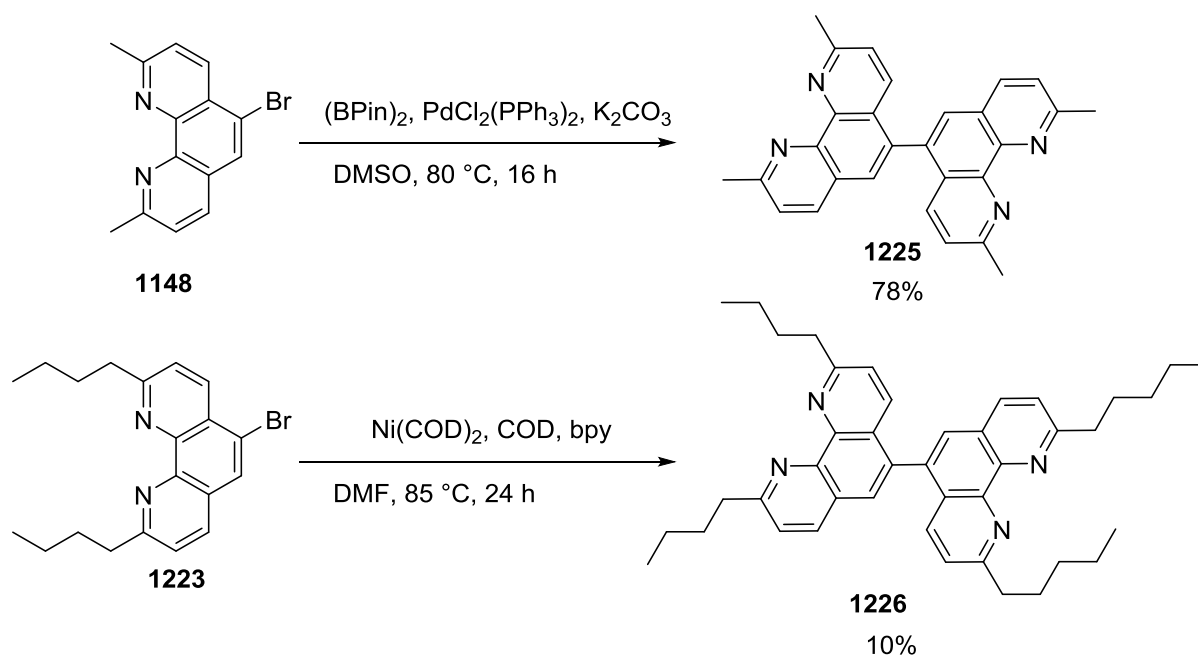
Scheme 257. Synthetic pathways for the bis-bromination of positions 5 and 6 of phen_{(2,9)sub}.

All in all, the fine control of the mono- and bis-bromination of phen_{(2,9)sub} is a challenge, and requires that attention be paid to the number of Br₂ equivalents, the temperature of the reaction and its duration.

Reactivity of the C-Br bond in 5-Br-phen_{(2,9)sub}

To this date, the only reactions which have been reported with 5-Br-phen_{(2,9)sub} and 5,6-Br₂-phen_{(2,9)sub} are metal catalysed cross-coupling reactions. For example, **1148** has been successfully involved in Suzuki,¹¹⁰⁵ Sonogashira,^{1106–1108} and Buchwald-Hartwig¹¹⁰⁸ couplings in classical conditions already described for **861**. Among all examples, the homo-coupling of **1148** via a Suzuki coupling is worth mentioning, leading to ditopic ligand **1225** used as spacer for the synthesis of self-assembled Ag(I), Ni(II) and Zn(II) coordination polymers **9** (Scheme 258).¹¹⁰⁵

Interestingly, the homo-coupling of **1223** has been reported too using a Ni⁰-mediated C-C coupling reaction. Ditopic ligand **1226**¹¹⁰⁹ was thus isolated, but with a much lower yield than **1225**. Using the same conditions with **1224** instead of **1223** lead to an organic polymer with improved solubility thanks to the *n*-butyl chains in positions 2 and 9 (Scheme 258).

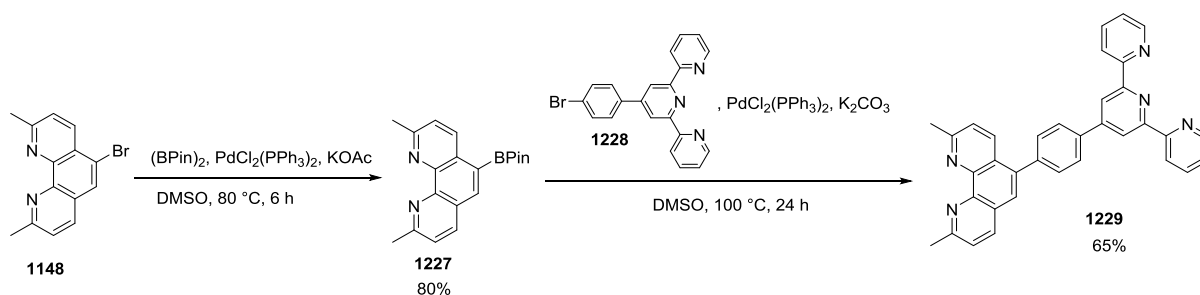


Scheme 258. Synthesis of ditopic ligands by homo-couplings of **1148** and **1223**.

Interestingly, **1148** can be turned into the boron pinacol derivative **1227** (Scheme 259) through a Miyaura–Ishiyama borylation reaction, in very similar conditions than those used

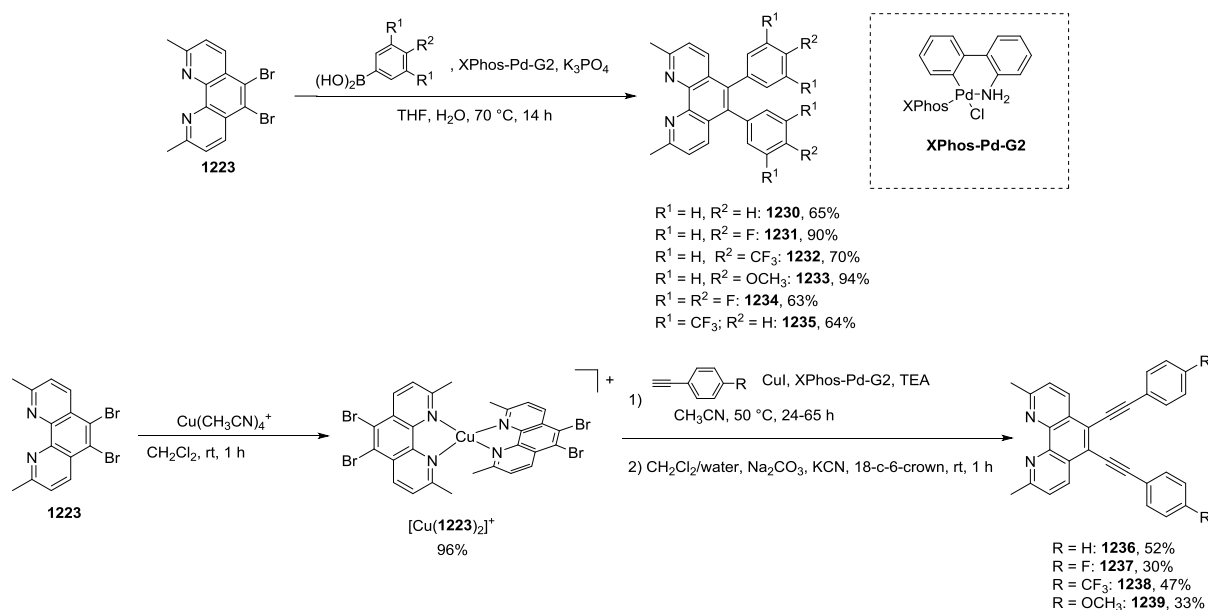
for the synthesis of homo-coupled **1225**.¹¹⁰ Incidentally, the authors report that significant amounts of **1225** can be formed during the reaction; the use of a mild base such as KOAc favours the borylation reaction while the stronger base K_2CO_3 accelerates the formation of **1225**.

1227 can, in principle, be coupled to any aryl halide, such as **1228**: this is a great advantage of **1227** over **1148**, because aryl halides are much more abundant and cheaper than the corresponding boronic acids or esters, thus allowing a greater structural diversity for the modified phen. Here, heteroditopic ligand **1229** has been obtained in two steps from **1148**, and used to design heterobimetallic coordination polymers.



Scheme 259. Synthetic pathway towards heteroditopic ligand **1229**.

It is worthwhile to mention that a double cross-coupling on positions 5 and 6 can be achieved using **1150**, despite the counter-productive steric strain. After a thorough optimization of the reaction conditions, in terms of catalyst, temperature and duration of the reaction, the target doubly cross-coupled molecules were obtained in good yields (Scheme 260).⁸¹ Interestingly, the Sonogashira reactions were all realized on the copper(I) complex $[Cu(\mathbf{1223})_2]^+$ rather than free **1223**. The authors saturated the phen cavity with copper(I) ions to avoid the deactivation of the CuI catalyst by coordination. The free ligands are retrieved by a simple treatment with KCN which efficiently disrupts the homoleptic complexes.



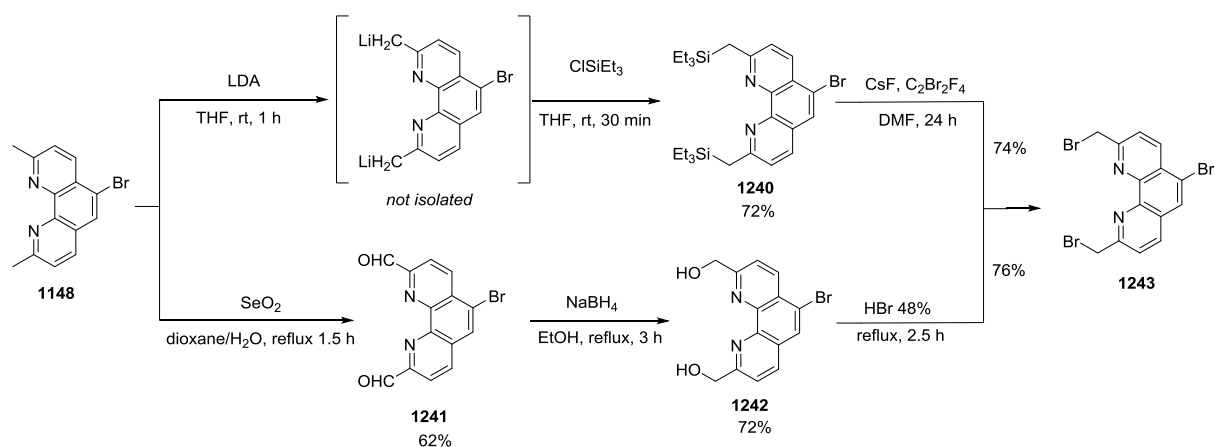
Scheme 260. Suzuki-Miyaura and Sonogashira cross-coupling reactions using **1223** as substrate

Further reactions on 5-Br-phen_{(2,9)sub} and 5,6-Br₂-phen_{(2,9)sub}

So far, the only examples in the literature reporting the decoration in all positions 2, 5, 6 and 9 starting from 5-Br-phen_{(2,9)sub} and 5,6-Br₂-phen_{(2,9)sub} involve synthons **1148** and **1223**. The reactivity of the latter is very similar to neocuproine's.

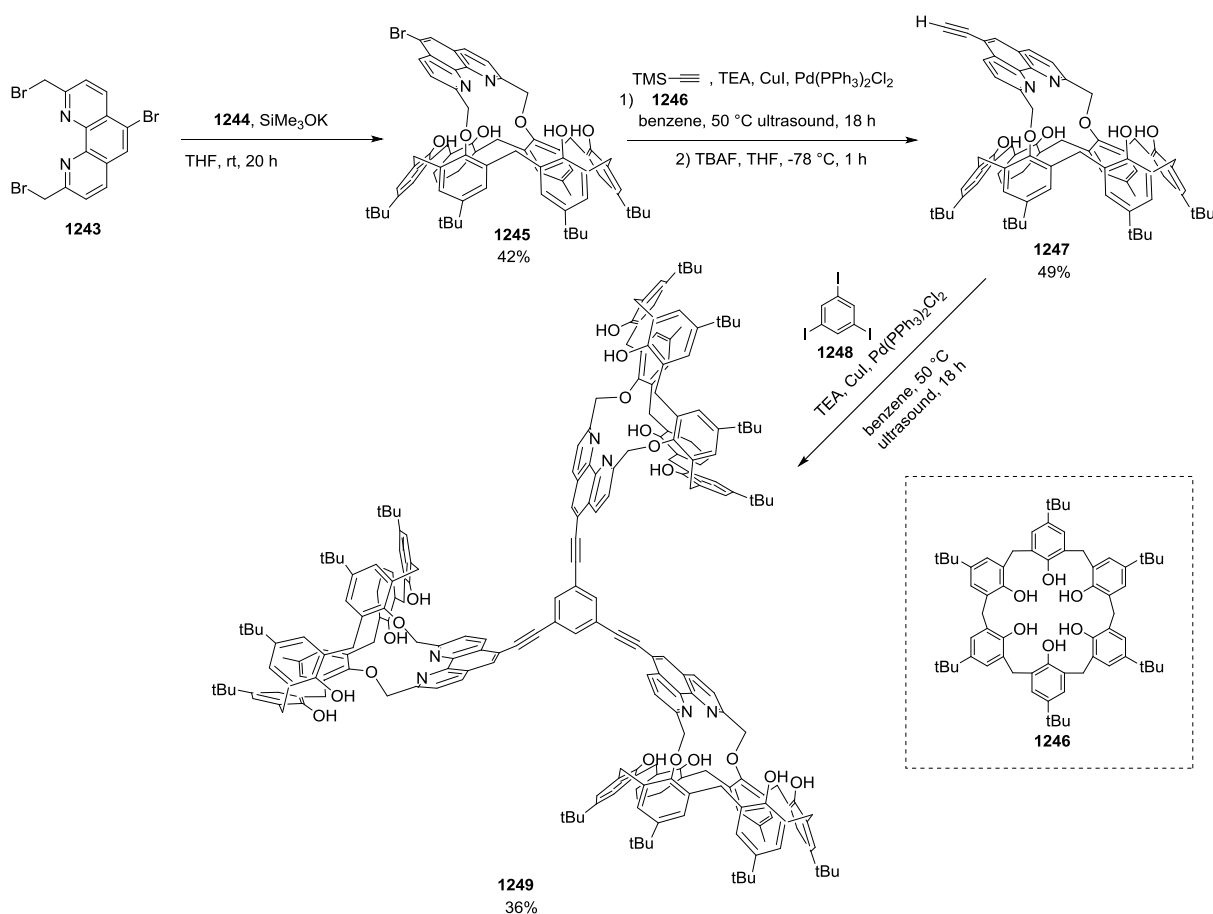
For example, Lüning and co-workers have developed an elegant route leading to trisbrominated compound **1243** in only two steps from **1148** relying on the deprotonation of **1148** by LDA.¹¹⁰⁴ The resulting bis-carbanion performs a nucleophilic attack on triethylchlorosilane affording **1240**. The latter, in presence of CsF and the electrophile Br₂C₂F₄ leads to the target compound **1243** with a fine overall yield of 53% from **1148** (Scheme 261).¹¹¹¹ The same compound could be obtained in the more traditional conditions developed by Chandler in the eighties, albeit with a smaller overall yield (34%).¹¹⁰⁴ Briefly, **1148** can endure the oxidation by SeO₂ leading to bis-aldehyde **1241**. The yield of the reaction partly depends on the duration of the reflux, from 60% (1.5 h)¹¹⁰⁴ to 90% (3 h).^{159,1070}

The aldehyde functions on **1241** can then be reduced by NaBH₄ into **1242** and the OH groups are finally substituted by bromine atoms in hot HBr leading to **1243** (Scheme 261).



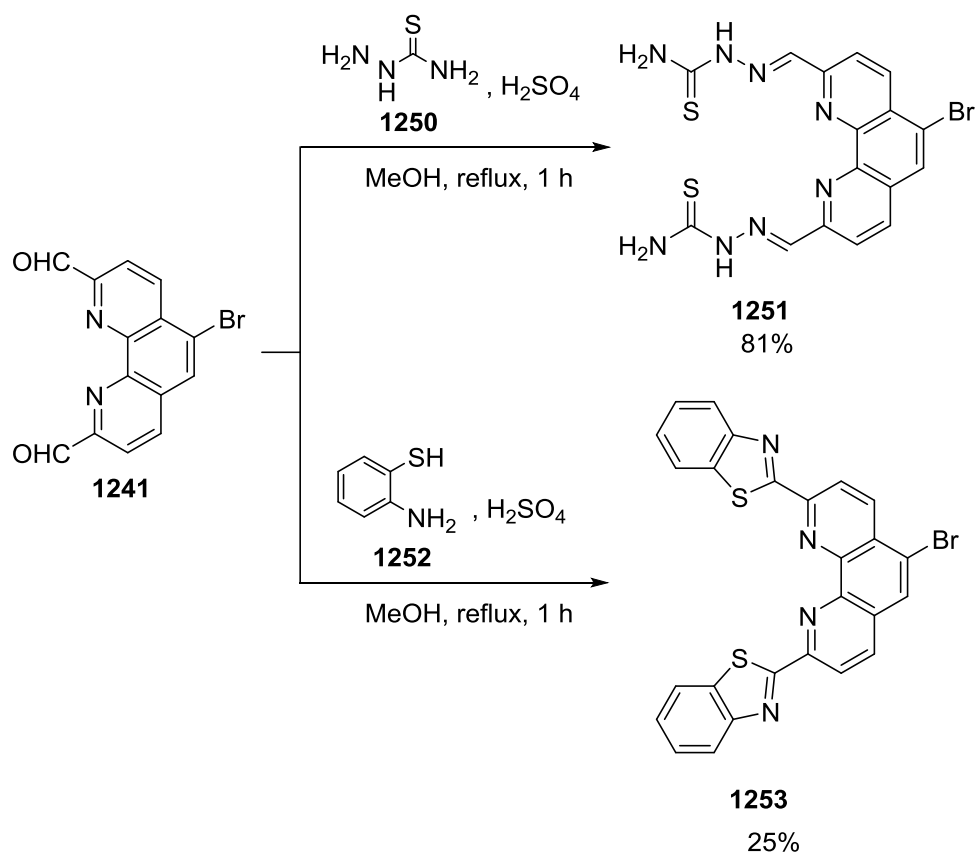
Scheme 261. Two possible pathways to perform the synthesis of **1243**

1243 contains three bromine atoms with different reactivities, a feat which has been exploited by Lüning and co-workers to design impressive calixarene dendrimers.¹¹⁰⁴ First, a nucleophilic attack of calixarene **1244** on the methylbromide groups of **1243** yields the hybrid compound **1245**. Then, a Sonogashira coupling allows to attach trimethylsilylacetylene **1246** in position 5 of the phen moiety. Deprotection followed by another Sonogashira coupling with 1,3,5-triiodobenzene **1248** finally lead to dendrimer **1249** in a decent yield for such an extended structure (Scheme 262).



Scheme 262. Synthesis of hybrid phen-calixarene dendrimer **1249**

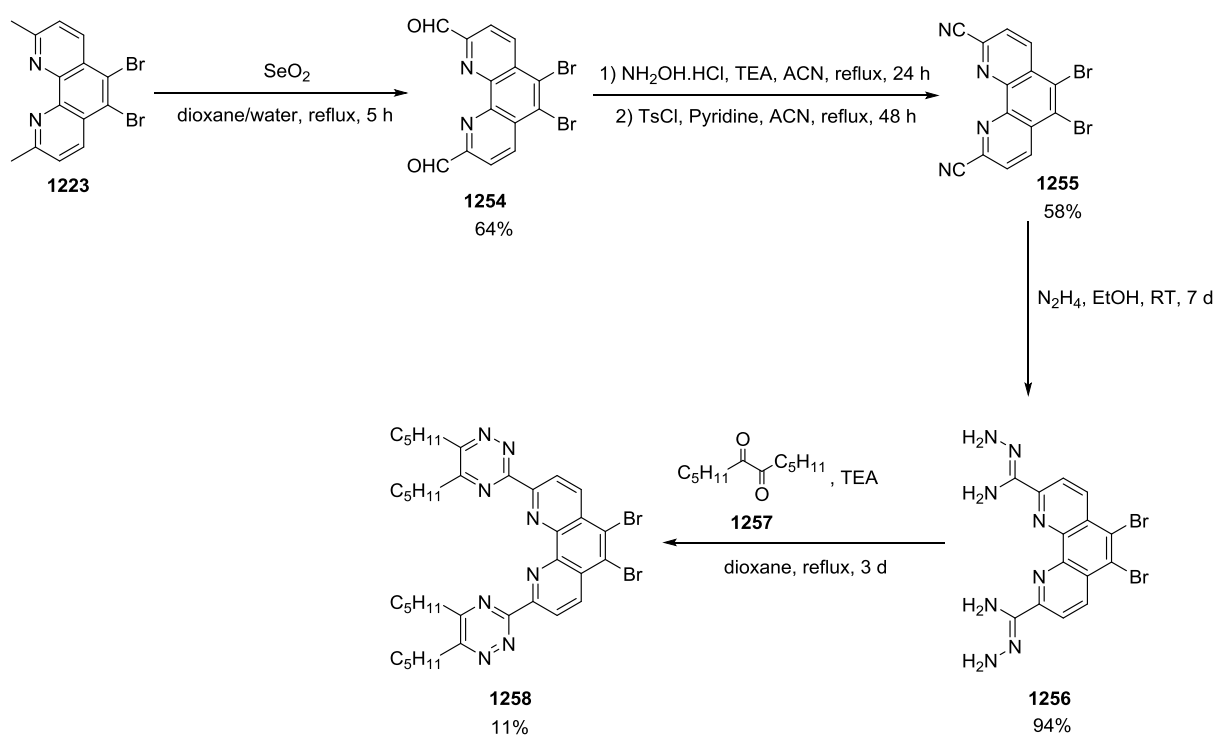
Reactions involving bis-aldehyde **1241** have been reported, for example the syntheses of imines- and thioimidazoles-functionalized phen **1251** and **1253** are reported in Scheme 263, following protocols reported before on **565** which will not be further developed.¹⁰⁷⁰ However, it is important to notice that the bromine atom in position 5 is not sensitive to the presence of nucleophiles (such as **1250** or **1252**). This is in line with the observations made on section 3.4.



Scheme 263. Examples of syntheses using the CHO functions of **1241**

Finally, **1223** can be oxidized into bis-aldehyde **1254** with SeO_2 too. Harwood and co-workers used **1254** to add another member to the family of BTPhen ligands, namely the bis-brominated version of the well-known ligand **616**_{C5} (i.e. molecule **616**, with $\text{R} = \text{C}_5\text{H}_{11}$) used to selectively coordinate radionucleides.¹⁵⁹ The motivation of this work was to exploit the electronic effects of bromine to “soften” the phen cavity of **616**_{C5} and therefore more adequate for the coordination of soft large cations like Am^{3+} and leading to an improved separation of actinide ions vs. lanthanide ions. The synthesis of **1258** is completely identical to the synthesis of **616** molecules as performed from **565** (Schemes 104 and 264). The same series of reactions has been performed on **1148** by the authors, but it is noteworthy that all reactions involving bis-brominated compounds **1223**, **1254**, **1255** and **1256** required longer reaction times than reactions using mono-brominated homologous compounds. This tends to show that

the bromine atom(s) decreases the overall reactivity of the methyl groups attached in α of the nitrogen atoms.



Scheme 264. Synthesis of bis-brominated phen_(2,5,6,9) **1258**

Summarily, considering the structures of synthons **1148** and **1223**, the bromine atoms in positions 5 and 6 are compatible with a quite large number of reactions aimed at decorating the methyl groups in positions 2 and 9, but one shall keep in mind that those atoms may affect their reactivity.

4.4. Synthetic methods for the construction of phen_(3,4,7,8)

There is no method to prepare phen_(4,7) from phen, and therefore the same consideration applies for phen_(3,8,4,7). This means that it is not possible to this date to transform any phen_(3,8) molecule into a phen_(3,4,7,8). On the other hand, transforming phen_(4,7) into phen_(3,4,7,8) by functionalization of C₃ and C₈ is feasible as will be shown below.

Nevertheless, we will mainly focus in this section on the decoration of phen_{(3,4,7,8)sub} synthons obtained by convergent methods. In this frame, the methods used to decorate phen_{(3,8)sub} (aromatic nucleophilic substitutions and metal catalysed cross-coupling on C_{3,8}-Br) and phen_{(4,7)sub} (aromatic nucleophilic substitutions and metal-catalyzed cross-coupling on C_{4,7}-Cl or Br; deprotonation or oxidation of C_{4,7}-CH₃) are naturally still valid to decorate phen_{(3,4,7,8)sub} molecules, bearing C_{3,8}-Br and C_{4,7}-X (X = Cl or Br or CH₃).

4.4.1. From phen to phen_{(3,4,7,8)sub}

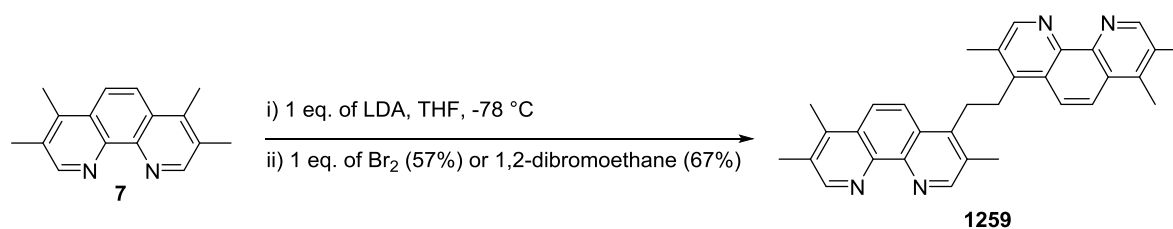
Only one paper has mentioned the synthesis of a phen_{(3,4,7,8)sub} from naked phen. Upon refluxing phen with excess phosphorus pentachloride and phosphoryl chloride for 72 h, 3,4,7,8-tetrachloro-1,10-phenanthroline **731** is formed with 94% yield, as already presented in Scheme 120.⁶⁵²

4.4.2. Decoration of phen_{(3,4,7,8)sub} obtained by convergent methods

Given the fact that no divergent method allows to append substituents on C₄ or C₇ of phen_{(3,8)sub}, we will focus here on the decoration of selected phen_{(3,4,7,8)sub} synthons bearing reactive groups X in positions 4 or 7 (X = CH₃ or halogen).

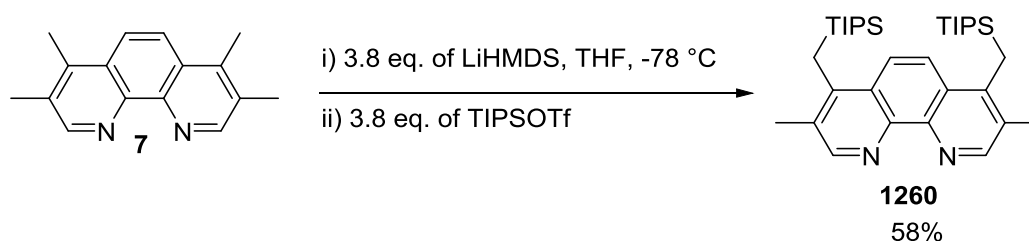
The reactivity of the C_{4,7}-CH₃ groups on selected phen_{(3,4,7,8)sub} is exemplified below. Lehn et al.⁵⁰¹ studied the effect of a base on the commercially available 3,4,7,8-tetramethyl-1,10-phenanthroline **7**. They precise that the (2,9) and (4,7) positions are much more reactive than the (3,8) positions to form carbanions. Regarding the base, t-BuOK and NaNH₂ are not sufficiently strong bases to deprotonate the methyl groups. On the other hand, BuLi leads to a mixture of products, with probable nucleophilic attacks of the organolithium reagent on positions 2 and 9 of phen. LDA allows the deprotonation of the methyl in position 4 of the phen at -78 °C. Thus, when **7** in THF is put in presence of one equivalent of LDA at -78 °C,

the monocarbanion forms (spotted as green species) and the solution is stirred for 4 h at -78 °C. Then one equivalent of an oxidant, in this case either Br₂ or 1,2-dibromoethane, is added and leads to the color disappearance of the solution. After warming to 0 °C, the mixture is finally quenched with water, affording the homocoupled bis-phenanthroline ligand **1259** (Scheme 265).



Scheme 265. Deprotonation on the 4-position to obtain 1,2-bis(1,10-phenanthrolyl)ethane ligand **1259**⁵⁰¹

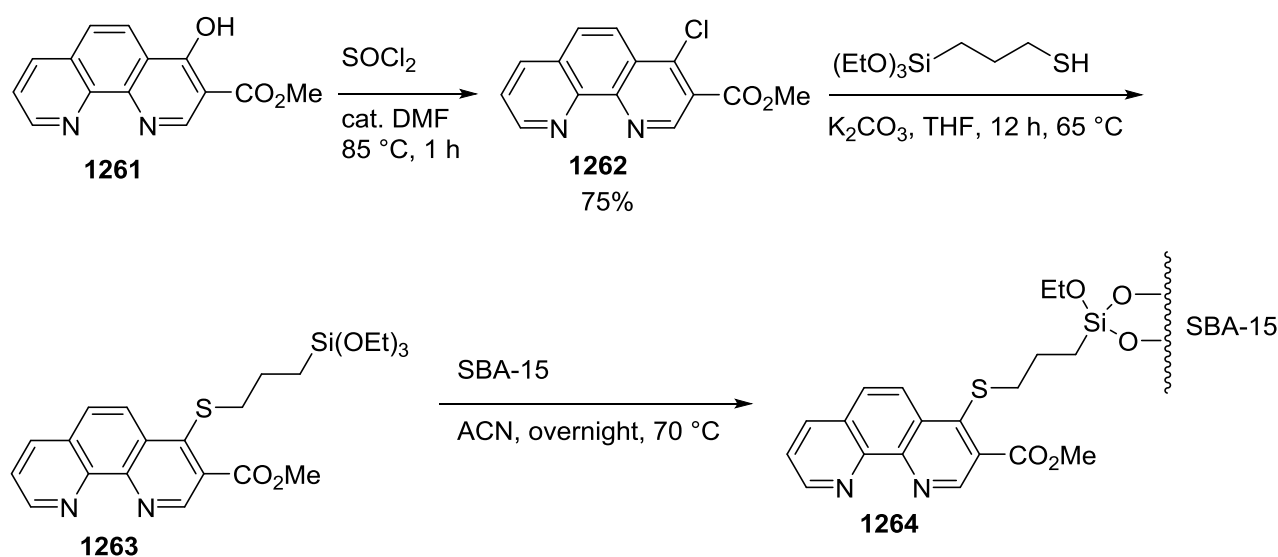
The authors mention that the mechanism is radical free and that 1,2-bis(1,10-phenanthrolyl)ethane forms through the formation of an intermediate arising from an electron transfer from the carbanion to the oxidant. A similar strategy was applied by Larsen et al.¹²⁵ who have deprotonated **7** with LiHMDS then performed a nucleophilic substitution on triisopropylsilyl trifluoromethanesulfonate leading to the addition of the TIPS functional group on positions 4 and 7 (Scheme 266).



Scheme 255. Deprotonation the methyl groups attached to positions 4 and 7 to obtain **1260**¹²⁵

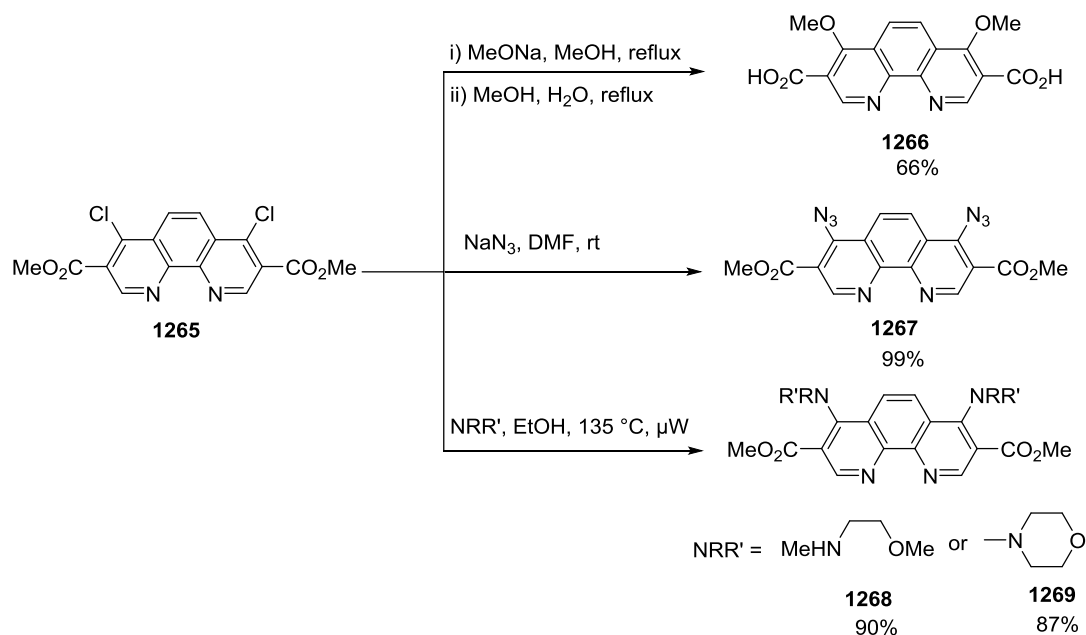
*Halogen atoms attached in positions 4 and 7 on phen_{(3,4,7,8)sub} can be easily used for aromatic nucleophilic substitutions like demonstrated before on **146**. For example, the 4-hydroxy-1,10-*

phenanthroline-3-carboxylic acid methyl ester **1261** (obtained from convergent methods as **198**) has been modified by Terry et al.¹¹¹² who have substituted the hydroxyl group by a chlorine atom with SOCl_2 then have performed an aromatic substitution on the hydroxy group to introduce a substituted thiol group (Scheme 267). This ligand has been then grafted onto SBA-15 silica, coordinated to manganese ions and was used as a supported catalyst in the epoxidation of olefins.



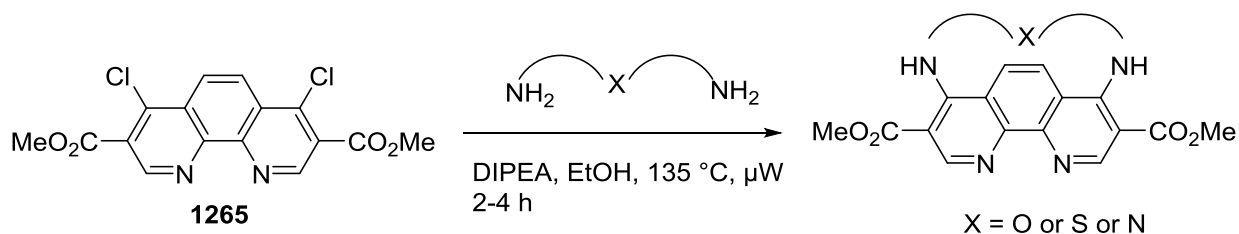
Scheme 267. Modification of the 4-hydroxy-1,10-phenanthroline-3-carboxylic acid methyl ester from Terry et al.¹¹¹²

Abel et al.¹⁸² formed the 4,7-dichloro-1,10-phenanthroline-3,8-dicarboxylic acid methyl ester **1265** through convergent method. From this synthon, they performed nucleophilic aromatic substitution to replace chlorine atoms with various nucleophile (Scheme 268).



Scheme 268. Nucleophilic aromatic substitution described by Abel et al.¹⁸²

They synthesized as well N-, O- and S-containing macrocycle by substituting chlorine atoms with oxadiazamines, thioxadiazamine and tetraamine of various chain length under microwaves irradiation (Scheme 269).

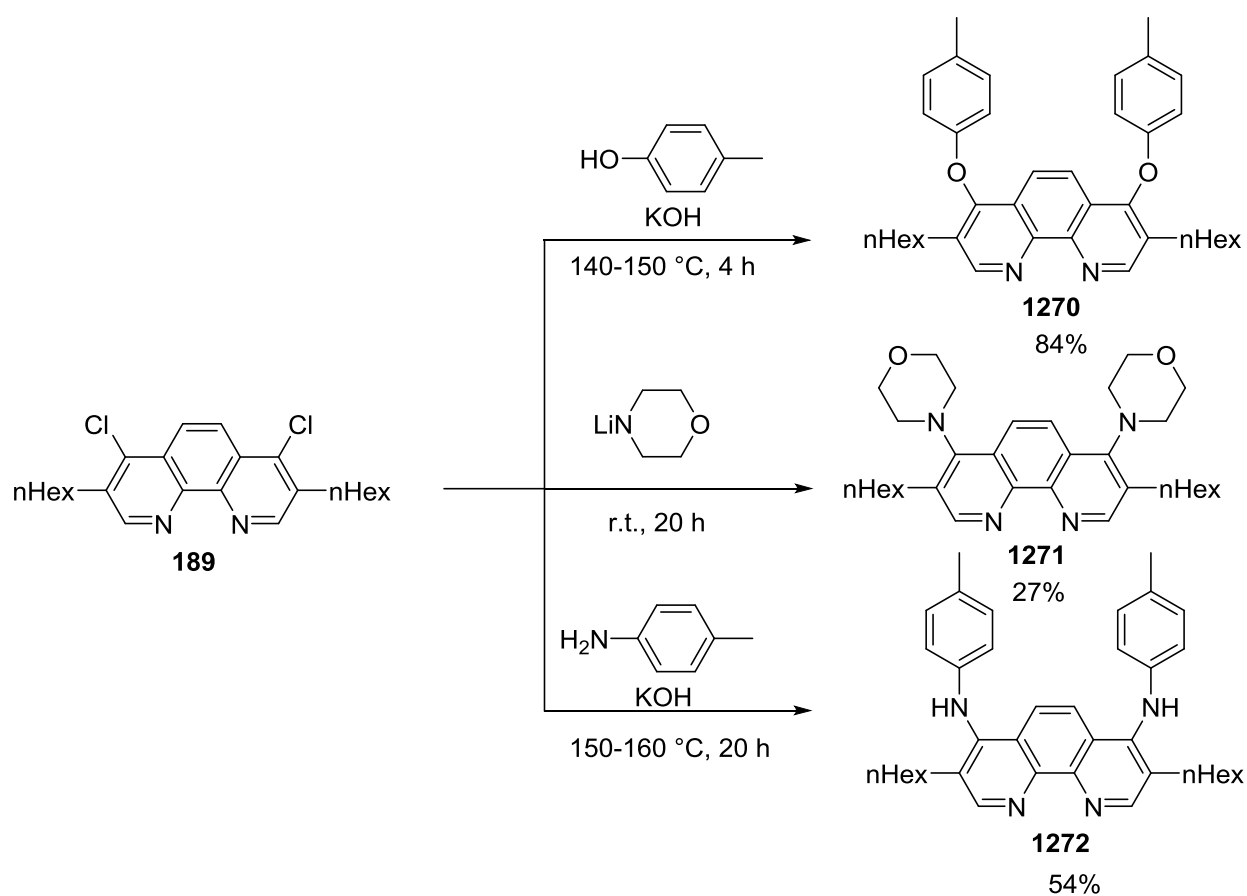


Scheme 269. Synthesis of N-, O- and S-containing macrocycle reported by Abel et al.¹⁸²

From the same synthon **1265**, Verheyde et al.¹¹¹³ synthesized dendrimers containing 1,3,4-oxadiazoles by performing a nucleophilic aromatic substitution on the chlorines atoms in the 4 and 7 positions.

Schmittl et al.²⁷⁴ have massively contributed to the elaboration of multifunctional phen_{sub}. In Scheme 270, they report on the synthesis of various phen_{(3,4,7,8)sub} through a convergent

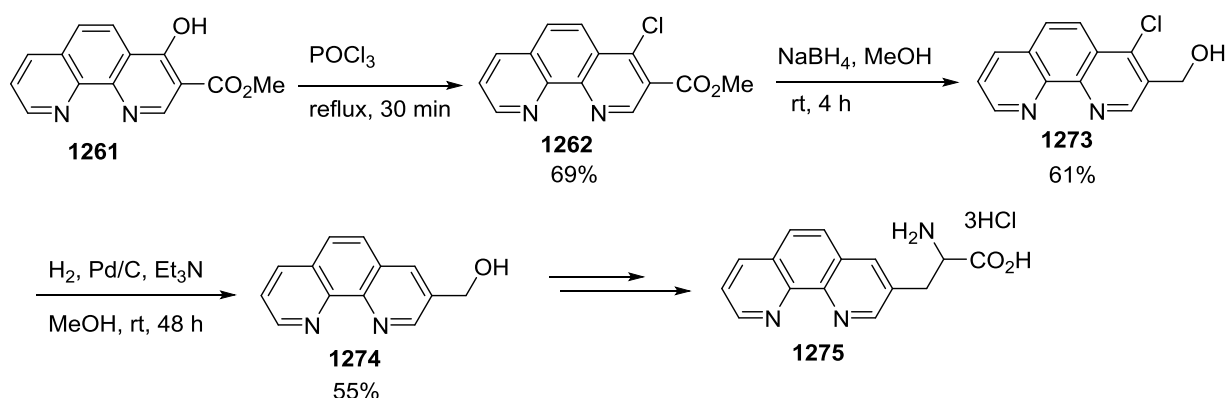
method (Scheme 20) and from those building blocks, they have showed that nucleophilic aromatic substitution is possible on the chlorine atoms in the 4 and 7 positions (Scheme 270).



Scheme 270. Nucleophilic aromatic substitution on the 4,7-halogeno-3,8-dialkylalkylated-phen as demonstrated by Schmittel and co-workers.

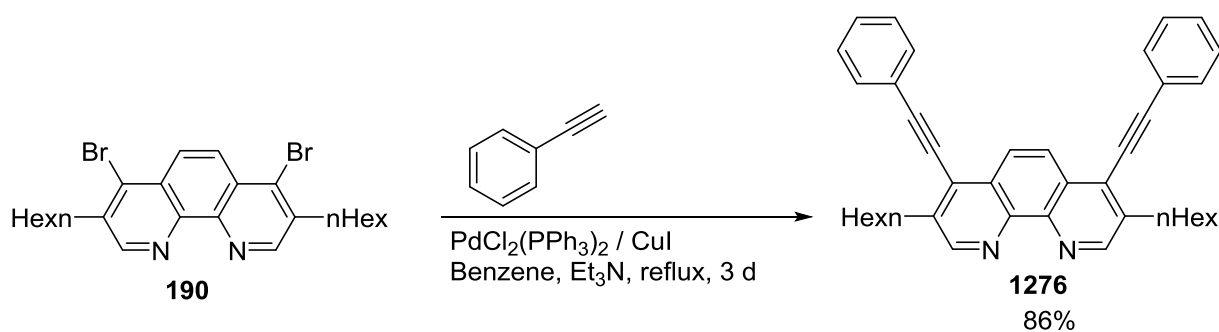
Metal-catalyzed C_{4,7}-C bond formation has been reported in many instances because of the well-known reactivity of C_{4,7}-Cl or Br bonds. Jin et al.¹¹¹⁴ have substituted the hydroxyl group of **1261** by a chlorine atom using POCl₃ instead of SOCl₂, then have reduced the ester into alcohol that was further modified into an alanine motif. The chlorine atom in the position 4 has been replaced by an hydrogen atom through a palladium catalyzed hydrogenolysis (Scheme 271). This phen-ala derivative is then incorporated into proteins in E. Coli and was shown to be a good alternative to metal-chelating amino acids to develop artificial

metalloproteins. This example is basically only a phen_{(3)sub} molecule, but we present it here since this molecule has been designed through methods involving phen_{(3,4)sub} intermediates.



Scheme 271. Synthesis of **1275** described by Jin et al.¹¹¹⁴

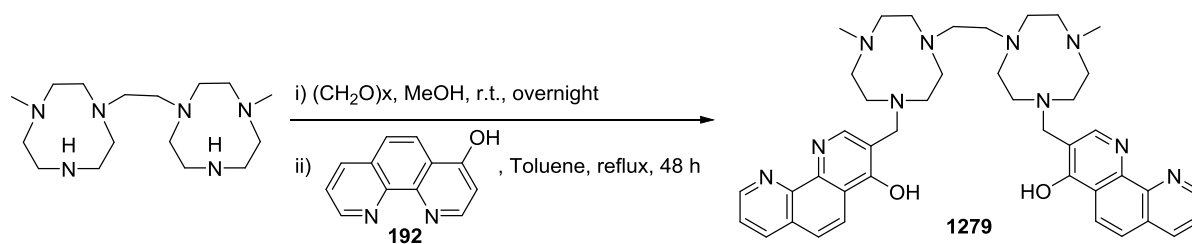
When bromine atoms are on the positions 4 and 7, a Sonogashira reaction is possible^{274,1115,1116} (Scheme 272) on synthon **190**. Garakyaraghi et al.²⁰² performed as well a Sonogashira reaction on the 4,7-dichloro (**1277**) or dibromo-3,8-dimethyl-phen (**1278**) using classical conditions and phenylacetylene with 72% yield when bromine atoms were on the 4,7 position.



Scheme 272. Nucleophilic aromatic substitution and one example of a Sonogashira reaction performed on the 4,7-halogenao-3,8-dialkylalkylated-phen²⁷⁴

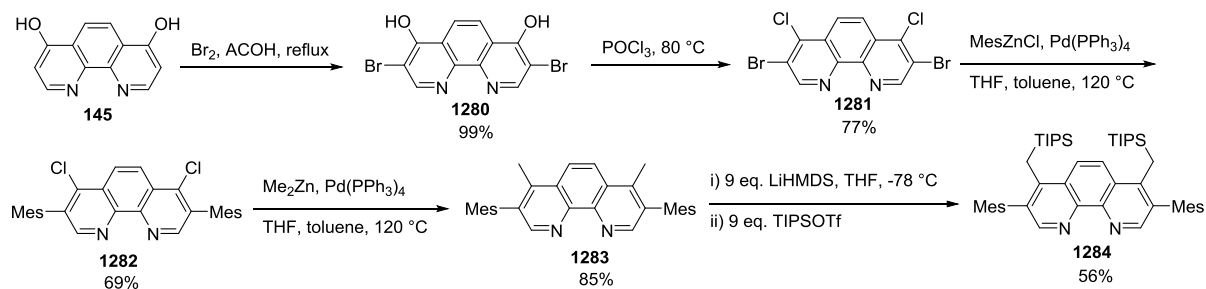
4.4.3. From phen_{(4,7)sub} to phen_{(3,4,7,8)sub}

Burdinski et al.¹¹¹⁷ used **192** obtained through convergent method and then performed a Mannich-type reaction using paraformaldehyde and a macrocycle (the dimethylated 1,2-bis(1,4,7-triazacyclonyl)-ethane) in refluxing toluene that has yielded a phen_{(3,4)sub} **1281** (Scheme 273).



Scheme 273. Mannich-type reaction on **192** developed by Burdinski et al.¹¹¹⁷

The regioselective bromination of **145** into **1280** is a key reaction to decorate phen in positions 3 and 8 following a divergent strategy. Larsen et al.¹²⁵ showed that it was possible to obtain **1281** from **145** obtained through convergent method. The bromine atoms are first introduced on the 3 and 8 positions of **145** with Br₂ and then the hydroxy group on the 4 and 7 positions are replaced by chlorine atoms using POCl₃. Then, a Negishi coupling with MesZnCl is performed and this reaction is remarkably selective of the C_{3,8}-Br bonds. A second Negishi coupling is then achieved using dimethylzinc, allowing the introduction of methyl groups on the 4 and 7 positions. This compound could then undergo deprotonation then silylation to yield **1284** (Scheme 274).



Scheme 274. Synthesis of 3,8-dimesityl-4,7-substituted phen¹²⁵

4.5. Synthetic methods for the construction of phen_{(3,5,6,8)sub}

There are again three possible methods to prepare phen_{(3,5,6,8)sub} by divergent methods: one can start from naked phen, functionalize phen_{(3,8)sub} in positions 5 and 6, or functionalize phen_{(5,6)sub} in positions 3 and 8.

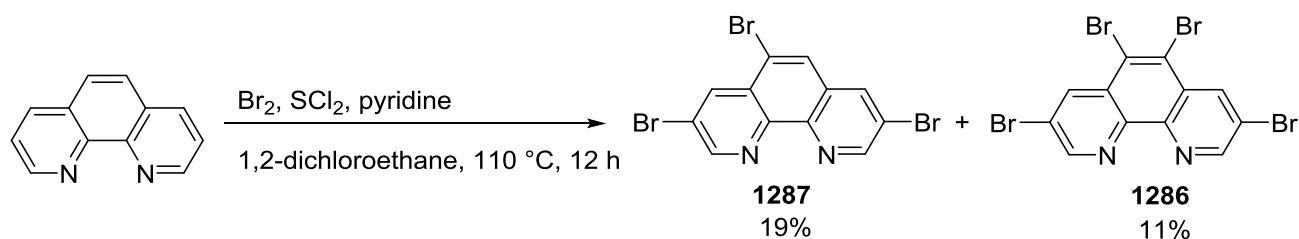
4.5.1. From phen to phen_{(3,6)sub}, phen_{(3,5,6)sub} or phen_{(3,5,6,8)sub} to phen_{(3,5,6,8)sub}

Contrary to the other cases exhibited so far, there is a significant amount of methods allowing to functionalize naked phen in positions (3,8) and (5,6) simultaneously.

For example, Vyprachticky et al.¹¹¹⁸ have yielded 20% of the 3,6-diBrphen **1285** by mixing the phen monohydrate with Br₂, a low amount of sulfur dichloride (SCl₂) and pyridine.

As mentioned in section 3.4, Denes et al.⁷⁶⁶ have performed the bromination reaction on the phen monohydrate in thionyl chloride and added 6 eq of bromine. The mixture is refluxed for 24 h. A mixture of 5,6-dibromo-phen (**863**), 3,5,6-tribromo-phen (**1285**, 11% yield) and 3,5,6,8-tetrabromo-phen (**1286**, ca. 6% yield) is obtained. Clearly those methods are not very high yielding because the compounds of interest in this section are by-products obtained during the synthesis of other targets. But the targets are particularly appealing versatile synthons and the protocols for their synthesis have been improved. By using a big excess of sulfur dichloride (SCl₂) and pyridine, Vyprachticky et al.¹¹¹⁸ have obtained a mixture of 3,5,8-tribromo-phen **1287** and 3,5,6,8-tetrabromo-phen **1287** by mixing the phen monohydrate with Br₂ (Scheme 275). According to them, this method is faster than using a Skraup reaction to obtain those compounds but implies the use of toxic reagents. The authors have noticed that Lewis acid sulfur dichloride is working much better than sulfur chloride used by Saitoh et al.⁶⁵⁵ to obtain poly-brominated phen. It seems that SCl₂ is a stronger Lewis acid than S₂Cl₂.

Incidentally, using the better Lewis acid SOCl_2 (neat) to run the reaction (reflux with Br_2 for 31 h) allows to isolate **1286** in high yield (50%).¹¹¹⁹



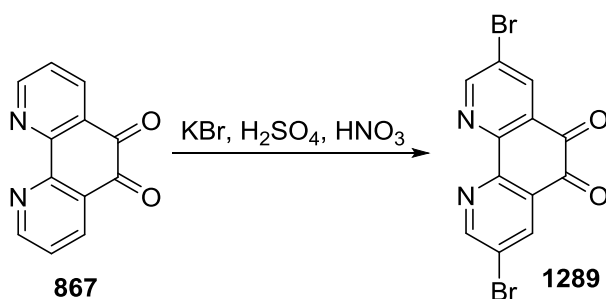
Scheme 275. Synthesis of 3,5,8-tribromo-phen **1287** and 3,5,6,8-tetrabromo-phen **1286** described by Vyprachticky et al.¹¹¹⁸

Manolikakes et al.¹¹²⁰ have synthesized **1286** using as well SOCl_2 and Br_2 (6 eq.). After refluxing the mixture for 40 h, the authors have isolated **1286** with 49% yield. Importantly, they have reported that water is important in this reaction and when anhydrous 1,10-phenanthroline is used as a starting material, the reaction fails. Either it is necessary to start with the 1,10-phenanthroline monohydrate reagent or to add a few drops of water on the anhydrous 1,10-phenanthroline. This brominated phen was then used as a ligand to promote a nickel catalyzed amination of aryl and heteroaryl chlorides.

Then, on **1286** synthesized as described by Rau et al.¹¹¹⁹ Mörtel et al. have tried to perform a regioselective Suzuki reaction on positions 3 and 8 with 2 eq. of phenylboronic acid but the 3,8-diphenyl-5,6-diBrphen was not obtained,¹¹²¹ probably because the $\text{C}_5\text{-Br}$ and $\text{C}_6\text{-Br}$ bonds got involved in the coupling too, leading to intractable mixture of compounds. They mentioned that **1286** was very poorly soluble in organic soluble which renders optimization of the conditions difficult.

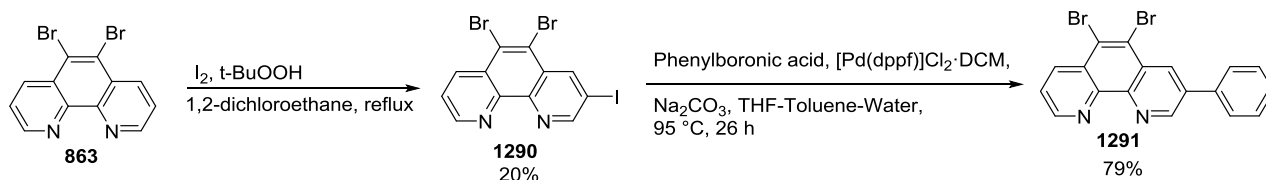
4.5.2. From phen_{(5,6)sub} to phen_{(3,5,6,8)sub}

There are not many reported strategies to functionalize phen_{(5,6)sub} in positions 3 and 8. Pakulski et al.¹¹²² have reported the synthesis of the 3-bromo-5,6-phenidione **1288** and 3,8-dibromo-5,6-phenidione **1289** using the phenidione as a starting material, using a mixture of H₂SO₄ / HNO₃ and KBr (Scheme 276). Br₂ is formed during the reaction and could in principle lead to the formation of C₃-Br and C₈-Br bonds. Since the same mixture of acid and KBr is used to prepare phenidione from phen, it is likely that traces of **1289** could form during the synthesis of phenidione itself.



Scheme 276. Bromination in positions 3 and 8 of phenidione

Very interestingly, iodination of **863** in presence of tert-butyl hydroperoxide lead to 5,6-dibromo-3-iodo-1,10-phenanthroline **1290** with 20% yield. Then, a Suzuki reaction was performed using phenylboronic acid in a mixture of solvent to yield 79 % of the 5,6-dibromo-3-phenyl-1,10-phenanthroline (Scheme 277).¹¹²¹ This is particularly appealing because other attempts to make regio-selective couplings on tetrabromophen have failed.¹¹²¹

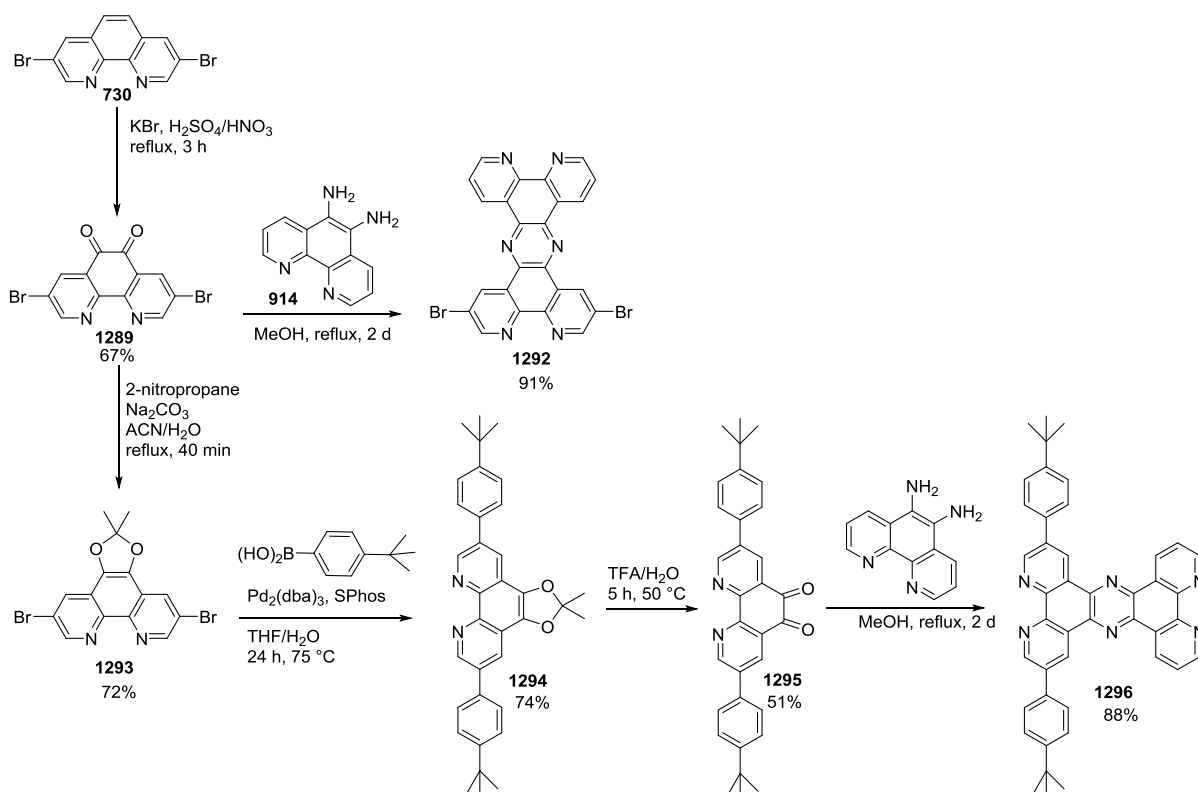


Scheme 277. Synthesis of 5,6-dibromo-3-phenyl-1,10-phenanthroline described by Mörtel et al.¹¹²¹

4.5.3. From phen_{(3,8)sub} to phen_{(3,5,6,8)sub}

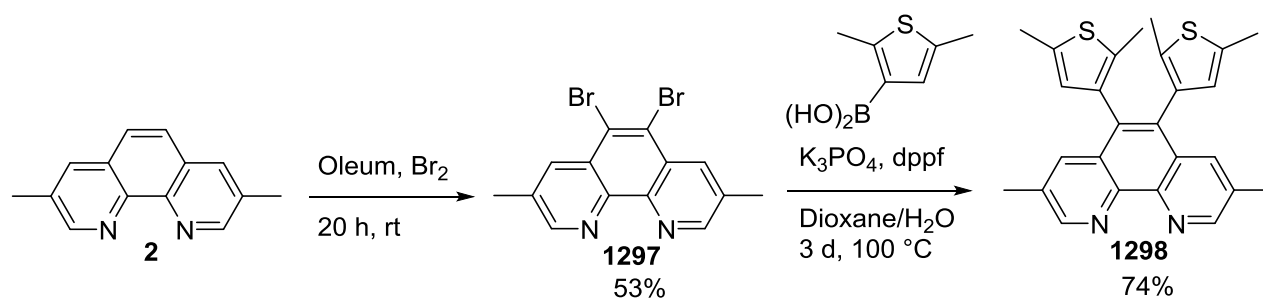
The functionalization of phen in positions 5 and 6 is realized by i) formation of the 5,6-diketone, ii) nitration of C₅, iii) bromination of C₅. As far as we can tell, the nitration of C₅ on phen_{(3,8)sub} has never been reported yet. The two other methods are however documented.

Karnahl et al.⁹⁴⁶ have succeeded to prepare **1289** described above by starting from **730**, with a classical protocol using potassium bromide, a mixture of concentrated H₂SO₄ and HNO₃ and reflux for 3 h. The authors have obtained the desired compound with 67% yield. This dione reacted with **914** in refluxing methanol to obtain the phenazine backbone with 91% yield (Scheme 278). On the **1289**, Ritter et al.¹¹²³ protected the phendione with 2-nitropropane, then performed a Suzuki reaction, deprotected the acetal to finally form the phenazine backbone (Scheme 278).



Scheme 278. Synthesis of **1289** and the corresponding phenazine derivatives **1292** and **1296**^{946,1123}

Mörtel et al.¹¹²¹ have performed a Suzuki reaction on the **730** to yield **738**. The subsequent bromination of the 5 and 6 position has failed and a polymerized compound is recovered. This means that the bromination reaction is not compatible with aromatic substituents placed in positions 3 and 8. On the other hand, **1297** can be prepared from **2** (obtained from a Doebner von Miller reaction and following a protocol described in literature²⁴¹) using oleum and Br₂. After the work-up and recrystallisation in chloroform, the compound is obtained with 53% yield.⁷⁶⁸ Then, a Suzuki reaction can be performed using (2,5-dimethylthiophen-3-yl)boronic acid, K₃PO₄ and dppf in a mixture of water and dioxane to yield **1298** (Scheme 279).



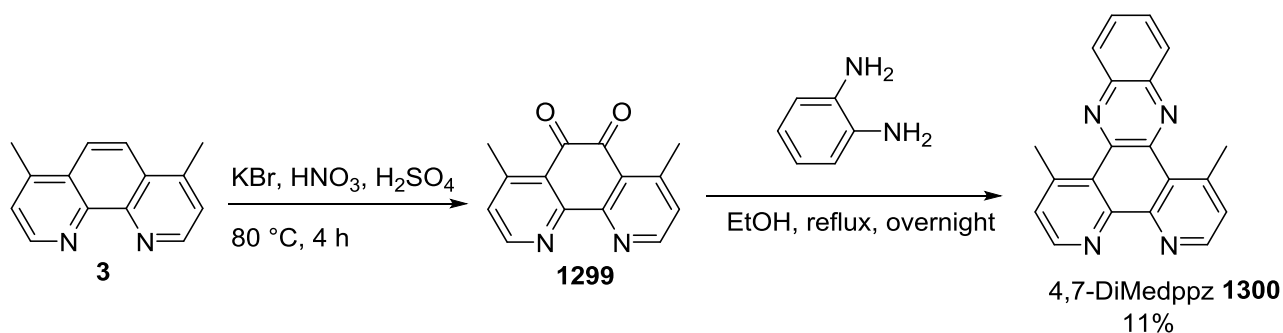
Scheme 279. Synthesis of **1297** followed by a Suzuki reaction as described by Mörtel et al.⁷⁶⁸

4.6. Synthetic methods for the construction of phen_{(4,5,6,7)sub}

Very few examples have been reported for the synthesis of phen_{(4,5,6,7)sub} by divergent methods. Unsurprisingly, it is not feasible at the moment to transform phen_{(5,6)sub} into phen_{(4,5,6,7)sub}. On the other hand, functionalizing C₅ and C₆ on phen_{(4,7)sub} can be done; there are however remarkably few examples.

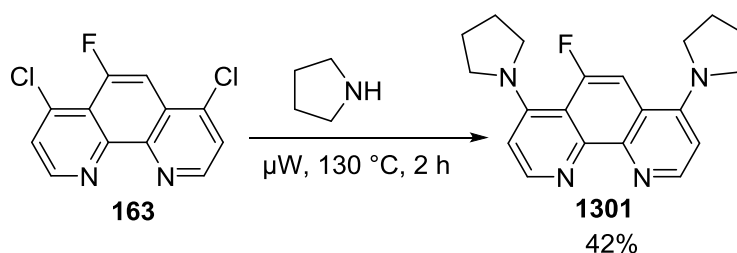
For instance, from **3**, the corresponding phendione **1299** is obtained using a mixture of HNO₃/H₂SO₄, KBr at 80 °C for 4 h. The latter is directly engaged in reaction with the *o*-phenylenediamine in refluxing EtOH overnight that leads to the ligand **1300** with 11% yield (Scheme 280).¹¹²⁴ Interestingly, Zheng et al.⁸⁶² mentioned that from **146** or **827**, it was not

possible to obtain the corresponding phendione when using their original oxidation method: potassium bromate and sulfuric acid at room temperature.



Scheme 280. Oxidation of **3** on the 5,6 positions

Finally, Nycz et al.²⁷¹ obtained **163** through convergent method and was successful in the aromatic nucleophilic substitution with pyrrolidine under microwaves conditions (Scheme 281).



Scheme 281. Aromatic nucleophilic substitution on phen_{(4,5,7)sub} **163**

5. Functionalization of phen one more than 4 different positions by divergent methods

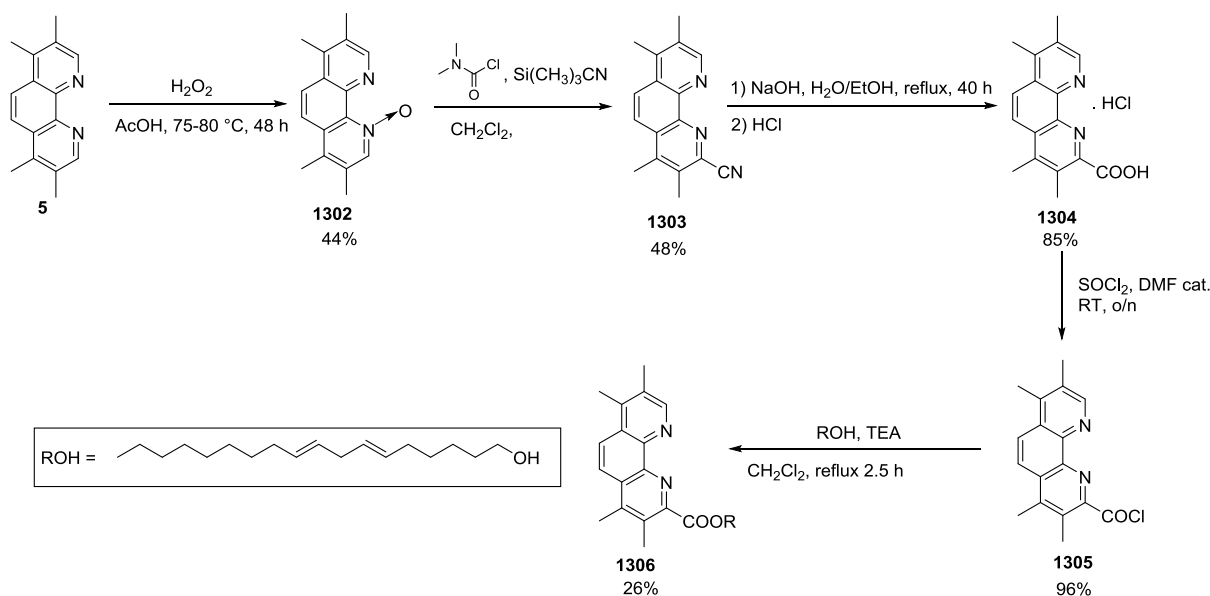
Functionalization of phen on six different positions or even in all positions is best achieved with the convergent strategy. It is challenging to do the same with the divergent strategy, but it is nevertheless feasible using methods which have been extensively described in the previous sections. The examples are scarce and will be presented below.

Importantly, we designate here by “multiply substituted phen_{sub}” or “polyfunctionalized phen_{sub}” phen derivatives with at least two non-symmetrical positions occupied by non-H substituents.

5.1. Appending a substituent in positions 2 and 9 on a poly-functionalized phen
(phen_{(3,4,7,8)sub}, phen_{(3,5,6,8)sub})

The functionalization of multiply substituted phen_{sub} in positions 2 and 9 relies on the same strategies than the functionalization of naked phen in positions 2 and 9: activation of the C2 position, organolithium chemistry and radical chemistry.

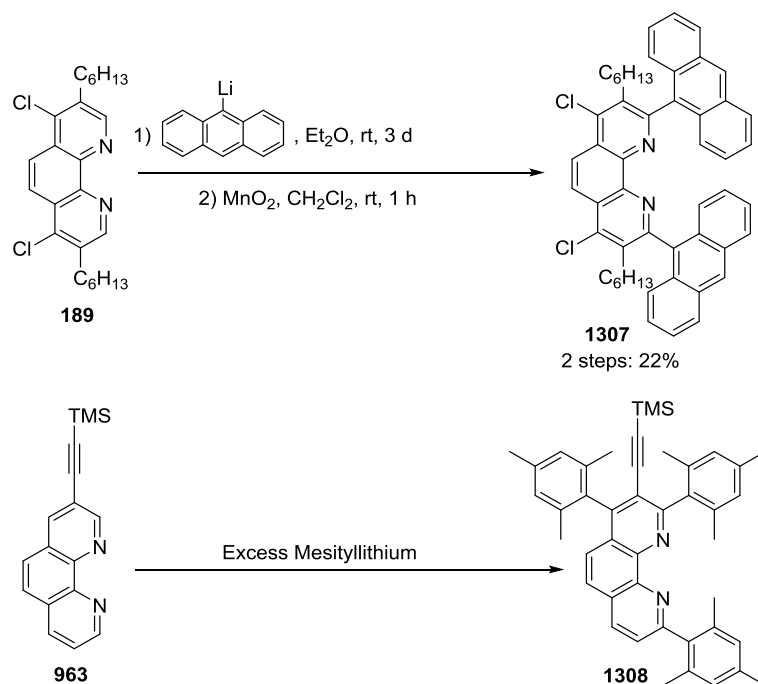
Activation of C₂: the most abundant examples concern the functionalization of **5** in positions 2 and 9 (where Me₄phen has been obtained by convergent methods). To begin with, the method developed by Corey to activate naked phen towards additions of nucleophiles in C₂ can be extended to Me₄Phen (Scheme 282).¹¹²⁵ The latter is first oxidized in presence of H₂O₂ and acetic acid in **1304**. The usual Reissert-Henze conditions do not work to convert **1302** into **1303** and have thus been optimized: dimethylcarbamoyl chloride and trimethylsilanecarbonitrile have been used instead of benzoylchloride (formation of a good leaving group on the N-oxide) and KCN. The resulting **1303** compound is obtained in 48% yield. As demonstrated before, the nitrile group can be hydrolyzed into the carboxylic acid derivative PX3. Esterification of **1304** via formation of the acyl chloride **1305** allows to prepare a phen_{(2,3,4,7,8)sub} **1306** with long C₁₈ unsaturated alkyl chains.



Scheme 282. Functionalization of **5** by a CN group in position 2 using the modified Reissert-Henze protocol.

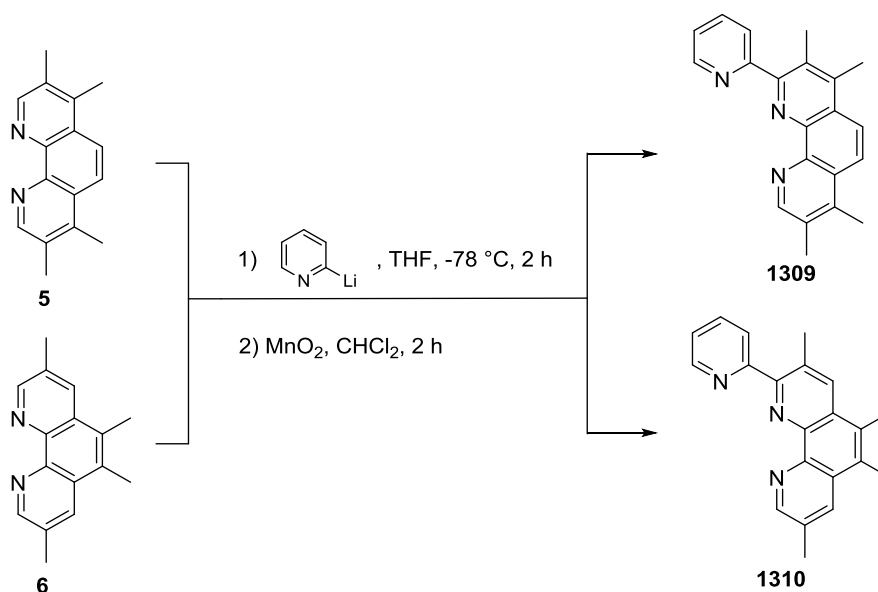
Nucleophilic addition of an organolithium reagent: organolithium reagents are fully compatible with Me4phen and have been often used to further functionalize the latter in positions 2 and 9. The protocols described before to functionalize naked phen in positions 2 and 9 can be applied directly.^{16,152,190} For example, Schmittel and co-workers have isolated **1307** from phen_{(3,4,7,8)sub} **189** (obtained *via* the convergent method) with anthracenyllithium, in two steps. It is noticeable that the addition of the bulky organolithium reagent on a **189** proceeded (albeit with a low overall yield) despite the significant steric bulk of linear hexyl chains tethered to positions 3 and 8. In addition, as remarked before, the chlorine atoms in positions 4 and 7 are compatible with anthracenyllithium and remain untouched (Scheme 283).

Interestingly, as observed before in the case of **1015** (Scheme 215), addition of excess organolithium reagent on phen_{(2,3)sub} **963** leads to traces of **1308** (Scheme 283).



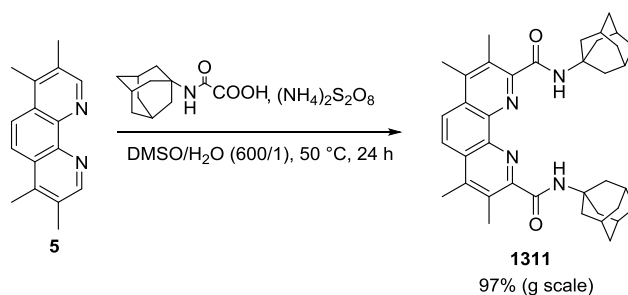
Scheme 283. Action of organolithium reagents on phen_{(3,4,7,8)sub}.

The action of organolithium reagents on methylated phen_{sub} is not dependent on the positions of the methyl groups. For example, phen_{(3,4,7,8)sub} **5** and phen_{(3,5,6,8)sub} **6** differ by the positions of two CH₃ groups and are efficiently converted into phen_{(2,3,4,7,8)sub} **1309** and phen_{(2,3,5,6,8)sub} **1310** (Scheme 284).¹⁵²



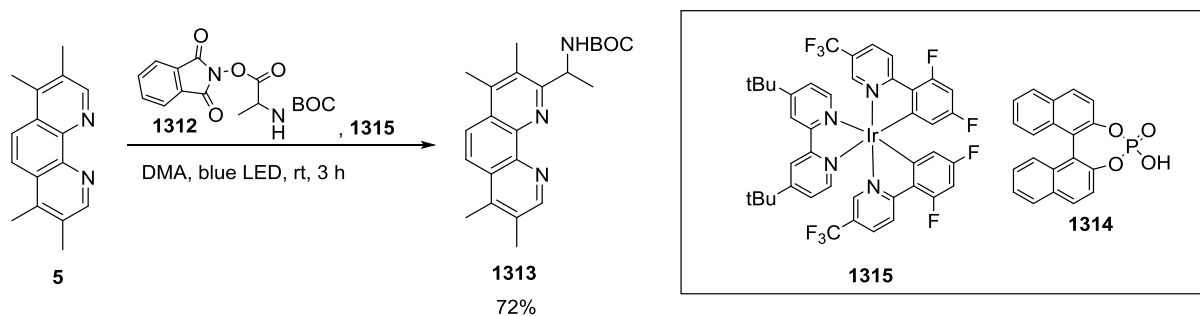
Scheme 284. Nucleophilic addition of 2-pyridinelithium on **5** or **6**

Nucleophilic radical addition: as presented before, organic radicals tend to perform nucleophilic attacks on C₂ and C₉ (and C₄ and C₇ when available) when the N[∧]N cavity is protonated. In many cases, radical precursors (e.g. formamide,⁷³⁴ oxamic acid,¹⁰¹⁷ Katritzky salts,^{64,1126,1127} alkyl oxalates)¹⁰²⁵ are first photochemically or thermally transformed in radicals. All cases where **2** or **3** have been functionalized by radicals are unsurprisingly working just as well with **5**, or sometimes even better,¹⁰¹⁷ possibly because methyl groups electronically enrich the aromatic cycle and favor the protonation of the N[∧]N cavity, a crucial step in all Minisci-like reactions (Scheme 285).



Scheme 285. Functionalization of Me₄phen with a nucleophilic carbamoyl radical generated from oxamic acid

α -aminoacids can be turned into original radical precursors as demonstrated by Shang, Fu and co-workers,¹¹²⁸ who developed a photochemical method leading to α -aminoalkyl phen derivative **1313**. Surprisingly, the reaction was tested only on **5**. The carboxylic function of α -aminoacids is first activated by formation of a phthalimide.¹¹²⁸ After optimization, the bulky phosphonic acid **1314** and the iridium complex Ir-cat were found to be the best acid co-reactant (protonation of **5**) and photocatalyst respectively. Upon excitation Single electron transfer from Ir-cat to N-(acyloxy)phthalimide **1312** leads to the α -aminoalkyl radical after decarboxylation. The latter attacks C₂ on protonated Me₄PhenH⁺, which eventually turns into the target compound **1313** (Scheme 286).



Scheme 286. Photo-induced decarboxylative α -aminoalkylation of **5**

Other methods to functionalize **3** which do not require activation of alkanes^{1129,1130} or bromoalkanes¹¹³¹ have been presented in section 3.3.1; again, those methods can be applied with no modification to the case of **5**.

Curiously, there is no report on the functionalization of $\text{phen}_{(2,3,4,7,8,9)\text{sub}}$ **8** at the level of the methyl groups in α of the chelating nitrogen atoms, despite the fact that they are likely to feature the same reactivity than the methyl groups of neocuproine **1**. Parasitic reactions involving the methyl groups appended in positions 4 and 7 could decrease the interest of such functionalization reactions.

5.2. Appending a substituent in positions 3 and 8 on a poly-functionalized $\text{phen}_{(2,4,5,7,9)\text{sub}}$

Accordingly, the functionalization of positions 3 and 8 of phen is challenging as demonstrated in the previous sections devoted to this endeavor. It is naturally even more difficult to achieve such functionalization on phen_{sub} species with available positions 3 and 8. Curiously, one $\text{phen}_{(2,3,4,7,8,9)\text{sub}}$ is commercially available (**1316**, Figure 38) and has been used as ligand to design aqueous sensors¹¹³², catalysts¹¹³³ and drugs¹⁰⁵³ but the synthesis of the latter is not reported, to the best of our knowledge.

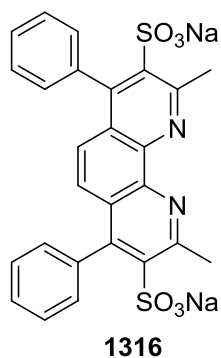
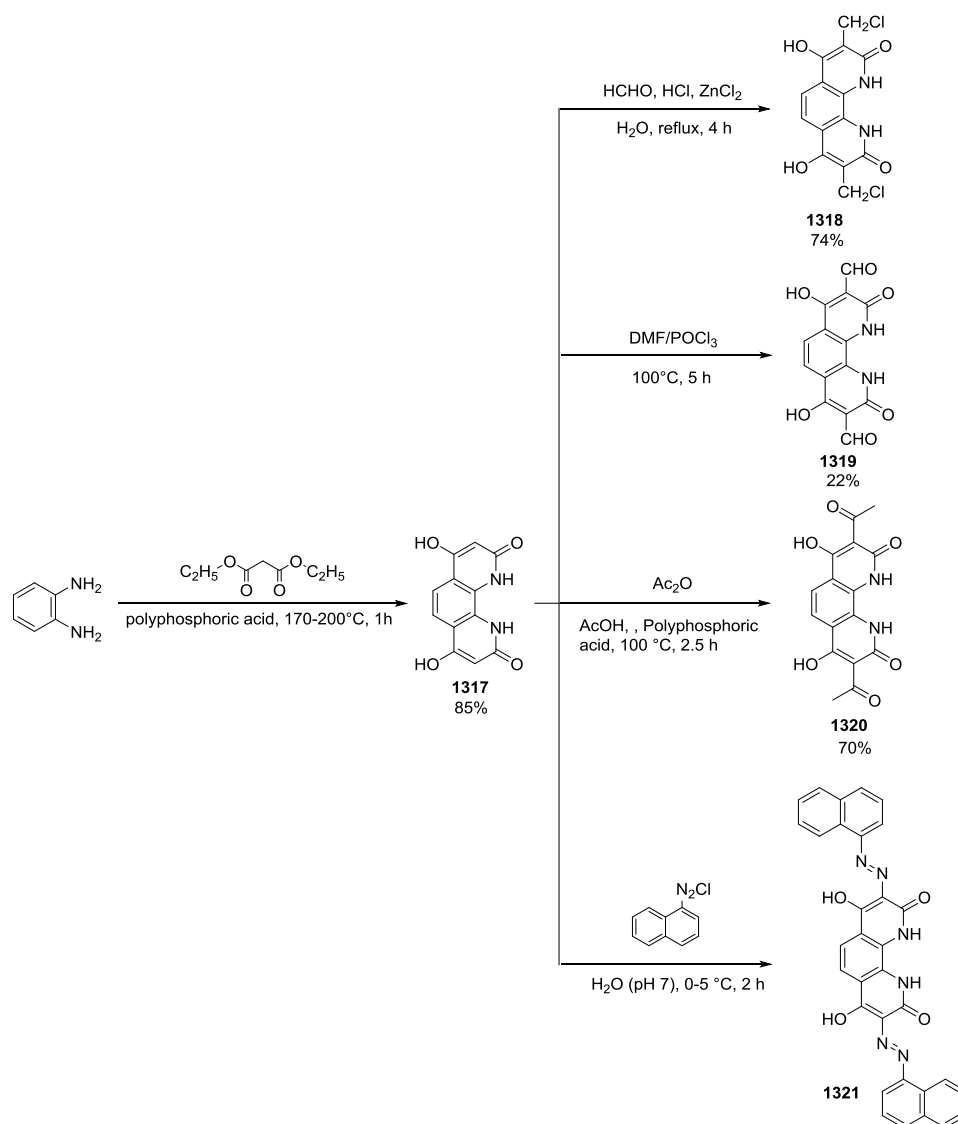


Figure 38. Structure of bathoneocuproine disulfonate, disodium salt (**1316**)

Although the final compounds are not phen_{sub} ligands *per se*, we wish to report the works of Patel et al.¹¹³⁴ which highlight the peculiar reactivity of positions 3 and 8 on the oxidized phen derivative **1317**. Indeed, the latter is obtained by convergent method by heating a mixture of orthophenylene diamine and diethylmalonate in polyphosphoric acid at high temperature (Scheme 287). The positions 3 and 8 of **1317** are particularly reactive and many different functionalization reactions can be envisioned as shown in Scheme 287.

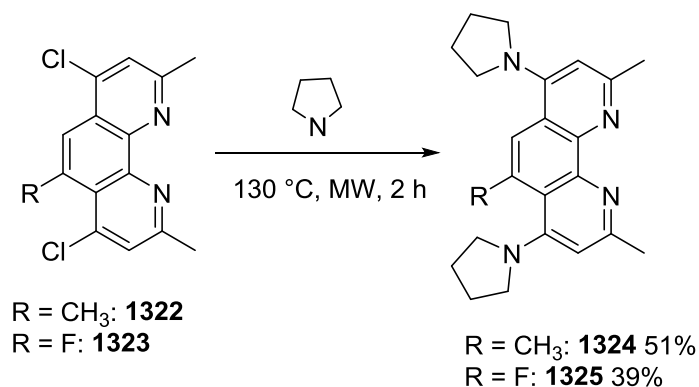


Scheme 287. Functionalization of **1317** in positions 3 and 8

Positions 3 and 8 have indeed a strong nucleophilic character, and can therefore react with numerous electrophiles such as formaldehyde (**1318**), the Vilsmeier reagent (**1319**), acetic anhydride (**1320**) to lead to interesting pro-phenanthroline building blocks. Reacting **1317** with diazonium salts affords diazo dyes for the textile industry (e.g. **1321**).¹¹³⁴ Unfortunately, those intriguing substrates were never re-aromatized.

5.3. Appending a substituent in positions 4 and 7 on a poly-functionalized phen ($phen_{(2,4,7,9)sub}$, $phen_{(3,4,7,8)sub}$)

There are not many different strategies to functionalize phen in positions 4 and 7 by divergent methods and this remains true for all kinds of $phen_{sub}$, and in particular in the case of multiply functionalized $phen_{sub}$ derivatives. Summarily, phen and $phen_{sub}$ bearing no substituent in positions 4 or 7 can be functionalized in those positions *via* Minisci-like radical additions. To the best of our knowledge, such reactions have not been yet reported for $phen_{(3,5,6,8)sub}$, $phen_{(2,5,6,9)sub}$ or $phen_{(2,3,8,9)sub}$. Alternatively, polyfunctionalized $phen_{sub}$ derivatives bearing chlorine atoms in positions 4 and 7 can be obtained by convergent methods and further functionalized as demonstrated in section 4. In this frame, $phen_{(2,4,5,7,9)sub}$ **1322** and **1323** were obtained by such methods and the reactivity of the chlorine atoms tethered to positions 4 and 7 has been exploited. Nucleophilic substitutions on both chlorinated positions by pyrrole was achieved under microwave irradiation (Scheme 288).

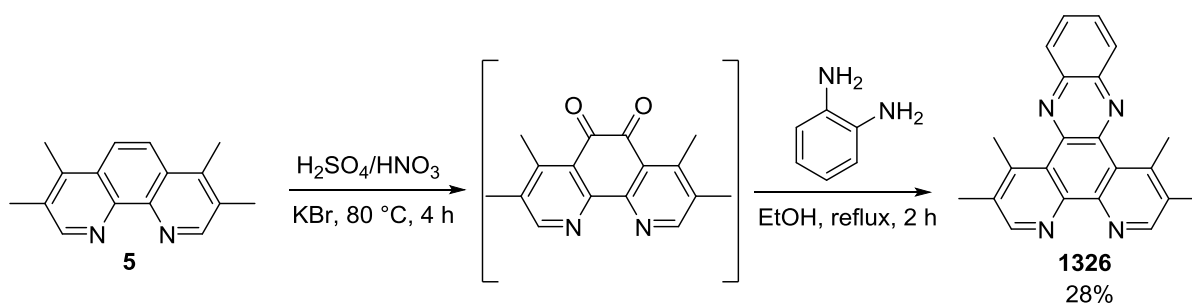


Scheme 288. Nucleophilic substitution on chlorinated derivatives **1322** and **1323**

As can be observed here, there are very few reports in the literature on the divergent functionalization in positions 4 and 7 of multiply substituted $phen_{sub}$ and this is probably due to the fact that convergent methods are preferred over divergent ones to reach such intricate structures.

5.4. Appending a substituent in positions 5 and 6 on a poly-functionalized phen (*phen*_(2,4,7,9), *phen*_(3,4,7,8))

Summarily, among the emblematic divergent methods used to functionalize positions 5 and 6 of phen, the oxidation of C₅-C₆ bond into a diketone is probably the most widespread. Thus, it is interesting to notice that it is possible to form the corresponding phendione from the 3,4,7,8-tetraMephen, that can further react with the orthophenylenediamine to obtain the dppz derivative **1326** with an overall yield of 28% (Scheme 289).¹¹²⁴



Scheme 289. Synthesis of dppz derivatives described by Oelerich et al.¹¹²⁴

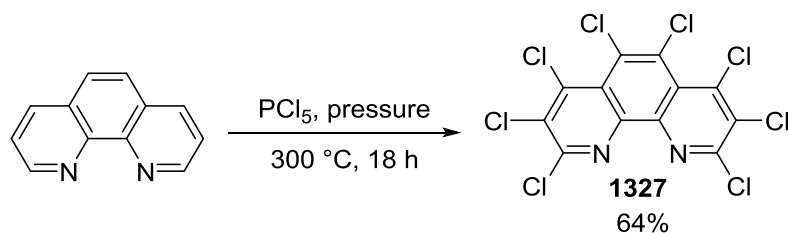
After carefully checking the literature, it appears that there is no other example of functionalization of multiply substituted phen_{sub} in position 5 or positions 5 and 6.

5.5. Functionalizing phen in all positions

As mentioned in the introduction, phen can potentially be functionalized in all eight positions. A few examples of such achievements can be found in the convergent method section, but only one in the present divergent method section, namely the perchlorination of phen.

2,3,4,5,6,7,8,9-octachloro-1,10-phenanthroline **1327** has been obtained by Titze et al.¹¹³⁵ via chlorination of phen with PCl₅ under pressure (300 °C, 18 h) with 64% yield (Scheme 290). However, this octa-chlorinated ligand showed weak coordination properties probably because

of a reduced basicity due to the eight electron-withdrawing Cl atoms. Only Cu(I) and Ag(I) ions successfully formed stable complexes while Fe, Mn, Ru, Ni, Zn and Cd failed.



Scheme 290. Polychlorination of phen to yield **1327** described by Titze et al.¹¹³⁵

6. Concluding remarks and perspectives

There is no need to elaborate on the fact that phen is a spectacularly versatile molecule with applications in a plethora of different domains. Throughout this review, we attempted to demonstrate that phen is very versatile in terms of synthesis too: each of the eight positions of phen can be functionalized using adequate, position-specific synthetic procedures, leading to extended polyfunctional molecular arrays.

First, it is possible to design phen precursors, which can be converted into phen after chemical treatment. This method is incredibly powerful to generate polyfunctional phen_{sub} when the phen precursors are cleverly designed. Those phen-precursors can be indeed heavily functionalized, and demand accordingly significant chemical engineering (which is the main issue of this strategy) until intramolecular cyclisation finally reveals the phen molecular skeleton, *converging* towards large polysubstituted phen-based arrays, hence the term “convergent method” to designate this synthetic strategy. The more heavily functionalized the precursors, the more impressive and rewarding the structure of the target phen_{sub}, but the design of the precursors therefore demands significant chemical engineering, namely time and chemicals, which is probably the main issue with this strategy.

Alternatively, functionalization of phen can be achieved by directly working on phen as starting material. We have qualified this approach as “divergent” because the molecular

structure grows *from* phen *towards* larger phen-based polyfunctional arrays. All positions on phen are not equal when considering their functionalization by divergent methods. The functionalization of phen in positions 2 and 9 is by far the most documented. C₂ and C₉ are strongly electrophilic and thus easily functionalized by nucleophiles. In addition, an impressive collection of very practical phen_{(2,9)sub} building blocks is readily available in a few steps from naked phen (or commercially available). Hence, a great number of phen_{(2,9)sub} is unsurprisingly involved in several fields, from anti-malarial drugs to molecular machines, because positions 2 and 9 are crucial to tune the affinity of phen for ions and because of the easy synthetic access to virtually any phen_{(2,9)sub} structure. Divergent functionalization of phen in positions 3, 4, 7 and 8 is much less documented. As a matter of fact, it would be virtually impossible without the assistance of pivotal synthons which are obtained by convergent methods. Finally, functionalizing positions 5 and 6 of phen is rather well documented and different strategies can be implemented.

In a sense, the convergent and divergent methods are complementary. Indeed, as the desired structure gets more and more complex (three, four or more substituents on phen, in different positions) the divergent strategy provides less and less alternatives, while the convergent strategy starts to be more and more adequate.

In a nutshell, the amount of possibilities is vertiginous (we have reported over 1000 molecular structures in this review and had to overlook many more for concision). This is certainly one of the reasons behind phen's popularity in fields as varied as anti-malarial drugs and chemical sensors.

On reading this work, one may think that the functionalization of phen in all possible positions has been extensively explored, and that there are virtually no more original synthetic procedures to determine. But this is actually far from true.

From the convergent synthesis point of view, in addition to the Skraup or Friedländer emblematic methods, there is a multitude of additional convergent strategies to prepare phen_{sub} molecules. This area is flourishing and the biggest issue has been to try and include them all in this review.

From the divergent synthesis point of view, great progresses are eagerly needed for phen functionalization. Generally speaking, functionalization of phen in positions 3 and 8 is much less documented than in all other positions, first because the position is less easy to modify on plain phen than positions 2,9 and 5,6; second, because there are many less commercially available pre-functionalized phen_{(3,8)sub} starting synthons. This has clearly hampered the development of functional phen_{(3,8)sub} molecules with interesting properties.

We have noted throughout the preparation of this manuscript that there are numerous “ghost synthons”, i.e. phen_{sub} molecules which are curiously missing. In Figure 39 are given examples of such structures. For example, 5-chloro-2,9-dihalogenated phen **1328-X** (X = Cl or Br) should be easily accessible applying Yamada’s protocol on 5-chlorophen **860**. This synthon could likely be selectively functionalized in positions 2, 9 and 5 since the reactivity of the C_{2,9}-Cl bond is expected to be very different from the reactivity of the C₅-Cl bond. Likewise, the synthesis of 2,9-dicarbaldehyde-4,7-dimethylphen **1329** has never been proposed. One may imagine that selective oxidation of the methyls in positions 2 and 9 of 2,4,7,9-tetramethylphen **7** would be a challenging endeavour. On the other hand, the 2,4,7,9-tetracarbaldehyde phen **1330** should be in principle accessible and could lead to impressive extended structure in only a few easy synthetic steps from **7**. 3,8-dicarbaldehyde-phen **1331** has barely been reported too (only in patents not written in English), although the synthesis of parent aldehyde-bearing phen has been reported in all other positions.

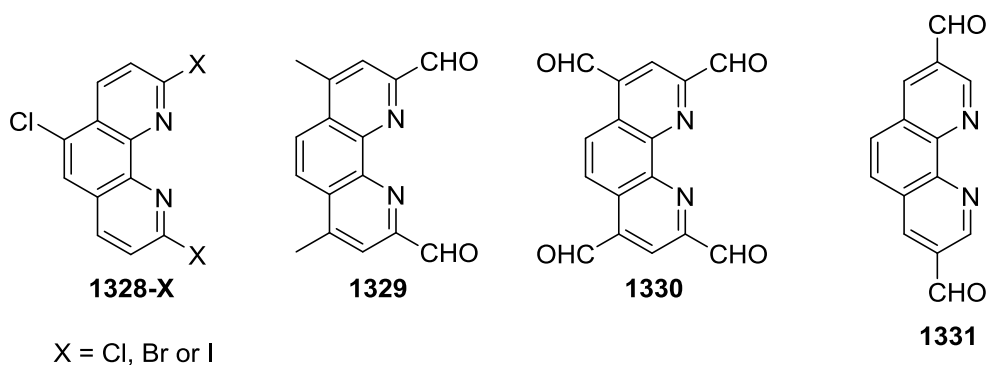


Figure 39. Examples of phen_{sub} whose structure has never been reported.

A number of “ghost reactions”, i.e. reactions which have never been implemented with a number of synthons, can be mentioned here too. For example, no Pd cross-coupling reaction on 3-chlorophen or 3,8-dichlorophen has ever been reported in the literature in English, but in a few patents.¹¹³⁶ This is intriguing since such coupling reactions have been extensively documented in all other positions. Clearly, the oxidative addition of phen on Pd is more difficult because the C_{3,8}-Cl bond is stronger than, for instance, the C_{3,8}-Br bond. Likewise, one is surprised to see that 4,7-dicyano-phen **821** has barely been used to generate extended structures, whereas the reactivity of parent 2,9-dicyano-phen **567** has been extensively explored..

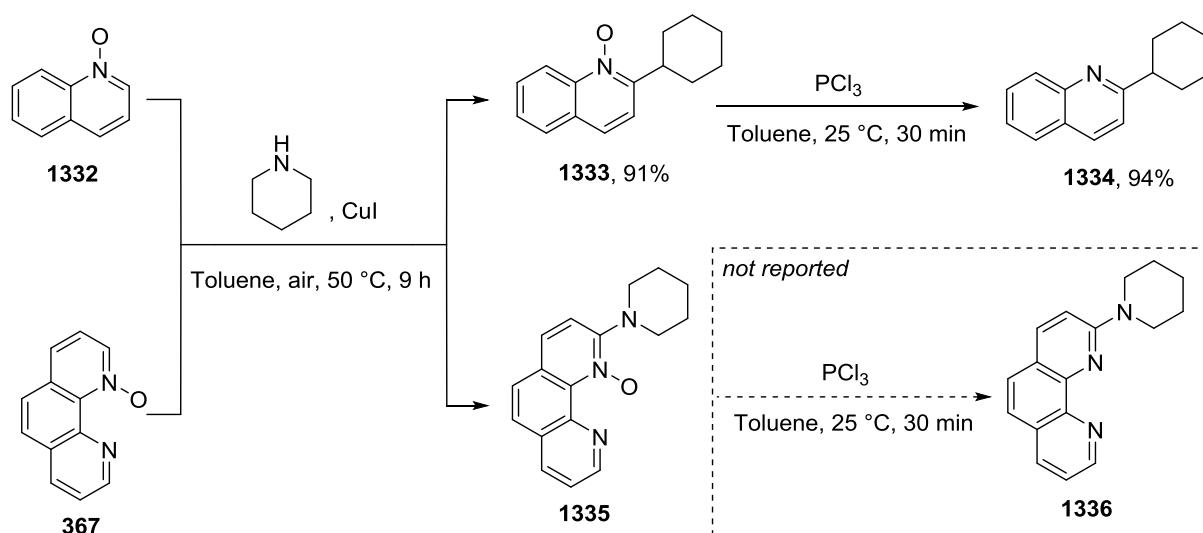
Another almost unexplored field of phen chemistry is the exploitation of the double bond character of the C₅-C₆ bond. Indeed, the $d_{C_5-C_6}$ is significantly shorter than $d_{C_2-C_3}$ or $d_{C_4-C_5}$. Accordingly, those structural considerations do not prove that C₅-C₆ will show the reactivity of an olefin. Yet 5-nitro-2,9-dimethyl-phen **1143** has “sufficient nitroalkene character”²⁰⁵ to undergo the Barton and Zard synthesis of fused pyroles (Scheme 241). We look forward to the implementation of other reactions involving the special character of C₅-C₆ (e.g. Diels-Alder reactions) which could open a new chapter in divergent phen functionalization in positions 5 and 6.

Other reactions have curiously not been documented for no obvious reason. For example, 2,9-dichloro-5-nitrophen **1155** or 2,9-dibromo-5-nitrophen **1156** were never involved in Pd-catalyzed cross-couplings, to the best of our knowledge, although such couplings have been performed on parent 2,9-dichloro and 2,9-dibromo phen **396** and **405**, respectively. The presence of the nitro group in position 5 should not be detrimental to the Pd insertion between C₂/C₉ and the Cl or Br atoms. The envisioned reactions show great potential, in particular, synthon 2,9-dichloro-5-nitrophen **1155** paves the way towards polyfunctional phen_{(2,5,9)sub} ligands with great versatility for the implementation of various different functionalities in positions 2, 5 and 9. Likewise, we eagerly look forward the implementation of Pd cross-coupling reactions involving heavily substituted **1327**, which could lead to impressive fully substituted phen_{(2,3,4,5,6,7,8,9)sub} molecules. The various reactivities of the C_n-Cl bonds (n = 2 to 9) would be particularly interesting to explore, and add precious pieces of information to delineate a reactivity trend associated to the different positions on phen.

Another whole area is apparently missing in the realm of phen decoration: to the best of our knowledge, C-H activation has never been used to functionalize phen in any position. This is surprising since other metal assisted catalytic processes (such as Stille, Suzuki couplings or copper-catalysed click reactions) have been amply reported in all positions of halogenated-functionalized phen. But the coordinating ability of phen is nevertheless a point of concern.^{1137,1138} Considering a C-H activation metal catalyst ML_n, the insertion of M between C_{phen} and H_{phen} (in any position) is probably less favourable than direct coordination of M by the N[∧]N chelate of phen. This issue was elegantly circumvented by You, Lan and co-workers who proposed a Pd-catalyzed direct arylation of phen in positions 3 and 8, using intermediate **401** instead of phen.⁶⁵⁷ This approach is shrewd because the annelated N[∧]N cavity is no longer interfering with Pd coordination. In addition, this is one of the very rare divergent

methods that can be used to get a phen_{(3,8)sub} molecule. We wish to highlight that this reaction, to the best of our knowledge, has never been further exploited despite its high potential impact. The fact that phen is a Lewis base is problematic in a number of cases, as demonstrated already in the case of copper-assisted Huisgen 1,3-dipolar addition of alkynes on azides, where coordination of the copper(I) ions occurred during the synthesis.⁵⁷⁴

To answer these problematics, and many more related to the basic nature of phenanthroline, we believe that the development of a protecting group for the chelate of phen (i.e. the implementation of a reaction where the N[∧]N cavity is willingly and reversibly blocked) would be very useful. There are indications in the literature that such a reaction is not difficult to envisage. For example, formation of the N-oxide (e.g. in presence of H₂O₂) significantly curbs the ability of phen to coordinate soft ions. Treatment of the N-oxide by PCl₃ seems to be a promising route to recover the N[∧]N chelate.¹¹³⁹ This strategy has been used to implement the copper(I)-catalyzed amination of quinolines (from **1332** to **1334**) and derivatives thereof, including phenanthroline (**1335**, Scheme 291). Frustratingly, the deprotection (from **1335** to **1336**) has however not been reported.



Scheme 291. Example of possible protection-deprotection of phen chelate.

It is worth reminding too the nice, yet under-employed, use of N-benzyl phenanthroline derivative **1013** as versatile platform for the straightforward polyfunctionalization of phen in positions 2, 4 and 9 (Scheme 214).¹⁰¹⁸ The capacity of this synthon to bind metals is significantly decreased because of the steric hindrance of the benzyl group. A simple HBr treatment seems sufficient to remove the benzyl group and lead to the reduced phen **1014**, which could in principle be re-oxidized into phen. This back-and-forth shift between two structures, involving a temporary blockage of the N $\widehat{\text{N}}$ cavity of phen, qualifies as a protection reaction.

To conclude, the aim of this review was of course to set a reliable picture of the state of the art for the synthesis of polysubstituted phen, and provide all synthetic and coordination chemists with a toolbox to design at-will, tailored-to-one's-needs phen_{sub} ligands. To facilitate the handling of this review, the most relevant and crucial phen_{sub} synthons are gathered in Chart 1.

Knowing that virtually all chemists are necessarily concerned by phenanthroline since this ligand appears in almost all the fields in chemistry, our ultimate goal, and our highest hope, is to inspire them all to make phen's chemistry even more flourishing and pursue the story with new fascinating chapters.

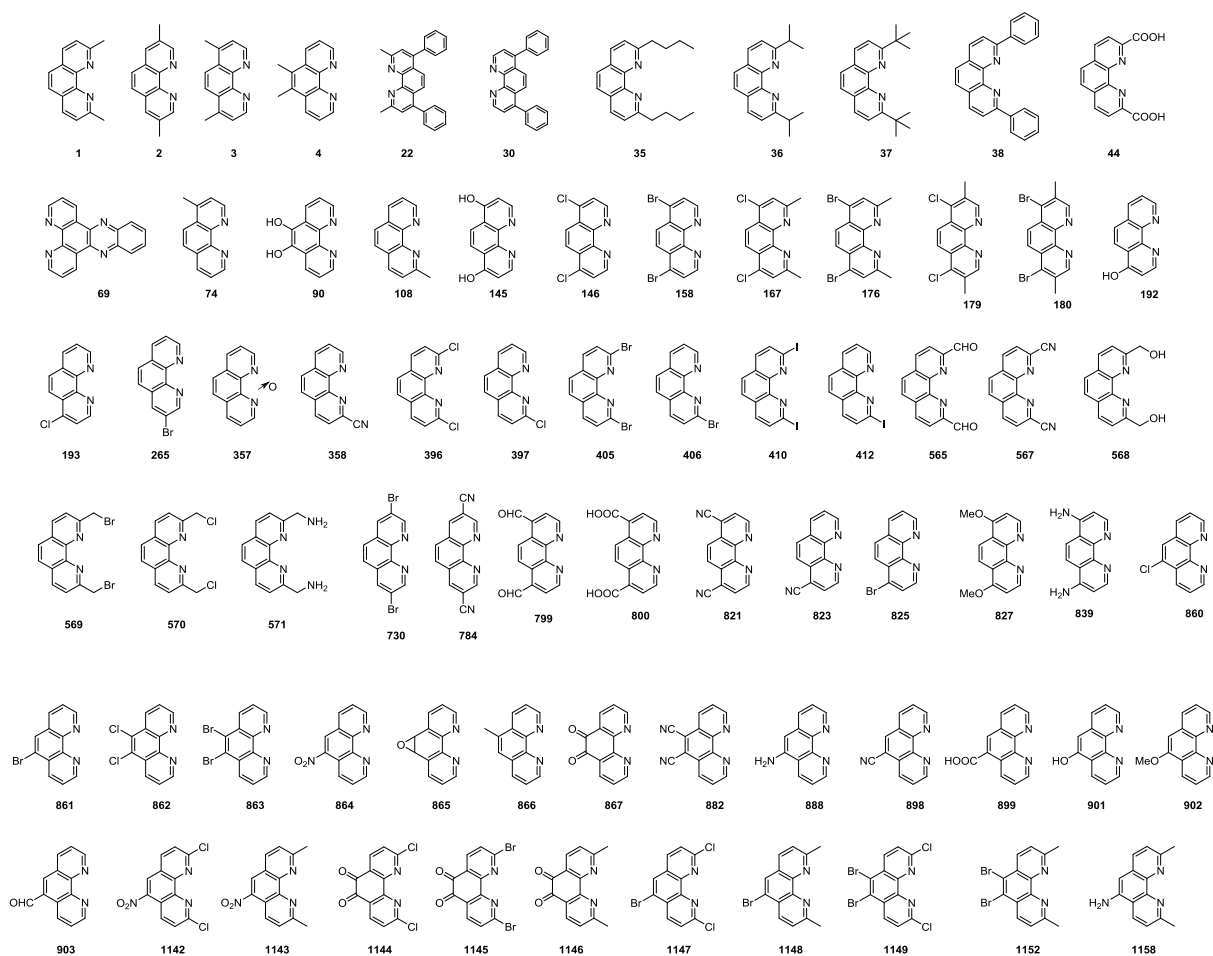


Chart 1. Useful synthons presented throughout this review.

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Notes

The authors declare no competing financial interest.

Biographies

Dr. Clémence Queffélec has received her Ph.D. degree in Organic Chemistry in 2007. After spending 18 months of postdoctoral research at the Department of Chemistry, TCU, Fort Worth, Texas with Pr. J-L within the field of phosphorus chemistry, she worked for one year

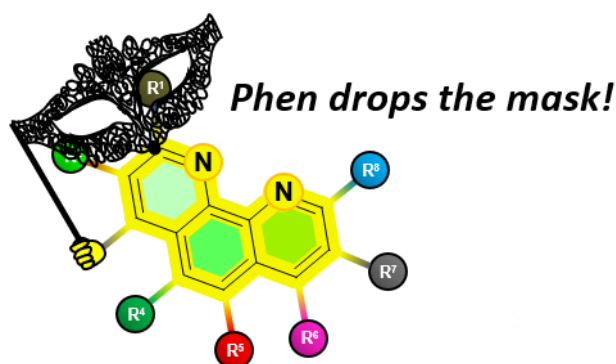
at the University of Paris XI on the enantioselective intramolecular hydroamination catalyzed by rare-earth metal complexes. In 2010, she was appointed Assistant Professor at the University of Nantes, joining the CEISAM laboratory. She has been working on phosphonate-based organic–inorganic hybrid materials applied to biotechnologies and supported catalysis. Since 2014, her current research interests focus on the use of plasmonically active nanoparticles as catalysts for organophosphate degradation and catalysis and she is developing phenanthroline based-catalysts for those plasmonically-catalysis studies.

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Dr. Yann Pellegrin has received his Ph.D. degree in coordination chemistry in 2004. After a three-year long postdoctoral fellowship in the National Centre for Sensor Research (Dublin City University) with Pr. Robert J. Forster and Pr. Tia E. Keyes in the field of luminescent probes for biological media, he was appointed CNRS research associate in CEISAM at Nantes University, where he has been working on the elaboration of dye sensitized solar cells and artificial photosystems for solar fuels generation. He has started developing original

copper(I)-phenanthroline copper(I) complexes and is now exploring in particular the design of new phenanthroline ligands to implement innovative photochemistry with related copper complexes. He has co-authored more than 100 articles in peer-review academic journals, 25% of them on phenanthroline functionalization.

Table of Content Graphical Abstract



Text for TOC: All synthetic strategies to reach functionalized 1,10-phenanthrolines

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