RECENT ADVANCES IN THE CHEMISTRY OF 1,10-PHENANTHROLINES AND THEIR METAL COMPLEX DERIVATIVES: SYNTHESIS AND PROMISING APPLICATIONS IN MEDICINE, TECHNOLOGY, AND CATALYSIS

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Abstract. *In consideration of the various structural and chemical properties of 1,10-phenanthrolines (o-phens) and their relevance to current research, this book chapter is devoted to the recent advances in the chemistry of o-phens, as well as their functional complexes, including applications in analytical, synthesis, and catalytic chemistry, and transformations for the development of molecular architectures as potential pharmacophores, fluorophores, and chromophores. The literature from 2007 onwards is highlighted.*

Contents

1. Introduction

Phenanthrolines (phens) are diazaphenanthrene analogs - polycyclic aromatic hydrocarbons present in sterols, sex hormones, cardiac glycosides, bile acids, and morphine alkaloids.[1] Among nitrogen heterocycles, phens and their derivatives represent an important class of organic molecules that have attracted considerable interest from both synthetic and medicinal chemists, due to the presence of the phen ring system as a structural pattern in several natural biologically important products, especially alkaloids.

A wide range of biological and physiological activities are displayed by phen derivatives; thus, the synthesis of new compounds containing this core is currently an interesting research proposal. In parallel with the growing interest in the synthesis of new phen derivatives to provide biologically active molecules, the *o*-phen deserves special interest, particularly as a heterocyclic moiety, since in its skeleton the arrangement of the atoms is ideal for chelation of various metal cations, including lanthanide ions.

Phens can also be prepared from phenylenediamines or aminoquinolines. The literature shows that the formation of two pyridine rings from derivatives of *m*-phenylenediamines may proceed in two possible ways to give either a 1,7-phenanthroline or a benzodipyridine. It is also known that in the formation of tricyclic compounds from *m*-phenylenediamine or quinoline derivatives, the angular structure is obtained in preference to the linear one when both are possible,[2-9] although some studies have shown the formation of isomer linear structures in larger quantities.[10]

The *o*-phen nucleus can be built from *o*-phenylenediamines[9,11] or aminoquinolines.[12] The traditional synthesis of *o*-phen derivatives occurs by double cyclization of *o*-phenylenediamines, using glycerol and sulfuric acid in the presence of an oxidizing agent (Skraup Reaction). Modifications and variations of these reactions have been done successfully.[11,13] In general, tricyclic compounds have been synthesized at good to excellent yields from low cost, easily available commercial reagents, using simple and convenient procedures.

2. 1,10-Phenanthrolines and derivatives: versatile building blocks

O-Phens haves attracted special interest from researchers due to their various structural and chemical properties; for example, rigidity, planarity, aromaticity, basicity, and chelating capability,[14] which makes them versatile starting materials in the area of materials science and in many fields of chemistry; for example, analytical, organic, inorganic, bioorganic, supramolecular coordination, and catalysis chemistry, as well as in the synthesis of photoactive molecules and as a versatile electron transfer reagent.[15,16]

O-Phens serve as versatile building blocks for the construction of linear or macrocyclic oligophenanthrolines.[17,18] Copper(I) complexes of oligophenanthroline ligands have been exploited for the preparation of [2]catenanes (containing one Cu(I) cation), Trefoil Knots (containing two Cu(I) cations), and Solomon Links (containing three Cu(I) cations).[19]

In the context of coordination chemistry, the generation of new molecular architectures is driven by the continued interest in researching their chemical and biological properties. The number of studies of the interactions of heterocyclic ligands with metal ions is growing. In this context, systems containing *o*-phen ligands (Figure 1) as key components are emerging as luminescent sensors for the efficient detection of metal ions.[15,20-23]
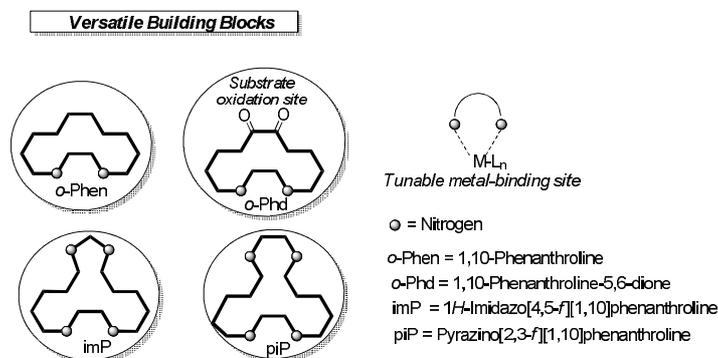

Figure 1. Representation of the chemical backbone of versatile building blocks.

3. Applications of 1,10-phenanthroline-based materials

Due to its superb ability to coordinate many metal ions, o-phen and its derivatives are frequently used in many processes involving metal complexes, in which they can be featured in many roles; for example, as ligands for catalysis,[24] or as stabilizing agents for nanoparticle synthesis.[25] O-Phens have been used as important heterocyclic ligands for a large number of metal complexes that play an important role in a variety of important technological and medicinal applications; for example, promising applications in the field of electroluminescent materials,[2,26-28] organic light-emitting devices (OLED),[29] organic semiconductors,[30] or as chemical nucleases and therapeutic agents, due to their ability to bind or interact with the DNA biomacromolecule.[14,22,31,32]

3.1. Metal complex derivatives: biological activity

A prominent area of research in coordination chemistry is the development of metal complexes that can act as artificial nucleases. There is a vast amount of literature on numerous bioactive complexes, and the number of studies on the interactions of heterocyclic ligands with metal ions demonstrating important chemical and biological properties has been growing. In particular, investigation of the interactions between metal complexes derived from o-phen, as well as derivatives of modified o-phen moieties, and DNA is an area of great interest, due to the high selectivity that o-phen compounds have demonstrated at the intercalation sites of the DNA molecule.[17] The complexes of metals with o-phens may be stabilized in DNA linked through a series of weak interactions (e.g. π-stacking) associated with intercalation between aromatic heterocyclic base pairs, hydrogen bonds, van der Waals interactions, and groups with hydrophobic effects.

Overall, synthetic DNA-cleaving reagents operate using one of two distinct mechanisms: (i) oxidative scission of deoxyribose residues through redox chemistry;[33] or (ii) hydrolysis of the phosphodiester sugar backbone.[34] The most classical example of oxidative DNA-cleavage activity is demonstrated by the Cu(II)-o-phenanthroline system, which has been utilized as a footprinting reagent for the evaluation of protein-DNA interactions, and also as a probe for DNA and RNA secondary structures.[35-40]

Recently, it has been discovered by Hernández-Gil et al. that quantum dots (QDs) cooperate and synergize with the Cu(II)-1,10-phenanthroline system for DNA cleavage, providing both the first example of cooperative DNA cleavage between inorganic nanoparticles (INPs), a small molecule-based synthetic metallonuclease, and a potentially new approach to developing more efficient DNA-cleaving systems.[41]

DNA-targeting Cu(II) reagents have emerged as suitable drug candidates, due to the clinical success of bleomycin, which is a copper-activated natural chemotherapeutic drug (Figure 2).
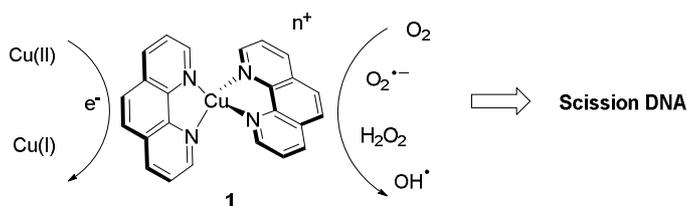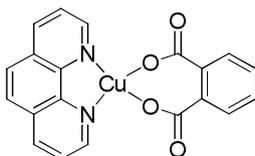

Figure 2. Generation of reactive oxygen species and DNA scission by complex [Cu(o-phen)$_2$]$^{2+}$ **1**.[31]

This agent and the synthetic chemical nuclease Cu(II)bis-1,10-phenanthroline (**1**) represent important templates for inorganic drug design, due to their ability to initiate free radical DNA scission.[31] In this intensively investigated system, [Cu(*o*-phen)$_2$]$^+$ is generated in the presence of a reducing agent and molecular oxygen to afford activated oxygen species for DNA cleavage, whereas the intercalation of *o*-phen into the DNA minor groove allows for DNA targeting.
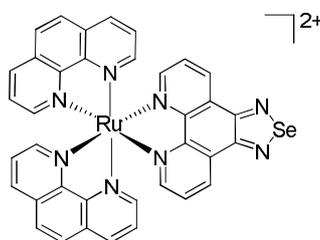
Kellett et al. reported the synthesis and characterization of a square-planar copper(II) complex incorporating the dicarboxylate *o*-phthalate and 1,10-phenanthroline ligands, [Cu(ph)(*o*-phen)].2H$_2$O (ph=*o*-phthalate) **2** (Figure 3). Compared to the metal-free *N,N'*-ligands, the *o*-phen complex displayed powerful, broad-spectrum activity against all the cancer lines evaluated-human-derived breast (MCF-7), prostate (DU145), colon (HT29), and intrinsically cisplatin-resistant ovarian (SK-OV-3) cancer cells-and the ability to cleave DNA through the generation of free radicals.[31]

[Cu(ph)(phen)].2H$_2$O **2**

Figure 3. Molecular structure of a square-planar copper(II) complex [Cu(ph)(*o*-phen)].2H$_2$O **2**.[31]

O-Phens serve as the scaffold for several potent stabilizers of DNA G-quadruplexes.[42,43] Recently, Li et al. described the synthesis and structural characterization of a Ru(II)-selenium complex [Ru(phen)$_2$L](ClO$_4$)$_2$ (phen=1, 10-phenanthroline, L=1,10-phenanthrolineselenazole) **3** (Figure 4). The interaction between human telomeric G-quadruplex DNA (HTG21) and the new compound was studied by emission spectra, visual detection assay, circular dichroism (CD) spectroscopy, and fluorescence resonance energy transfer (FRET) melting assay. The results show that the complex interacts with human telomeric G-quadruplex DNA, which is visually detected. Moreover, the Ru(II)-selenium complex exhibited good inhibitory activity for telomerase and cancer cells. The results suggest that the Ru-complex may be a potential telomerase inhibitor for cancer chemotherapy.[22]

Ru(phen)$_2$L](ClO$_4$)$_2$ **3**
Potential anticancer drug

Figure 4. The synthetic route of [Ru(phen)$_2$(phenSe)](ClO$_4$)$_2$ **3**.[22]

The interaction of the ruthenium complex $[Ru(phen)_2(mitatp)]^{2+}$ (phen=1,10-phenanthroline, mitatp=5-methoxy-isatino[1,2-b]-1,4,8,9-tetraazatriphenylene) with DNA was demonstrated by Yua et al.[44] Their studies indicate that $[Ru(phen)_2(mitatp)]^{2+}$ can efficiently photocleave pBR322 DNA under irradiation with visible light, and that the oxygen singlet $^1O_2$ was proven to be a reactive species in the photocleavage process. Cytotoxicity has also been evaluated using the MTT method-$[Ru(phen)_2(mitatp)]^{2+}$ has shown prominent anticancer activity against various cancer cells. Live cell imaging studies and flow cytometric analysis demonstrate that the complex could cross cell membrane, thus accumulating in the nucleus and inducing cell death by induction of G0/G1 cell cycle arrest and apoptosis.[44]

According to Thomas et al., in the search for new biological imaging agents, metal coordination compounds that are able to emit from the triplet metal-to-ligand charge-transfer (MLCT) state offer many advantages as luminescent probes of DNA structure. However, poor cellular uptake restricts their use in live cells. In view of this, these authors explored the potential of two dinuclear ruthenium(II) systems (**4** and **5)** as cellular DNA stains (Figure 5).[45] This study described the successful application of a dinuclear Ru(II) polypyridyl 'light switch' complex as a multifunctional biological imaging agent staining the DNA of eukaryotic and prokaryotic cells for both luminescence and transition electron microscopy. This MLCT 'light switch' complex directly images nuclear DNA of living cells without requiring prior membrane permeabilization. According to this study, despite the hydrophilicity of the molecule, it is taken up by live cells via a structure-specific and temperature-dependent non-endocytic mechanism. For the authors, the most fascinating attribute of $[(phen)_2Ru(tpphz)Ru(phen)_2]^{4+}$ complex **4** as a new imaging tool is the existence in DNA binding of multiple emission peaks, which suggests that this complex may find future application as an *in cellulo* DNA structural probe, specifically for quadruplex DNA.[45]
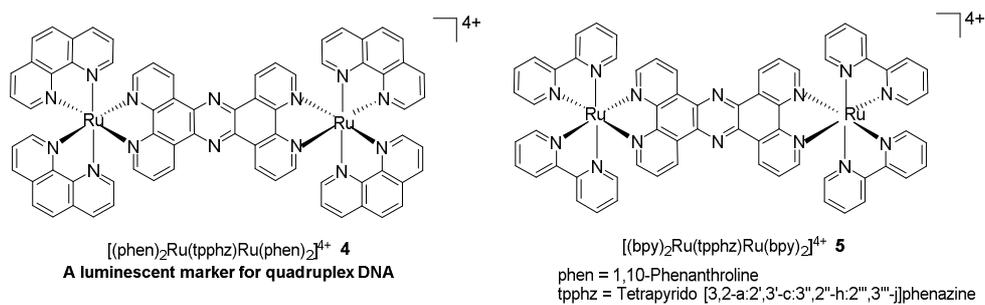

$[(phen)_2Ru(tpphz)Ru(phen)_2]^{4+}$ **4**
A luminescent marker for quadruplex DNA

$[(bpy)_2Ru(tpphz)Ru(bpy)_2]^{4+}$ **5**
phen = 1,10-Phenanthroline
tpphz = Tetrapyrido [3,2-a:2',3'-c:3",2"-h:2''',3'''-j]phenazine

Figure 5. Molecular structures of dinuclear Ru(II) tpphz complexes.[45]

Over recent decades, water-soluble conjugated polymers (CPs) have gained increasing attention as optical platforms for sensitive detection of biomacromolecules (DNA, protein, and cell) due to the amplification of fluorescent signals.[46] Simple, quick, and sensitive technologies for detecting nucleic acid modifications have important applications in genetic analysis, clinical diagnosis, and molecular biology. Because genetic modifications such as single nucleotide polymorphisms (SNP), DNA methylation, and other lesions can serve as hallmarks of human disease, interest in such methods has increased in recent years. For the optical detection of the DNA targets, researchers have extensively investigated anionic and cationic CPs as optical transducers in highly sensitive biosensors, due to their unique signal amplification properties.[47]

Chen et al. prepared a streptavidin sensor based on water-soluble anionic CP as sensitive material. In the experiments, a biotinylated Re(I) complex, [Re(N-N)(CO)$_3$ (py-CH$_2$-NH-biotin)](PF$_6$) [N-N=2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline; py-CH$_2$-NH-biotin=N-[(4-pyridyl) methyl] biotinamide] (Re-Biotin) **6** (Figure 6) was used as a quencher tether ligand (QTL) probe. The study demonstrates that in both non-buffer systems and various buffer systems, streptavidin sensor and avidin sensor mechanisms using Re-Biotin as the QTL probe based on water-soluble CP are the same and stable. Transition metal complex QTL probes have significant potential application in the design of biosensors.[48]
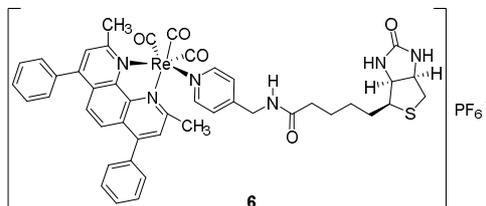

Figure 6. Chemical structure of Re-Biotin **6**.[48]

Gan et al. demonstrated that an imidazo-phenanthroline-containing ruthenium(II) complex [Ru(bpy)$_2$(mbpibH2)]$^{2+}$ (bpy=2,20-bipyridine, mbpibH2=1,3-bis([1,10]phenanthroline[5,6-d]imidazol-2-yl)benzene) **7** (Figure 7) with a free bi-dentate coordination site can bind DNA through groove binding and/or non-classical intercalation modes. The results from this study provided an effective method for the fabrication and tuning of a DNA-based solid luminescence film, using Ru(II) complexes as DNA-concentrating and signal-sensing agents.[49]

Figure 7. Representation of the binding of the complex [Ru(bpy)$_2$(mbpibH2)]$^{2+}$ **7** with DNA.[49]

3.2. Conjugated systems: structure and photophysical properties of imidazo-phenanthrolines

Aryl-imidazo-phenanthrolines have been actively investigated from a materials science perspective, due to their strong optoelectronic responses. These compounds have played an important role in medicinal chemistry, with applications as ligands and in the synthesis of metal complexes, and also in the formation of

large building blocks for the synthesis of sensors, probes, or new therapeutic agents, due to their ability to bind or interact with the structure of the DNA molecule.[49] The interesting photophysical properties of compounds such as arylthienyl-imidazo-phenanthrolines can be attributed to the presence in their molecules of different chromophores: imidazole, phenanthroline, and the functionalized arylthienyl systems.[50,51]

Batista et al. described the synthesis and structural characterization of hyperpolarizable chromophores **8-12** based on functionalized thiophene donors and an imidazo-phenanthroline acceptor moiety (Figure 8).[50] Their approach to the design of new π-conjugated systems for several potential optical applications is based on the use of electron-rich five-membered heteroaromatics, such as thiophenes and imidazoles, in the conjugation pathway, combined with electron-deficient heterocycles such as *o*-phenanthroline, which also act as acceptor groups due to the electron density deficiency in the ring's C atoms. Furthermore, the planarity and the extension of the conjugation of the phenanthroline moiety with imidazole and oligothienyl units leads to an increase in the overall conjugation. Additionally, for the structural characteristics described above, these π-conjugated systems also exhibit high thermal stabilities, which make them interesting for several applications in materials chemistry. The authors reported the synthesis of chromophores with an (oligo)thienyl π-conjugated system attached to an imidazo-phenanthroline moiety. The donor/acceptor π-conjugated phenanthrolines and bis-phenanthroline displayed solvatochromic behavior with nonlinear optical properties and thermal stability.[50]
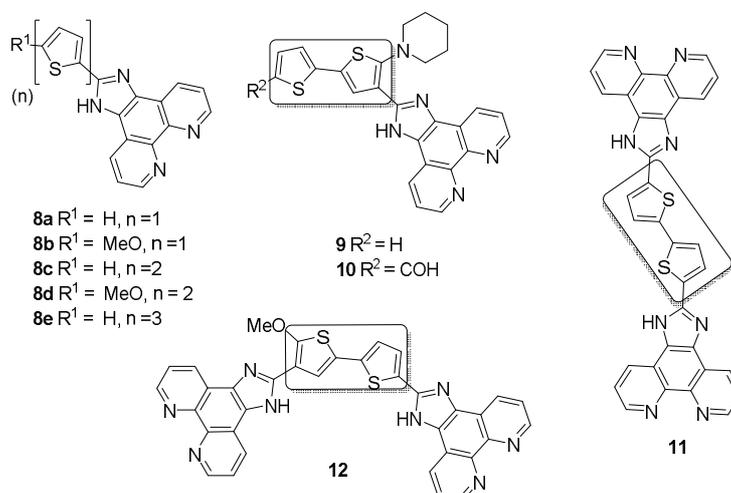

8a R^1 = H, n =1
8b R^1 = MeO, n =1
8c R^1 = H, n =2
8d R^1 = MeO, n = 2
8e R^1 = H, n =3

9 R^2 = H
10 R^2 = COH

Figure 8. Molecular structures of hyperpolarizable chromophores.[50]

Given the continuing interest in developing chromophores for several optical applications, Batista et al. explored the synthesis, thermal stability, and solvatochromic and nonlinear optical properties of a series of imidazo-phenanthroline type heterocyclic chromophores (**13-19**) containing an arylthienyl moiety substituted with various groups such as alkoxy, *N*,*N*-dialkylamino, cyano, and nitro (Figure 9).[51] A comparison between the nonlinear optical data of the arylthienyl-imidazo-phenanthrolines and (oligo)thienyl-imidazo-phenanthrolines showed that the substitution of a benzene ring with a thiophene on

the π-conjugated bridge (but maintaining the same donor group), produced a bathochromic shift on the absorption wavelength maxima and larger values of the molecular hyperpolarizability β, which could be explained by taking into account the bathochromic effect of sulfur, the partial decrease in the aromatic character of the thiophene heterocycle compared to benzene, and also the increase in the overlap between the thiophene units.[51]
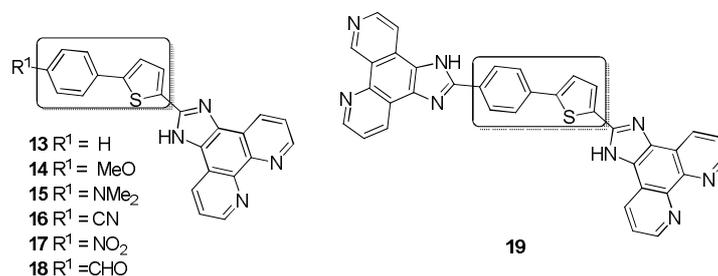

13 R[1] = H
14 R[1] = MeO
15 R[1] = NMe$_2$
16 R[1] = CN
17 R[1] = NO$_2$
18 R[1] = CHO

Figure 9. Molecular structures of hyperpolarizable chromophores based on functionalized arylthiophene donors and an imidazo-phenanthroline acceptor moiety.[51]

Yin et al. did a density functional theory study and demonstrated the effect of ancillary ligands on the photophysical properties of Ru(II) complexes bearing a highly conjugated diimine ligand. The bis-heteroleptic Ru(II) complexes [Ru(bpy)$_2$(pcip)]$^{2+}$ (bpy=2,2'-bipyridine, pcip=2-[4-phenylcarboxy]-1H-imidazol[4,5-f][1,10]phenanthroline) **20** and [Ru(phen)$_2$(pcip)]$^{2+}$ (phen=1,10-phenanthroline) **21** (Figure 10) were prepared and isolated as their PF$_6$ salts. The bpy-compound showed better photophysical properties (e.g. emission quantum yield, lifetime of the emitting state, and radiative decay rate constant) than the phen-derivative.[52]

20 bpy
21 phen

Figure 10. Representation of the Ru(II) complexes.[52]

3.3. 1,10-Phenanthrolines as coordination ligands for detection of metal ions: photophysical properties of derivatives

The detection of heavy metals in a sample is physiologically and environmentally important. The recognition of harmful ions and detection of their analytical concentrations is a subject of great interest in analytical chemistry. Several analytical methods, including atomic absorption spectroscopy (AAS), inductively coupled plasma atomic emission spectrometry (ICP-AES), and inductively coupled plasma mass

spectrometry (ICP-MS) have been widely used for the detection of heavy metals, even at very low concentrations. However, these methods are relatively expensive and difficult to apply. As an alternative to these expensive methods, a large number of optical sensors have been developed. Optical sensors have a number of advantages including low cost, high sensitivity, absence of electrical interference, security, and ease of use.[53-55] Accordingly, fluorescence provides high sensitivity and, moreover, significant advantages over other methods because it is easy to handle and cheaper. Thus, the search for the development of new ways of generating fluorophore agents containing chelating groups could contribute to the efficient detection of heavy metals. In this context, *o*-phen derivatives, with an arrangement of the ideal nitrogen atoms for chelation, are very important in the coordination chemistry of heterocyclic bases as ligands for metals, and their use in analytical applications has increased interest in the study of new synthetic procedures.

Thus, systems containing *o*-phen ligands as key components are emerging as luminescent sensors for the efficient detection of metal ions.[15, 20-23] Spectral shifts occur in the *o*-phen moiety after binding of the metal ion results in changes in its coloration. The chemical versatility of *o*-phens has been explored in recent investigations to develop several organic derivatives and coordination compounds with transition metals [Ru(II), Os(II), Rh(III), Cr(III), Pt(II), Zn(II), Cu(I), Ag(I)], lanthanides [Eu(III),Tb(III), Yb(III), Nd(III), Er(III)], and luminescents (UV-Vis-NIR).[15] Dietrich-Buchecker et al. investigated *o*-phens tetrasubstituted at positions 2, 3, 8, and 9a from Suzuki coupling reactions, in order to build more sophisticated chelating agents that incorporate various transition metals such as iron, zinc, and vanadium, among others.[56]

Recently, Sangeetha et al. reported the synthesis of two fluorophores with open coordination sites for specific sensing of Cu^{2+} **22** and Ni^{2+} **23** ions via a simple synthetic route (Figure 11). In order to evaluate the selectivity of the fluorophores towards the analyte, their fluorescence behavior was examined after addition of various transition and heavy metal ions such as Cr^{3+}, Mn^{2+}, Fe^{2+}, Fe^{3+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Mg^{2+}, Cd^{2+}, Hg^{2+}, and Pb^{2+}. The fluorescence activity was completely quenched in coordination of the metal ions with the *o*-phen ring present in the molecular structures of the fluorophores.[21]
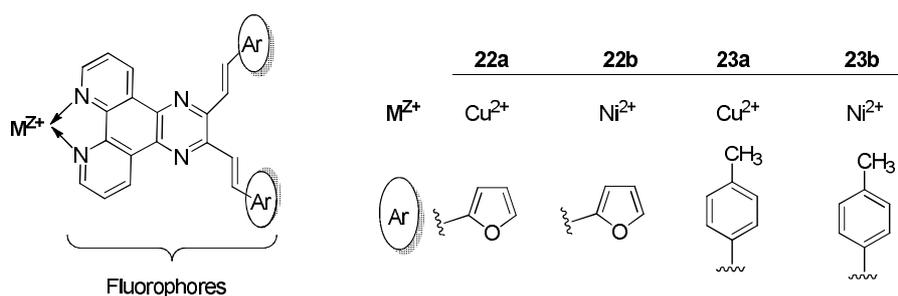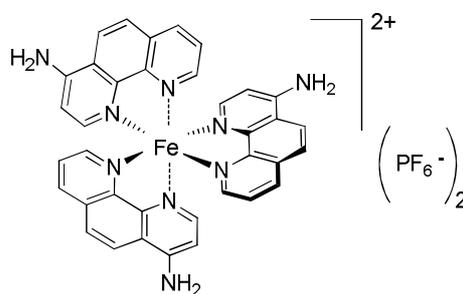

Figure 11. Two fluorophores with open coordination sites for specific sensing of Ni^{2+} and Cu^{2+}.[21]

Furthermore, the utility of *o*-phen complexes as ion carriers for potentiometric sensor applications is indicated by the inclusion of tris(1,10-phenanthroline)iron(II) in a number of commercially available nitrate electrodes. Bachas et al. described the preparation of polymer films on the surface of glassy carbon electrodes (GCEs) by electrochemical polymerization of transition-metal complexes of 5-amino-1,10-phenanthroline (aphen).[57] The electrochemical polymerization and precipitation of films directly on a surface

of the electrode has some advantages compared to the chemical deposition of preformed polymers. Electropolymerization enables the deposition of insoluble polymers, uniform coating on uneven surfaces, and easy electrochemical control of the film thickness.[58]

Bachas et al. used 5-amino-1,10-phenanthroline (aphen) **24**, which provided a readily oxidizable amino fraction and a coordinating site for the metal, to synthesize the complex [Fe(aphen)$_3$]$^{2+}$, thereby producing a nitrate ions selective sensor (Figure 12).[57]

[Fe(aphen)$_3$]$^{2+}$ **24**: Nitrate ions selective sensor

Figure 12. Nitrate ion selective sensor [Fe(aphen)$_3$](PF$_6$)]$_2$.[57]

The cationic iridium complex [Ir(dfppy)$_2$(dpphen)]PF$_6$ **25** (Figure 13), in which dfppy is 2-(2,4-difluorophenyl)pyridine, dpphen is 4,7-diphenyl-1,10-phenanthroline and PF$_6^-$ is hexafluorophosphate, was synthesized and had its photophysical and electrochemical properties investigated by Sunesh et al. Light-emitting electrochemical cells (LECs), which are based on this complex and emit yellowish greenish light, were fabricated using air stable electrodes. The effect of two different imidazolium-based ionic liquids (ILs) i.e. 1-butyl-3-methylimidazolium hexafluorophosphate (BMIMPF$_6$) and 1-ethyl-3-methylimidazolium hexafluorophosphate (EMIMPF$_6$), on the active layer was studied. Luminance and current density of the devices were found to be enhanced by the increase in ionic conductivities.[59]

Recently, Zheng et al. reported a luminescent lanthanide complex-based anion sensor with electron-donating methoxy groups for monitoring multiple anions in environmental and biological processes.
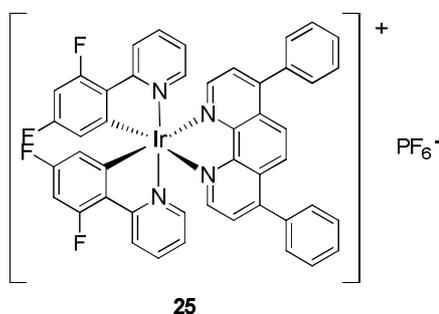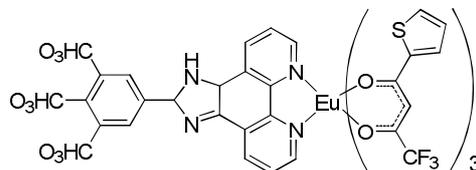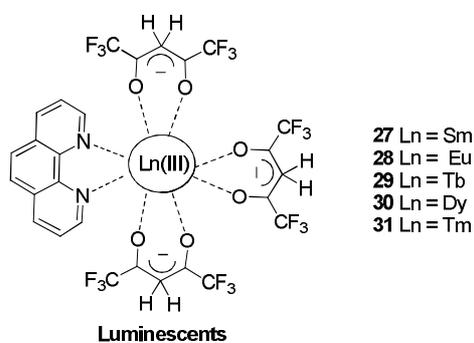

25

Figure 13. Luminescent cationic iridium complex [Ir(dfppy)$_2$(dpphen)]PF$_6$ **25**.[59]
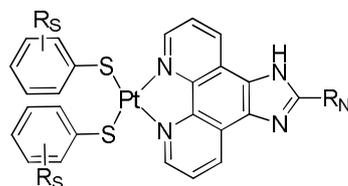
A ternary europium(III) tris(2-thenoyltrifluoroacetonate) with 2-(3,4,5-trimethoxy phenyl)imidazo[4,5-*f*]-1,10-phenanthroline **26** (Figure 14) can detect various anions such as F⁻, $H_2PO_4^-$, and AcO⁻. Spectroscopic studies of UV-vis, fluorescence, and NMR show that the sensor undergoes notable emission changes for fluoride (purple), acetate anions (green), and $H_2PO_4^-$ (blue), respectively. More importantly, thick transparent hybrid films (poly-methyl methacrylate) show intense red emissions and give rise to luminescence change in fluoride anions containing DMSO solution.[60]

26

Figure 14. Ternary europium complex-based luminescent anion sensor **26**.[60]

Ahmed and Iftikhar described the synthesis and luminescence properties presented by eight-coordinate Sm, Eu, Tb, Dy, and Tm complexes of the [Ln(hfaa)3(phen)] type (in which hfaa=hexafluoropentanedione and phen=1,10-phenanthroline) **27-31** (Figure 15). Large upfield and downfield shifts were observed in their ¹H NMR spectra. The lanthanide-induced chemical shifts in these paramagnetic complexes are dipolar in nature. The H(2) and H(4) proton resonances of the *o*-phen of the thulium complex have been shifted to highfields, which is unusual. Inter- and intra-molecular chemical shift ratios are similar for Sm and Eu complexes, because they are isostructural in solution. The quantum yields (U=46% for Eu, 32% for Tb, 2.7% for Sm, and 2.1% for Dy) of the complexes indicate that energy transfer from ligands (hfaa and phen) to Ln(III) is efficient. The luminescence in the Dy(III) complex is the least intense, due to poor intramolecular energy transfer match, when compared to the rest of the complexes. The lanthanide ions in these complexes have low symmetry sites.[2]
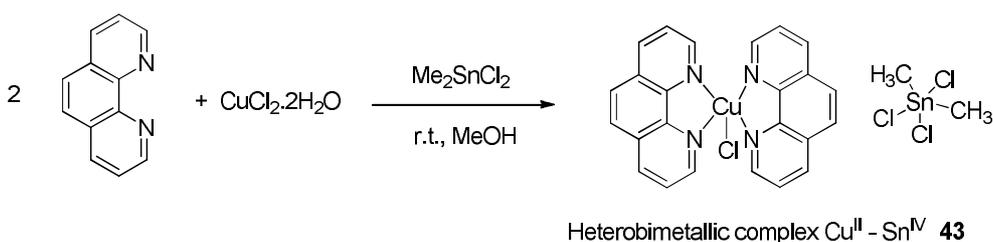
Shavaleev et al. employed the planar aromatic imidazo[4,5-*f*]-1,10-phenanthroline ligands (imP) to prepare platinum(II) chloride and thiolate complexes **32-42** (Figure 16).

27 Ln = Sm
28 Ln = Eu
29 Ln = Tb
30 Ln = Dy
31 Ln = Tm

Luminescents

Figure 15. Molecular structure of Ln(III) complex luminescents.[2]

Pt(imP)(S-R$_S$)$_2$ **32-42**

R$_N$ = *t*-Bu, Ph, 4-*t*BuPh, 4-OMePh, 4-NMe$_2$Ph, 4-NO$_2$Ph

R$_S$ = *t*-Bu, 2-Me and 4-*t*Bu, 2-CO$_2$Me

Figure 16. Thiolate complexes Pt(imP)(S-R$_S$)$_2$.[61]

The X-ray structures of two thiolate compounds showed column-like packing in the solid state due to intermolecular aromatic π-π interactions. The compounds absorb moderately in the visible region, due to charge-transfer-to-diimine electronic transition.[61]

A heterobimetallic Cu^{II}-Sn^{IV} complex with a bioactive 1,10-phenanthroline pharmacophore ligand scaffold **43** was synthesized by Arjmand et al. (CuCl$_2$.2H$_2$O, Me$_2$SnCl$_2$, methanol, r.t.) (Figure 17).[62] Studies of in vitro DNA binding of this complex with CT DNA were done by performing various biophysical and molecular docking techniques, which revealed that the complex binds to DNA through intercalation in the minor groove which possesses AT-rich sequences. The complex exhibits high chemical nuclease activity that cleaves supercoiled pBR322 DNA via a hydrolytic pathway, which was further evidenced by T4 DNA ligase assay. The complex shows high inhibitory activity against Topo I at a very low concentration (15 mM), suggesting that the complex is an efficient catalytic inhibitor of human Topo I, which is further validated by molecular docking studies.

Figure 17. Synthetic route for the heterobimetallic complex **43**.[62]

Chesneau et al. reported an efficient synthesis of versatile building blocks for the straightforward synthesis of the 5,6-dithio functionalized 1,10-phenanthroline-based system **44** and its corresponding ruthenium(II) complex **45** (Figure 18). Interest in such a system is supported by the use of the 2-cyanoethylsulfanyl-protecting group and the high efficiency of the selective sequence of deprotection-alkylation reactions of thiolate groups. This attractive thiofunctionalization, at both the 5 and 6 positions, offers a broad range of possibilities for an approach to new symmetrical and unsymmetrical 1,10-phenanthroline-based systems and related organometallic complexes. Moreover, the ready access to the

dithiolate intermediates from building blocks gives rise to two distinct coordinating sites. This opens a wide range of possibilities for easy access to multinuclear complexes exhibiting promising electrochemical and physical properties.[63]
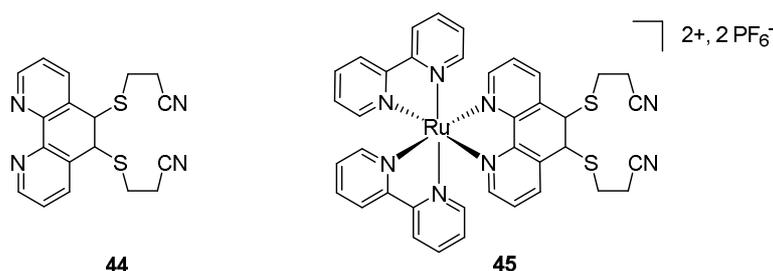

Figure 18. 5,6-Bis(2-cyanoethylsulfanyl)-1,10-phenanthroline (**44**) and its Ru(II) bipyridil complex (**45**).[63]

Park et al. studied the coordination chemistry of Ru(II)-M(I) (M=Rh and Ir) bimetallic complexes based on a bridging ligand composed of 1,10-phenanthroline and *N*-heterocyclic carbine, and they demonstrated the detection property of carbon monoxide. A series of mono-Ru[II] and di-nuclear complexes, [Ru[II]-M[I](COD)Cl and Ru[II]-M[I](CO)$_2$Cl] (M=Ir, Rh), was prepared using a bridging ligand, 1,3-dibutyl-2,3-dihydro-1*H*-imidazo[4,5-*f*][1,10]phenanthroline-2-yl (IL) **46-49** (Figure 19). This bridging ligand consists of 1,10-phenanthroline and *N*-heterocyclic carbene (NHC) and has two coordinating sites which can bind two different metals. These complexes exhibited typical π-π* and MLCT bands in the UV and visible regions, respectively. The compounds Ru[II]-Ir[I](CO)$_2$Cl and Ru[II]-Rh[I](CO)$_2$Cl showed stronger emission intensities and longer luminescence lifetimes than those of Ru[II]-Ir[I](COD)Cl and Ru[II]-Rh[I](COD)Cl, respectively. Complex Ru[II]-Ir[I](COD)Cl was used to detect carbon monoxide.[64]

46 M = Ir [Ru-Ir(COD)Cl], R = *n*-Butyl
47 M = Rh [Ru-Rh(COD)Cl], R = *n*-Butyl

48 M = Ir [Ru-Ir(CO)$_2$Cl], R = *n*-Butyl
49 M = Rh [Ru-Rh(CO)$_2$Cl]

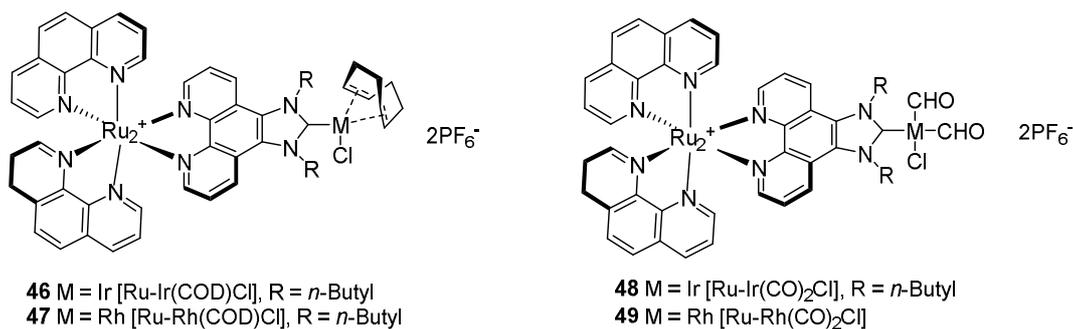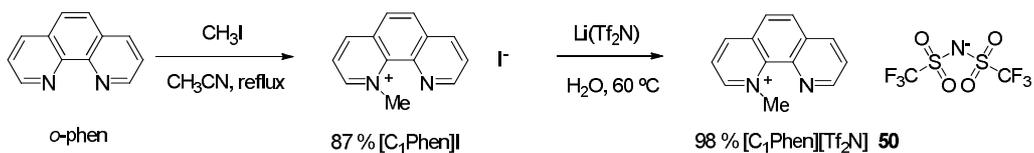**Figure 19.** Molecular structures of the di-nuclear complexes **46-49**.[64]

3.4. Catalytic approaches: 1,10-phenanthroline and derivatives as useful catalyst ligands for several reactions
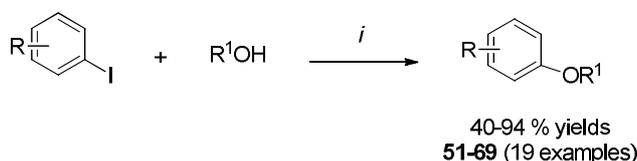
1,10-Phenanthrolinium-based ILs exhibit exceptional solvation abilities for 1,10-phenanthroline and its metal complexes, and, therefore, facilitate the use of ILs as solvents for the full range of phenanthroline-

based applications, such as catalysis and nanoparticle synthesis. Their ability to immobilize metal catalysts in solution makes them especially suitable for use in biphasic and supported IL-phase (SILP) catalysis.[14] The synthetic route for the preparation of 1,10-phenanthrolinium-based IL [C$_1$Phen][Tf$_2$N] **50** is shown in Scheme 1.

Scheme 1

Catalytic copper systems have facilitated the coupling of aryl halides with primary aliphatic alcohols and secondary benzylic, allylic, and propargylic alcohols under relatively mild conditions, with short reaction times and moderately low amounts of catalyst, allowing the use of a variety of groups in electrophilic or nucleophilic functional compounds **51-69**. The research group of Buchwald has employed a Cu/1,10-phen ligand system in coupling reactions with high efficiency under mild conditions (Scheme 2).[65-68] Buchwald et al. described a domino copper-catalyzed C-O coupling-claisen rearrangement process.[65]

40-94 % yields
51-69 (19 examples)

i = CuI (10 mol%), *o*-Phen (20 mol%), Cs$_2$CO$_3$, 110 °C, 18-24 h

R = Aryl (3,3-di-Me, 3-OMe, 3-NH$_2$, 3-CN, 4-OMe, 4-NH$_2$, 2-Me, 2-OMe, 2-NH$_2$) and Heteroaryl

R^1 = 1° and 2° Alkyl, Cycloalkyl

Scheme 2

In a continuation of their studies, the authors reported that the use of 3,4,7,8-tetramethyl-1,10-phenanthroline (Me$_4$-Phen), a commercially available ligand, improved the Cu-catalyzed nucleophilic substitution reactions of aryl iodides and alkyl-substituted vinyl iodides with amino alcohols and allylic alcohols, respectively.[66,67] More recently, the authors explored the utility of Me$_4$Phen as a ligand in the Cu-catalyzed cross-coupling reactions of aryl iodides and bromides with alcohols (Scheme 3). The authors propose that chemists in both academic and industrial laboratories will find this improved catalyst system useful in their work.[68] The cross-coupling reactions of aryl iodides with alcohols can be done under mild conditions without the required use of excess quantities of nucleophile in the reaction. This catalyst system complements Pd-based catalyst systems, as well as traditional Williamson reactions and nucleophilic substitution reactions of activated aryl halides for the preparation of alkyl aryl ethers **70-92**.[68]

59-94 % yields
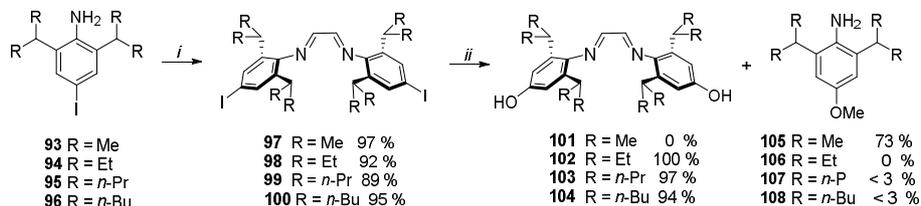**70-92** (23 examples)

i = CuI (5 mol%), Me$_4$Phen (10 mol%), Cs$_2$CO$_3$, toluene, 80-130 °C, 9-24 h
R = Aryl (4-OMe, 3,-OMe, 2-OMe, 2-Me, 2-Cl, 4-Br, 4- Cl, 4-F, 4-NH$_2$, 4-COO-^{t}E
4-CF$_3$, 4-Me, 1*H*-pyrrolyl) and Heteroaryl (pyridine, thiophene), 1-naphthyl
R^1 = 1° and 2° Alkyl, Benzyl, Allyl, Propargyl
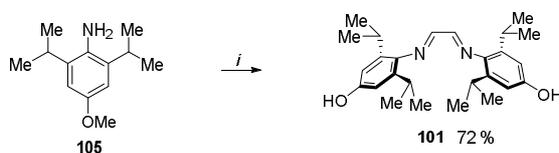X = Br, I

Scheme 3

Meiries et al. developed a new methoxylation strategy and demonstrated that 1,10-phenanthroline is a suitable ligand, since no anhydrous conditions were required. This methoxylation procedure is straightforward and convenient, requiring only minimal purification. The methoxylation of *p*-iododiimine **93** containing methyl substituents (R=Me) underwent tsimultaneous cleavage of the diimine bridge over the course of the reaction, providing the free *p*-methoxyaniline **105** rather than the expected *p*-methoxydiimine **101** (Scheme 4A).[69] On the other hand, methoxylation of *p*-iododiimines **94-96**, in which R=Et, *n*-Pr or *n*-Bu, showed only traces of free p-methoxyanilines **106-108** (<3%).

A) New methoxylation strategy

93 R = Me
94 R = Et
95 R = *n*-Pr
96 R = *n*-Bu

97 R = Me 97 %
98 R = Et 92 %
99 R = *n*-Pr 89 %
100 R = *n*-Bu 95 %

101 R = Me   0 %
102 R = Et   100 %
103 R = *n*-Pr 97 %
104 R = *n*-Bu 94 %

105 R = Me   73 %
106 R = Et   0 %
107 R = *n*-P < 3 %
108 R = *n*-Bu < 3 %

B) Preparation of diimine (R = Me)

105

101 72 %

C) Preparation of p-methoxylatedimidazolium chlorides

101 R = Me
102 R = Et
103 R = *n*-Pr
104 R = *n*-Bu

110 R = Me   88 %
111 R = Et   65 %
112 R = *n*-Pr 60 %
113 R = *n*-Bu 66 %

i = Glyoxal (40% in H$_2$O), HCOOH (cat.),
MeOH, r.t., overnight

ii = CuI, Cs$_2$CO$_3$, *o*-phen, MeOH, overnight,
120 °C, sealed tube

iii = (CHO)$_n$ **109,** ZnCl$_2$, HCl (4 M in dioxane),
THF, 70 °C

Scheme 4

The free *p*-methoxyaniline **105** (with R=Me) was easily obtained and purified by distillation under reduced pressure. It was subsequently converted into the corresponding diimine **101** using the standard procedure (Scheme 4B). Diimines **101-104** were all converted into their corresponding imidazolium chlorides **110-113** via the usual $(CHO)_n$ **109**/$ZnCl_2$/HCl procedure, at good yields (60-88%) (Scheme 4C). The diimine bridges (R=Et, *n*-Pr or *n*-Bu) were easily cleaved to release the free anilines **106-108**. The *p*-methoxydiimines were easily and efficiently deprotected for the free anilines **101-104**, at good yields (85-89%) and excellent purity, proving that the diimine functionality can also be considered to be an inexpensive conventional protecting group.[69]
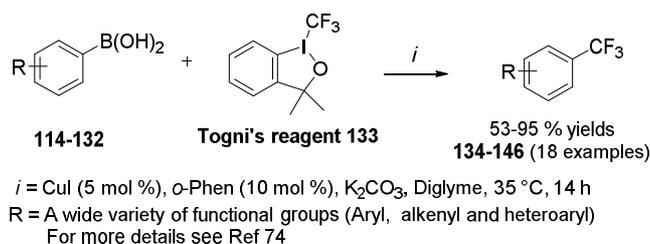
The incorporation of trifluoromethyl groups (CF_3) into organic structures could dramatically improve their physical, chemical and biological properties such as metabolic stability and lipophilicity.[70] Many biologically active pharmaceuticals and agrochemicals contain CF_3 groups as the indispensable moiety. Consequently, the development of methodologies for the introduction of trifluoromethyl groups into organic molecules has received much attention.[71-76] Among various methods for the synthesis of trifluoromethylated compounds, metal-catalyzed trifluoromethylation reactions are particularly important. A number of examples have been demonstrated in the literature for Pd- or Cu-catalyzed trifluoromethylation of boronic acids and aryl C-H bonds, using trifluoromethylating reagents (e.g. Togni's reagent) as the CF_3 source.[74-76]

Liu et al. described the first CuI/1,10-phenanthroline-catalyzed trifluoromethylation of aryl- and alkenylboronic acids **114-132** with Togni's reagent **133**, an electrophilic trifluoromethylating reagent, providing compounds **134-146** at 53-96% yields (Scheme 5). The reaction proceeded well for a range of different substrates, including heteroarylboronic acids and substrates with a variety of functional groups (e.g. aryl-, alkenyl-, and heteroaryl-substituted) under mild reaction conditions.[74]
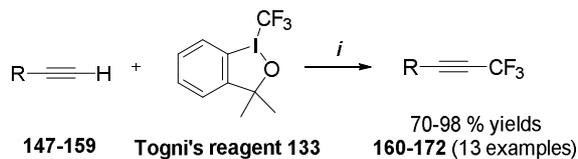

i = CuI (5 mol %), *o*-Phen (10 mol %), K_2CO_3, Diglyme, 35 °C, 14 h
R = A wide variety of functional groups (Aryl, alkenyl and heteroaryl)
For more details see Ref 74

Scheme 5

Weng et al. have initiated research programs aimed at the development of copper-catalyzed trifluoromethylation reactions. These researchers developed an effective copper catalyst system for the trifluoromethylation of terminal alkynes **147-159** with Togni's reagent **133** at room temperature and with tolerance of a variety of functionalities; for example, alkoxyl, amino, and halide groups, which furnish compounds **160-172** at 70-98% yields (Scheme 6).[75]

Recently, Weng et al. described the copper-catalyzed trifluoromethylation of arylsulfinate salts **173-184**, using Togni's reagent **185**, which provided compounds **186-197** at 38-88% yields (Scheme 7).[76]
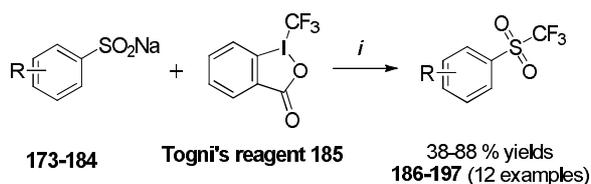
Yang et al. developed an efficient copper-catalyzed method for Sonogashira couplings of aryl halides **198-209** with terminal alkynes 2**10-212** in water. The protocol uses inexpensive CuBr as the catalyst, 1,10-

phenanthroline as the ligand, tetrabutylammonium bromide (TBAB) as the phase-transfer catalyst, and environmentally friendly water as the solvent to synthesize various internal alkynes **213-236** at good to excellent yields (48-92%) (Scheme 8).[77] It is interesting that the method shows good tolerance towards various functional groups in the substrates.
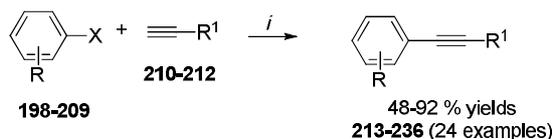

70-98 % yields
147-159   **Togni's reagent 133**   **160-172** (13 examples)

i = CuI (20 mol %), *o*-Phen (40 mol %), KHCO$_3$, CH$_2$Cl$_2$, Rt, 24 h
R = 4-MePh, 3-MePh, 4-EtPh, 4-*n*PrPh, 4-*n*BuPh, 4-OMePh, 4-(OPh)Ph,
    2-BrPh, 4-BrPh, 3-NH$_2$Ph, Bn, thiophene, phenanthrene

Scheme 6

38-88 % yields
173-184   **Togni's reagent 185**   **186-197** (12 examples)

i = [Cu] (20 mol %), *o*-Phen (40 mol %), *n*-Bu$_4$NF, 130 °C, 8.5 h, DMSO
R = Alkyl, Ph, OMe, CN, NO$_2$, F and Heteroaryl, Naphthyl sulfinate

Scheme 7

198-209   **210-212**   48-92 % yields
213-236 (24 examples)

i = CuBr, *o*-Phen, *n*-Bu$_4$NF, NaOH, H$_2$O, N$_2$, 120 °C, 24 h
X = Br, I
R = 4-Me, 4-^{i}Pr, 4-OMe, 4-Ph, 4-Cl, 4-NO$_2$, 4-Br, 3-Me, 3-Cl,
    3,3-di-F, 3,3-di-Me and 2-Naphthyl
R^1= Ph, 4-FPh, Hexyl

Scheme 8

Yang et al. also described the reaction between 2-iodophenol **236** and phenylacetylene **237** to furnish 2-phenylbenzofuran **238** at a 74% yield (Scheme 9).[77]

Huang and Batey described the copper-catalyzed cross-coupling of various arylboronic acids **239-249** with sodium sulfinate and *p*-toluenesulfinate salt **250** for the preparation of aryl and alkenylsulfones **240-261** (Scheme 10).[78] Optimized conditions utilize a catalytic amount of copper(II) acetate monohydrate with 1,10-phenanthroline as ligand in the presence of 4 Å molecular sieves. The method tolerates a variety of

substituents in organoboronic acid, including amide, aldehyde, halide, and nitro functionalities, as well as *ortho*-substituents. In general, the reaction is found to be less efficient using arylboronic acids bearing electron-withdrawing substituents or using aryltrifluoroborate salts.

i = CuBr (10 mol %), *o*-Phen (20 mol %), *n*-Bu$_4$NF (20 mol %), NaOH, H$_2$O, N$_2$, 120 °C, 24 h

Scheme 9

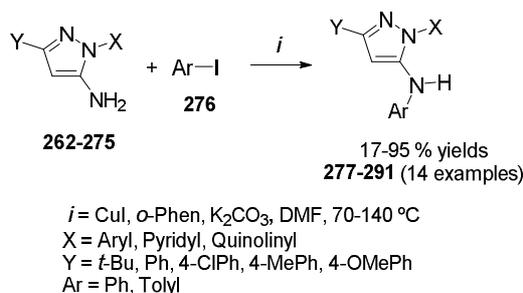*i* = Cu(OAc)$_2$. H$_2$O (10 mol %), *o*-phen (20 mol %), CH$_2$Cl$_2$/DMSO (15:1), O$_2$, 4A° MS, 40 °C, 72 h

Ar = Ph, 4-MePh, 4-OMePh, 4-ClPh, 4-CF$_3$Ph, 4-CHOPh, 3-NO$_2$Ph, 2-MePh, 2,2-di-MePh, 2-CF$_3$Ph, 2-Naphthyl

Scheme 10

Chang et al. described the synthesis of 5-arylamino-1-arylpyrazoles **277**-**291** from 5-aminopyrazoles **262**-**275** with arylhalides (e.g. **276**) via CuI-catalyzed Ullman coupling reaction (Scheme 11).[79]

i = CuI, *o*-Phen, K$_2$CO$_3$, DMF, 70-140 °C
X = Aryl, Pyridyl, Quinolinyl
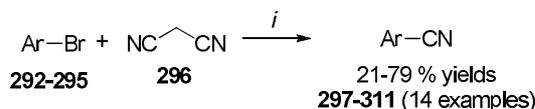Y = *t*-Bu, Ph, 4-ClPh, 4-MePh, 4-OMePh
Ar = Ph, Tolyl

Scheme 11

Recently, Lu et al. developed a novel and alternative route for the synthesis of aryl nitriles **297**-**311**, from the cyanation of aryl bromides **292**-**295** with malononitrile **296** via carbon-nitrile bond cleavage mediated by a copper-catalyzed reaction (Scheme 12).[80]

Hattori et al. reported important reactions for the direct functionalization of indazoles via an efficient palladium- and copper-*o*-phen-catalyzed protocol for the C-H arylation of 1*H*- and 2*H*-indazoles (**320** and **321**) with haloarenes (**312**-**319**) (Scheme 13). The authors explored the effect of aryl-coupling partners in the C-H arylation of 2-phenyl-2*H*-indazole, as well as the effect of indazole substituents in the C-H arylation of 2*H*-indazoles (**322**-**342**). A PdCl$_2$/*o*-phen/Ag$_2$CO$_3$/K$_3$PO$_4$ catalytic system was effective for the C-H
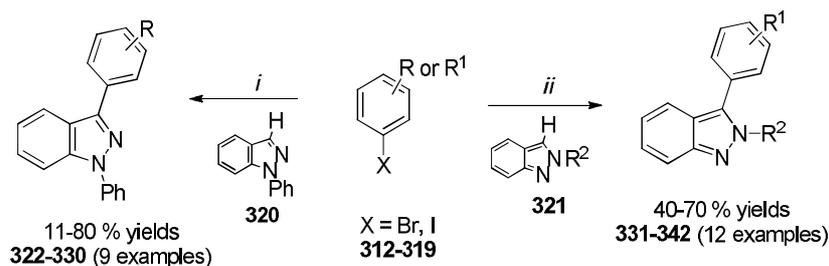
arylation of 1*H*- and 2*H*-indazoles with haloarenes; whereas a less expensive CuI/phen/LiOt-Bu catalytic system was efficient for the C-H coupling of substituted 2*H*-indazoles and iodoarenes. The utility of this catalyst was demonstrated in the rapid synthesis of YC-1 (an antitumor agent) and YD-3 (platelet anti-aggregating agent).[81]

Ar—Br + NC⌒CN $\xrightarrow{i}$ Ar—CN

292-295   **296**   21-79 % yields
297-311 (14 examples)

i = Pd(Amphos)$_2$Cl$_2$, CuI, *o*-Phen, *t*-BuONa, KF, DMF, 130 °C, 24 h

Ar = Aryl,1-Naphthyl, 2-Naphthyl, 2-Pyridyl

Scheme 12

11-80 % yields
322-330 (9 examples)   **320**   X = Br, I
312-319   **321**   40-70 % yields
331-342 (12 examples)

i = PdCl$_2$/*o*-Phen (10 mol %), Ag$_2$CO$_3$, K$_3$PO$_4$,DMAc, 165 °C, 12 h

ii = CuI/*o*-Phen (10 mol %), LiO*t*-Bu, DMF, 110 °C, 15 h

R = 2-Me, 3-Me, 4-Me, 4-Cl, 4-OMe, 4-CF$_3$ and Heteroaryl

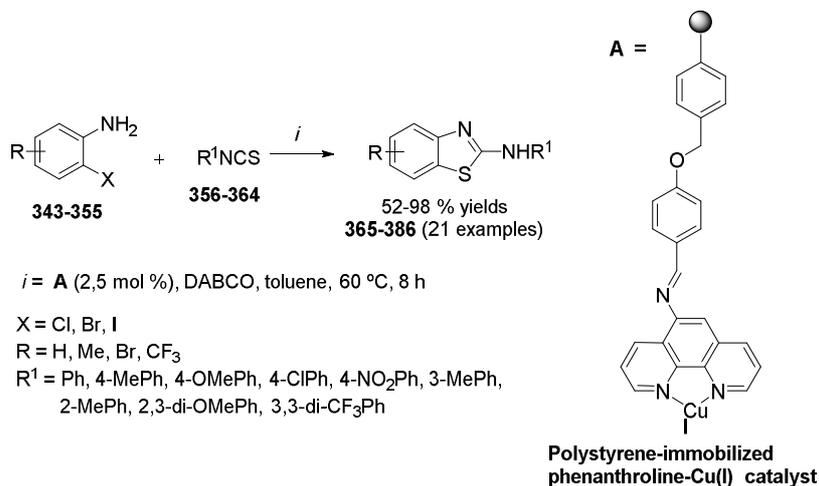R^1 = 2-Me, 3-Me, 4-Me, 4-Cl, 4-OMe, 4-CF$_3$, 2,2-di-Me
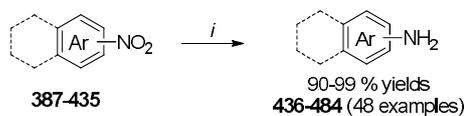
R^2 = Me, Ph, 4-MePh, 4-OMePh

Scheme 13

Yang et al. described the Merrifield resin supported phenanthroline-Cu(I) as a highly efficient and recyclable catalyst for the synthesis of 2-aminobenzothiazoles via the reaction of 2-haloanilines with isothiocyanates (Scheme 14).[82] The reactions were applicable for a variety of 2-halobenzenamines **343-355** and isothiocyanates **356-364**, and generated the corresponding 2-aminobenzothiazoles **365-386** at good yields (52-98%) under mild reaction conditions. Moreover, the catalyst was quantitatively recovered from the reaction mixture through simple filtration, and it was reused for ten cycles with nearly universally consistent activity.

Jagadeesh et al. described an efficient and highly selective iron-phenanthroline system for the reduction of structurally diverse nitroarenes **387-435** to anilines **436-484** at 90-99% yields (Scheme 15).[83]
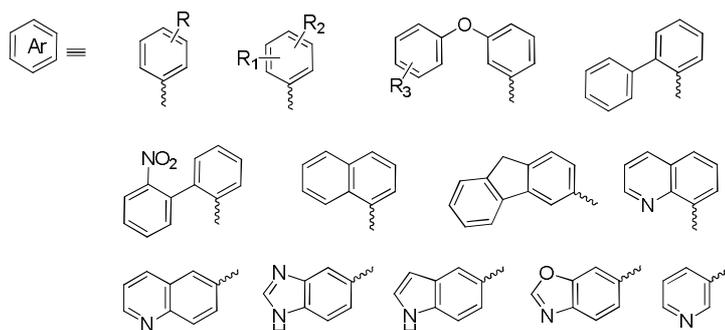
Yang et al. described alkoxylation reactions of aryl halides **485-501** catalyzed by CuFe$_2$O$_4$ (Scheme 16).[84]

A =

**Polystyrene-immobilized
phenanthroline-Cu(I) catalyst**

i = **A** (2,5 mol %), DABCO, toluene, 60 °C, 8 h

X = Cl, Br, I
R = H, Me, Br, CF$_3$
R^1 = Ph, 4-MePh, 4-OMePh, 4-ClPh, 4-NO$_2$Ph, 3-MePh,
 2-MePh, 2,3-di-OMePh, 3,3-di-CF$_3$Ph

343-355 + 356-364 → 365-386 (21 examples)
52-98 % yields

Scheme 14

387-435 → 436-484 (48 examples)
90-99 % yields

i = Fe-(o-Phen)/C (1 mol % Fe), 4 Equiv. N$_2$H$_4$. H$_2$O, THF, 100 °C, 10 h

R = H, 4-F, 4-Cl, 4-Br, 4-I, 2-Cl, 3-Cl, 3,5-dichloro, 3,4,5-trichloro, 4-Me,
 4-ethyl, 4-iPr, 4-t-butyl, 4-CF$_3$, 4-NH$_2$, 4-N(CH$_3$)$_2$, 4-NO$_2$, 4-OMe,
 4-SMe, 4-OPh, 4-OH, 4-CN, 4-CH$_2$=CH$_2$, 4-CH$_2$=CHPh,
 4-CH$_2$=CH(COOEt), 4-CH≡CH, 4-COOMe

R^1 = 1-Me 1-CF$_3$ 4-Me 1-Me 1-Me
R^2 = 1-Me 4-Br 3-NH$_2$ 3-NH$_2$ 3-NO$_2$
R^3 = H, 4-NO$_2$

Scheme 15

An efficient method was developed for C-O coupling reactions between various kinds of unactivated alkyl alcohols **502**-**506** and aryl halides **485**-**501**, using CuFe$_2$O$_4$ as catalyst, which makes the method simple, air stable, low cost, easily separable, and regenerable. The reaction selectively proceeds to C-O bond formation in compounds **507**-**523** when other sensitive substituents, such as free amino groups and double bonds, exist in the system. Also, it prefers the C-I bond over the C-Br bond in the substrate. Additionally, primary aliphatic, cyclic alkyl, benzylic, and allylic alcohols are all suitable substrates for this method.
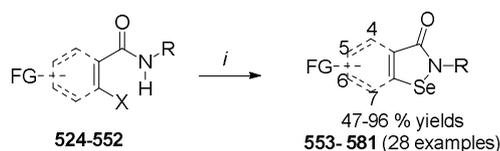

485-501   **502-506**

44-83 % yields
507-523 (16 examples)

i = CuFe$_2$O$_4$ (2,5 mol %), o-phen (5 mol %), CS$_2$CO$_3$, 110 °C, 12 h
X = C, N; R = Br, I; R^1 = H, 4-Br, 4-Me, 4-OMe, 2-Me, 3-NH$_2$
R^2= n-Butyl, Ethyl, n-Propyl, n-Amyl, n-Hexyl, i-Propyl, Cyclopentyl, Bn

Scheme 16

Organochalcogen compounds, in turn, are important reagents that are widely used in organic synthesis and are the subject of significant interest, due to their specific properties. The activity of organic selenium compounds has been extensively investigated for in vitro and in vivo models, in relation to the antioxidant power in biological systems. Thus, the development and study of new synthetic routes, in order to obtain compounds containing selenium in their molecular structure, has attracted the interest of the scientific community.[22] Ebselen (2-phenyl-1,2-benzisoselenazol-3-(2H)-one), for example, is an organic selenium compound that reduces lipoperoxides and hydroperoxides by mimicking the activity of glutathione peroxidase. Additionally, it has excellent cytoprotective, antioxidant, and anti-inflammatory properties. The neuroprotective role of Ebselen was evaluated in experimental models of cerebral ischemia, which indicated significant neurologic recovery, with reductions in lesions in neurons and oligodendrocytes after treatment with this compound.[85]

Kumar et al. studied the scope of a Cu/o-phen ligand system in an efficient method for the synthesis of biologically important Ebselen and Se-N heterocycle analogs **553**-**581**. The authors developed a copper-catalyzed carbon-selenium-nitrogen bond-forming reaction from 2-halobenzamides **524**-**553** and selenium powder in an organic solvent, DMF (Scheme 17).[86]

524-552

47-96 % yields
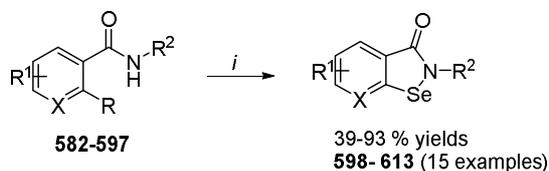**553- 581** (28 examples)

i = CuI/o-phen, Se powder, K$_2$CO$_3$, DMF, 100-110 °C, 8-36 h

X = Cl, Br, I; FG = Ph, 5-NO$_2$, 6-NO$_2$, 7-NO$_2$, 7-Me, 7-CO(NH)Ph, 7-CO(NH)Bn, Naphthyl
R = H, Ph, Bn, Me, Cyclohexyl, Phenylethyl, 2-BrPh, 4-BrPh, 6-ClPh, 5-F, 6-F, 5,6-di-F, 4-CO$_2$EtPh

Scheme 17

According to the authors, the copper-catalyzed reaction tolerates functional groups such as amides, hydroxyls, ethers, nitro, fluorides, and chlorides. This was the first report of a catalytic process of selenation and Se-N bond formation reaction.[86,87]

In 2011, Kumar et al. described an efficient synthetic methodology for construction of Ebselen and related isoselenazolones **598**-**613** from 2-halo-arylamides **582**-**597** through copper iodide catalyzed/mediated Se-N coupling reaction (Scheme 18).[88]
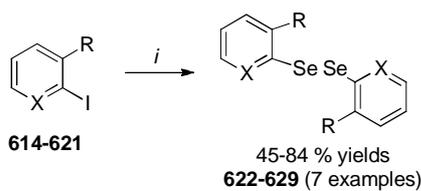

582-597

39-93 % yields
598- 613 (15 examples)

i = CuI/*o*-phen, DMF, Se powder, K$_2$CO$_3$, N$_2$, 90-110 ºC, 12-48 h
X = C, N; R = Cl, Br, I
R^1 = H, OMe, SMe; R^2 = Ph, Benzyl, *n*-Butyl, Cyclopentyl

Scheme 18

Kumar et al. also demonstrated that copper-catalyzed selenium-nitrogen coupling reactions can be applied to the synthesis of diaryl diselenides **622**-**629** (due to them having methoxy, amine, and amide functionality) from the respective aryl iodides **614**-**621**, in the presence of stoichiometric amounts of succinimide as an external Se-N coupling partner (Scheme 19).[87]
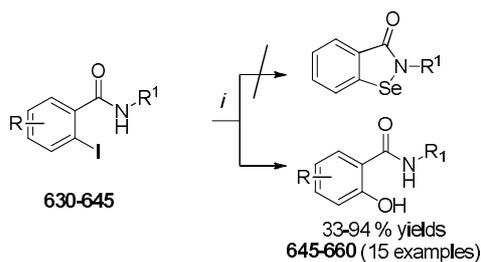

614-621

45-84 % yields
622-629 (7 examples)

X = C, N
i = CuI/*o*-phen, Pyrrolidine-2,5-dione, Se powder, K$_2$CO$_3$
R = H, OMe, NH$_2$, NHAc, CO(NEt$_2$) and Heteroaryl

Scheme 19

In a continuation of their studies, Balkrishna and Kumar demonstrated that when the same reaction was performed in water as solvent, the reaction does not proceed to form Se-N heterocycles; however, the reaction afforded 2-hydroxybenzamide at a 96% yield for 15 min (Scheme 20). This excellent result under benign reaction conditions in neat water led the authors to develop a simple reaction protocol for the synthesis of some important 2-hydroxybenzamides **645**-**660**, which are not accessible by other methods. In this paper, the authors described the first catalytic route for the synthesis of 2-hydroxybenzamides in one pot from hydroxylation of 2-chlorobenzamide substrates. The reaction system requires readily available

substrates and reagents such as 2-chloroaroyl chlorides, primary amines, copper iodide, 1,10-phenanthroline, potassium hydroxide, and eco-friendly solvent water. The mild reaction conditions and simple purification procedure make this method highly practical.[88]
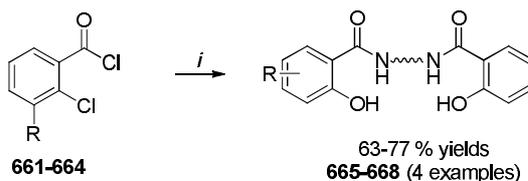

630-645

33-94 % yields
645-660 (15 examples)

i = 1) BnNH$_2$, CH$_2$Cl$_2$; 2) CuI (10 mol %), *o*-Phen, KOH, H$_2$O, 100 °C, 10 h

R = H, F, Cl, NO$_2$, OMe and heteroaryl
R^1 = Ph, Bn, 1-(naphthalen-1-yl)ethyl, 1-(2-hydroxyethyl)

Scheme 20

After studying the synthesis of 2-hydroxybenzamides **645-660**, the authors explored the synthesis of bis(2-hydroxybenzamide) compounds **665-668**, which have been used as ligands for metal complexation reactions.[88-90] The research proposed that 2-chlorobenzoyl chlorides **661-664** treated with diamines, such as ethylenediamine, propylenediamine, and 1,2-diaminocyclohexane, resulted in diamide substrates, which furnished bis(2-hydroxybenzamides) **665-668** in one pot (Scheme 21) for copper-catalyzed hydroxylation reactions.[88]

661-664

63-77 % yields
665-668 (4 examples)

i = 1) Diamine, CH$_2$Cl$_2$; 2) CuI , *o*-phen, KOH, H$_2$O, 100 °C, 10 h

Diamine = Ethane-1,2-diamine, Propane-1,3-diamine, Hexane-1,6-diamine, Cyclohexane-1,2-diamine
R = H, NO$_2$

Scheme 21

In their recent studies, Wendlandt and Stahl[91] reported a new strategy for aerobic oxidation of secondary amines that employs 1,10-phenanthroline-5,6-dione (phd) as a bifunctional *o*-quinone catalyst, providing an important foundation for development of aerobic oxidation reactions employing quinone-based catalysts. According to the authors, copper amine oxidases, which are a family of enzymes with quinone cofactors, are responsible for oxidizing primary amines to aldehydes via an iminoquinone intermediate that

promotes high selectivity for reactions with primary amines, thereby constraining the scope of potential biomimetic synthetic applications.

Thus, these authors developed a bioinspired quinone catalyst system consisting of 1,10-phenanthroline-5,6-dione/ZnI_2 that bypasses these constraints via an abiological pathway involving a hemiaminal intermediate. The ZnI_2 cocatalyst activates the quinone toward amine oxidation and provides a source of iodide, which plays an important redox-mediator role in promoting aerobic catalytic turnover. The results demonstrated an efficient aerobic dehydrogenation of non-native secondary amine substrates, including pharmaceutically relevant nitrogen heterocycles. The reaction mechanism involves an addition-elimination pathway rather than the transamination pathway employed by copper amine oxidase enzymes and many quinone model systems. The catalyst system, which has been used in the efficient synthesis of imines, 3,4-dihydroisoquinolines, 3,4-dihydro-β-carbolines, quinazolines, and indoles, has proven to be useful for a wide range of synthetic applications.[91]

4. Conclusions

In summary, 1,10-phenanthroline and its derivatives present a wide range of applications. Therefore, the synthesis of new compounds containing this core represents an interesting research proposal for chemists in both academic and industrial laboratories. In view of what has been highlighted herein, we believe that the construction of new 1,10-phenanthroline derivatives is an alternative to the future development of probes for investigating DNA building sites, among other important technological applications.

Thus, considering the various structural and chemical properties of 1,10-phenanthrolines and their relevance to current research, we hope to contribute to increasing interest in the development of new molecular architectures as potential pharmacophores, fluorophores, chromophores, and heterocyclic base ligands, as well as the development of functional complexes with potential use in a variety of important chemical, medicinal, and technological applications.

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