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New Ligands Bearing Chiral Bioactive Fragments

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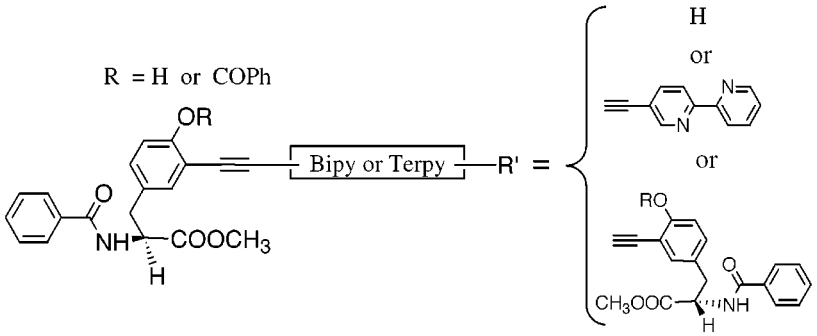
ABSTRACT



Reliable and practical synthetic routes for the construction of hybrid molecules bearing both a chelating center and a useful biofunction are presented. They comprise the sequential cross-coupling reaction between ethynylated synthons with iodo-substituted L-tyrosine derivatives and provide access to various rationally designed chiral ligands.

For the past three decades, there has been a steady and progressive interest in the synthesis of oligopyridines, and an impressive number of such substances are now known.[1−3] The interest in the synthesis of metal complexes has driven research into finding new and improved oligopyridines, and such complexes figure prominently in historical accounts of both coordination and analytical chemistry.[2] More recently, metal oligopyridines have been used to construct exotic molecular architectures,[4] to sensitize photoelectrochemical cells,[5] to label biomaterials,[6] as the basis for selective sensors,[7] and as magnetic materials.[8] In the future oligopyridines will be used in even more applications, especially as material scientists seek to develop miniaturized devices.[9]

We have previously argued the case that alkynylated oligopyridines endow certain metal complexes with special properties, and this claim is the result of a determined and sustained effort to produce a comprehensive catalog of suitably derivatized compounds.[2,10] In extrapolating that work to ligands bearing chiral fragments, the palladium(0)-catalyzed cross-coupling reaction was utilized as a method of carbon−carbon bond formation because of the ready availability of the precursors and the minimal number of side reactions that occur when a Sonogashira−Hagihara approach is used.[11−13]

In the present Letter, we outline a synthetic strategy for

(1) Munakata, M.; Wu, L. P.; Kuroda-Sowa, T. *Adv. Inorg. Chem.* **1999**, *46*, 173.
(2) Ziessel, R. *Synthesis* **1999**, 1839.
(3) Thummel, R. P.; Chamchoumis, C. M. *Adv. Nitrogen Heterocycles* **2000**, *4*, 107.
(4) Tschierske, C. *Angew. Chem., Int. Ed.* **2000**, *39*, 2454.
(5) Hagfeldt, A.; Grätzel, M. *Acc. Chem. Res.* **2000**, *33*, 269.
(6) Evangelista, R. A.; Pollak, A.; Allore, B.; Templeton, E. F.; Morton, R. C.; Diamandis, E. P. *Clin. Biochem.* **1988**, *21*, 173.
(7) Ziessel, R. *J. Incl. Phenom. Macro. Chem.* **1999**, *35*, 369.
(8) Ziessel, R. *Mol. Cryst. Liq. Cryst.* **1995**, *273*, 101.
(9) Reed, M. A.; Zhou, C.; Muller, C. J.; Burgin, T. P.; Tour, J. M. *Science* **1997**, *278*, 252. Collier, C. P.; Wong, E. W.; Belohradsky, M.; Raymo, F. M.; Stoddart, J. F.; Kuekes, P. J.; Williams, R. S.; Heath, J. R. *Science* **1999**, *285*, 391. Collier, C. P.; Mattersteig, G.; Wong, E. W.; Luo, Y.; Kristen, K.; Sampaio, J.; Raymo, F. M.; Stoddart, J. F.; Heath, J. R. *Science* **2000**, *289*, 1172. Gittins, D.; Bethell, D.; Schiffrin, D. J.; Nichols, R. J. *Nature* **2000**, *408*, 67.
(10) Ziessel, R. *J. Chem. Educ.* **1997**, *74*, 673. Harriman, A.; Ziessel, R. *Coord. Chem. Rev.* **1998**, *171*, 331 and references therein.
(11) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, L., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1990; Vol. 3, pp 545−547.

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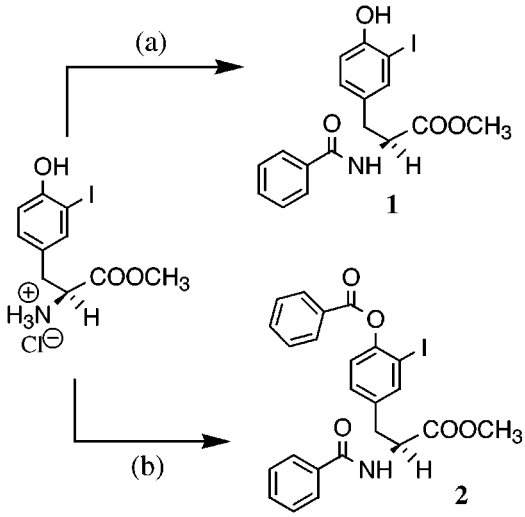
the grafting of one or two chiral L-tyrosine fragments to a variety of different oligopyridines via ethynyl spacers. The choice of tyrosine as biofragment reflects the thinking that it would act as an efficient electron relay in model systems, mimicking the natural water oxidation machinery, but also act as a possible anchor for binding to oligopeptides or oligonucleotides.[14−16] In natural photosynthesis, light absorption drives electron transfer from water to carbon dioxide, producing atmospheric oxygen and providing the biosphere with an inexhaustible amount of reducing power. Light-driven oxidation of water is catayzed by a reaction center, the so-called photosystem II (PS II), which is composed of arrays of chlorophyll molecules (e.g., P_{680}), electron acceptors (quinones), and donors (tyrosines). In brief, the oxidized P_{680} retrieves an electron by oxidation of a nearby tyrosine residue which then forms a neutral radical. This radical in its turn oxidizes a tetranuclear Mn cluster bound to PS II. After four consecutive turnovers, two water molecules are oxidized and one oxygen molecule is produced. In short, one of the key steps is the electron-transfer retrieval from the tyrosine.

The aim of the present work is to construct artificial systems able to mimic part of the electron-transfer reaction in PS II. The synthetic routes have been adapted to ensure that various protecting groups, such as benzoyl, can be attached either to the amine or to the amine and phenol fragments and to provide a means by which to tune the electron-transfer process in subsequent photophysical experiments.

Access to this family of ligands requires the synthesis of the key building blocks **1** and **2**, which have been prepared from the esterified tyrosine salt[17] (Scheme 1), using a methodology commonly and widely used in amino acid/peptide chemistry.

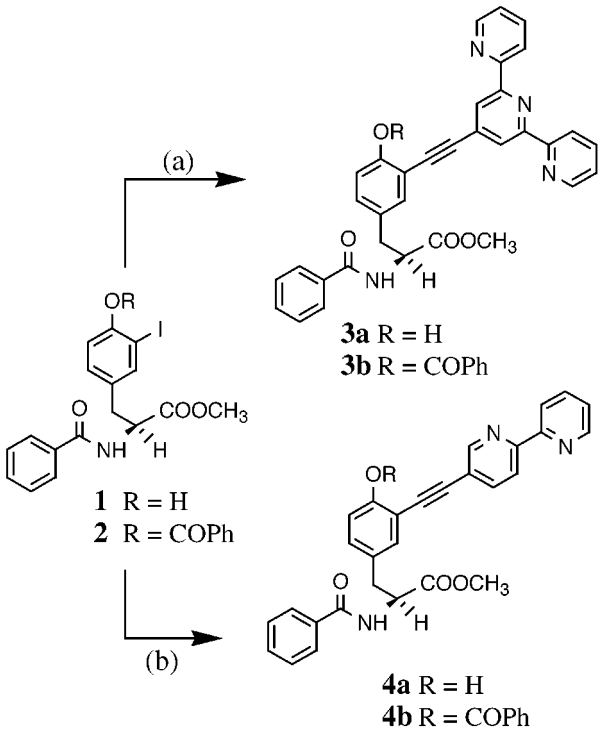
Scheme 1[a]



[a] (a) Benzoyl chloride (1 equiv), triethylamine (2 equiv), rt, 89%; (b) benzoyl chloride (2 equiv), triethylamine (6 equiv), rt, 73%.

Quite selective formation of the amide-protected compound **1** could be achieved in the presence of 2 equiv of base and equimolar amounts of benzoyl chloride under mild temperature conditions. The synthesis of **1** requires special conditions and is prone to low yield in the presence of an excess of acid chloride or base as well as at higher temperature. Indeed, the diprotected compound **2** is prepared with 2 equiv of benzoyl chloride and excess base. The tyrosine-grafted monotopic bipy and terpy ligands **3a/b** and **4a/b** are readily synthesized via a Sonogashira−Hagihara cross-coupling reaction between respectively 4′-ethynyl-2,2′:6′,6″-terpyridine[18] and 5-ethynyl-2,2′-bipyridine[18] and iodo-functionalized L-tyrosine compound **1** or **2** (Scheme 2).

Scheme 2[a]



[a] (a) 4′-Ethynyl-2,2′:6′,6″-terpyridine (1 equiv), $[Pd(PPh_3)_2Cl_2]$ (6 mol %), CuI (6 mol %), THF, $^iPr_2NH$, rt, 42% for **3a** and 49% for **3b**; (b) 5-ethynyl-2,2′-bipyridine (1 equiv), $[Pd(PPh_3)_2Cl_2]$ (6 mol %), CuI (6 mol %), THF, $^iPr_2NH$, rt, 57% for **4a** and 60% for **4b**.

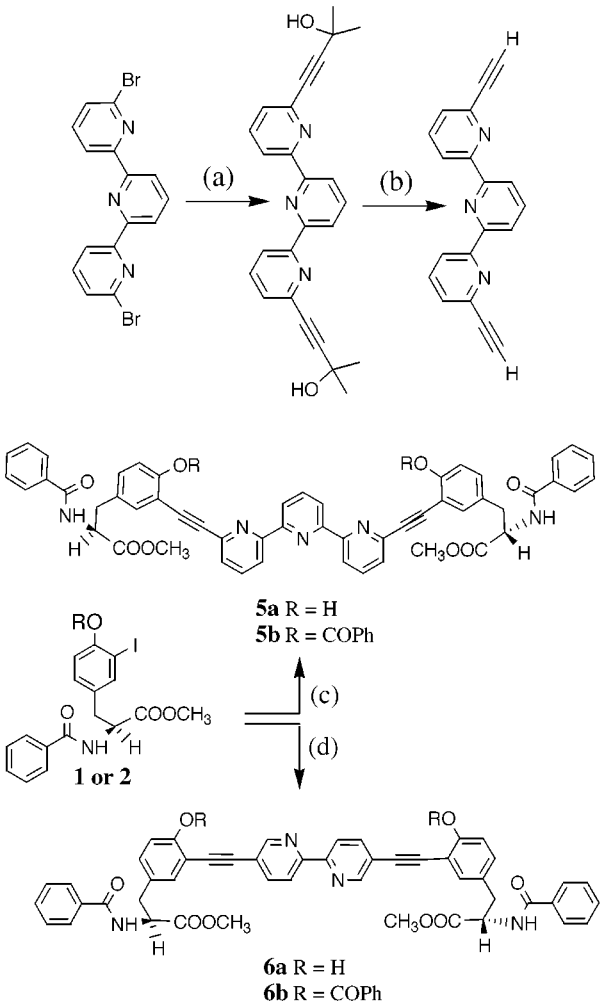
This is a convenient and versatile method for the connection step because of the required mild conditions and the tolerance of various functions such as an amide, an ester, and/or a phenol. In fact, the Pd(0) catalyst precursor was prepared in situ from Pd(II) and Cu(I) salts and a large excess of a secondary base was needed to quench the nascent acid. It was soon established that the phenol-protected tyrosine derivative **2** also reacted smoothly under similar conditions

(12) Ziessel, R.; Suffert, J.; Youinou, M.-T. *J. Org. Chem.* **1996**, *61*, 6535.
(13) Tour, J. M. *Chem. Rev.* **1996**, *96*, 537 and references therein.
(14) Barber, J.; Andersson, B. *Nature* **1994**, *370*, 31 and references therein.
(15) Magnuson, A.; Berglund, H.; Korall, P.; Hammarström, L.; Akermark, B.; Styring, S.; Sun, L. *J. Am. Chem. Soc.* **1997**, *119*, 10720.
(16) Hurley, D. J.; Tor, Y. *J. Am. Chem. Soc.* **1998**, *120*, 2194.
(17) Jung, M. E.; Rohloff, J. C. *J. Org. Chem.* **1985**, *50*, 4909.
(18) Grosshenny, V.; Romero, F. M.; Ziessel, R. *J. Org. Chem.* **1997**, *62*, 1491.

with the bipy- and terpy-alkyne functionalized cores providing ligands **3b** and **4b** in acceptable yields (Scheme 2). It is worth noting that these doubly protected compounds are also conveniently prepared from derivatives **3a** and **4a** by reaction of benzoyl chloride in excess triethylamine. Molecules **3b** and **4b** will be important test compounds in subsequent photophysical experiments in which electron transfer from the phenolic moiety to, for example, a ruthenium triplet excited state is expected to be strongly inhibited in contrast to the related derivatives **3a** and **4a**.

Consequently, the success achieved in the palladium-catalyzed coupling reaction with tyrosine fragments prompted us to investigate the functionalization of dibromo-substituted starting materials. The synthesis of the chiral di-tyrosine ligands **5** and **6** could be achieved in good yields under similar conditions starting respectively from 5,5′-diethynyl-2,2′-bipyridine[18] and 2″,6-diethynyl-2,2′:6′,6″-terpyridine (Scheme 3).

Scheme 3[a]

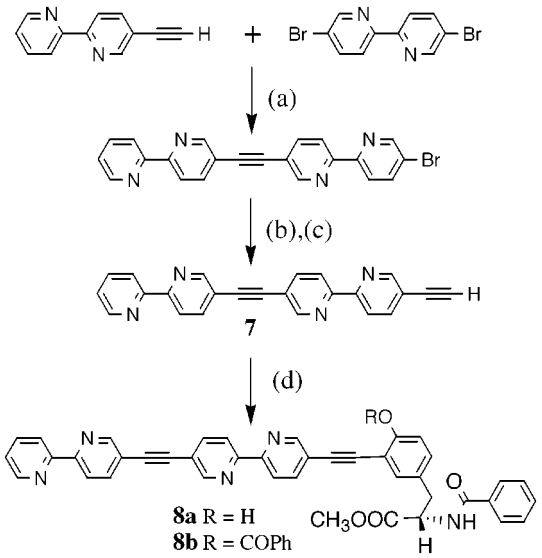


[a] (a) 2″,6-Dibromo-2,2′:6′,6″-terpyridine, HC≡C(CH$_3$)$_2$OH (2.5 equiv), [Pd^0(PPh$_3$)$_4$] (6 mol %), ^{n}PrNH$_2$, 60 °C, 70%; (b) NaOH (excess), toluene, 100 °C, 89%; (c) 2″,6-diethynyl-2,2′:6′,6″-terpyridine (0.5 equiv), [Pd(PPh$_3$)$_2$Cl$_2$] (6 mol %), CuI (6 mol %), THF, ^{i}Pr$_2$NH, rt, 70% for **5a** and 72% for **5b**; (d) 5,5′-diethynyl-2,2′-bipyridine (0.5 quiv), [Pd(PPh$_3$)$_2$Cl$_2$] (6 mol %), CuI (6 mol %), THF, ^{i}Pr$_2$NH, rt, 76% for **6a** and 74% for **6b**.

The diethynyl-terpy building block is prepared by taking advantage of well-established protocols[18] from 2″,6-dibromo-2,2′:6′,6″-terpyridine[19] and propargylic alcohol. The resulting 2″,6-diethynyl-2,2′:6′,6″-terpyridine (70%) is completely deprotected in refluxing toluene under basic conditions (NaOH pellets), affording the bis-terminal alkyne in good yield (89%). It is worth pointing out that quite selective monodeprotection could be provided by varying the experimental procedure. According to previous observations with 1,4-(2-methyl-3-butyn-2-ol)-2,5-didodecyloxybenzene,[20] selective monodeprotection was achieved by heating the reaction to reflux in benzene under basic conditions for relatively short reaction times. During the grafting of the tyrosine residue, the formation of a side product assigned as the monosubstituted derivatives could not be prevented entirely despite varying the experimental conditions, including a large excess of derivatives **1** or **2**. It is surmized that the deactivation of the Pd catalyst is possibly due to chelation of the polypyridine fragment to the metal center, a process which had not been envisaged in previous experiments. One other possibility is that the coupling of one tyrosine residue to the bipy or terpy skeleton deactivates the compound with respect to further reaction. It is worth pointing out that addition of another 6 mol % of [Pd(PPh$_3$)$_2$Cl$_2$] and CuI during the course of the reaction does not significantly improve the final yields of the target derivatives.

A further synthetic application of the present reaction is demonstrated by the cross-coupling reaction of the pivotal intermediates **1** and **2** with the ethynyl-functionalized ditopic module **7**, itself prepared by a multistep and linear procedure from 5,5′-dibromo-2,2′-bipyridine and 5-ethynyl-2,2′-bipyridine (Scheme 4).[21]

Scheme 4[a]



[a] (a) [Pd(PPh$_3$)$_4$] (6 mol %), benzene, ^{i}Pr$_2$NH, 80 °C, 74%; (b) TMSC≡CH, [Pd(PPh$_3$)$_2$Cl$_2$] (6 mol %), CuI (10 mol %), THF, ^{i}Pr$_2$NH, rt, 60%; (c) K$_2$CO$_3$, CH$_3$OH, rt, 89%; (d) **1** or **2** (1 equiv), [Pd(PPh$_3$)$_2$Cl$_2$] (6 mol %), CuI (6 mol %), THF, ^{i}Pr$_2$NH, rt, 49% for **8a** and 50% for **8b**.

Here, the relatively low yields of the final coupling reaction providing compounds **8a/b** could be due to the sparingly soluble ethynyl starting material and/or to the presence of a strong σ-withdrawing effect[22] of the alkyne spacer spanning the two bipy modules. Complexation of both bipy subunits in ligands **8a** and **8b** will increase the charge density of the luminophoric label (4+ vs 2+ for the others derivatives), and it is anticipated that interaction with anionically charged microstructures such as DNA, micelles, dendrimers, or polyelectrolytes will be significantly strengthened.[23]

The next phase of this work is to complex the empty coordination sites with ruthenium(II) precursors and to study the efficiency of electron transfer from the tyrosine moieties to the ruthenium triplet excited state. It is forseen that the triple bond will serve as an efficient conduit for channelling the electron. The development of these new chiral photosensitizers would expand the opportunities for applications in the field of sensors and bioactive chromophores. The study of these scaffoldings is currently underway, and the results will be disclosed in the near future.

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Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Burstall, F. H. *J. Chem. Soc.* **1938**, 1662. Uchida, Y.; Okabe, M.; Kobayashi, H.; Oae, S. *Synthesis* **1995**, 939.
(20) Khatyr, A.; Ziessel, R. *J. Org. Chem.* **2000**, *65*, 3126.
(21) Khatyr, A.; Ziessel, R. *J. Org. Chem.* **2000**, *65*, 7814.
(22) Eastmond, R.; Johson, T. R.; Walton, D. R. M.*J. Organomet. Chem.* **1973**, *50*, 87.
(23) Turo, N. J.; Barton, J. K.; Tomalia, D. A. *Acc. Chem. Res.* **1991**, *24*, 332 and references therein.