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SYNTHESIS OF NOVEL OXAZOLINE LIGANDS DESIGNED FOR ATTACHMENT TO GOLD NANOPARTICLES[†]

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Abstract – The synthesis of new modified 2-aryloxazoline ligands is described. The aromatic portion of the oxazoline has been appended with an amide linked thioctic acid derived group that is designed to facilitate attachment of the ligand to gold nanoparticles. This represents the first examples of ligands within the class of monodentate oxazolines that have been modified for this specific function.

INTRODUCTION

The attachment of metal-containing species onto solid supports (*e.g.* Pd on charcoal) represents an important class of heterogeneous catalysts used in both industrial and academic settings.[1] The desire for increased catalyst specificity and activity has led to the design of "heterogenised" systems in which a (typically) mono-metallic complex of known design is attached *via* a linker group to an inert support. These frameworks can include inorganic compounds (*e.g.* silica),[2] polymers[3] or other macro-molecules (*e.g.* dendrimers).[4] Homogeneous (liquid) systems provide a means for maintaining high reaction rates while catalyst recovery can be facilitated *via*, for example, ultrafiltration technology.[5]

We are interested in the possibility of supporting organometallic complexes onto soluble macromolecules such as metallic nanoparticles. Our initial objectives are to synthesise ligands that can bind robustly to transition metal fragments but at the same time provide strong covalent attachment to the surface of a (soluble) Au nanoparticle. The use of disulfides for this latter purpose is well known and can lead to the formation of two S-Au bonds (*via* S-S bond rupture).[6] This facet may provide a strong kinetic barrier to ligand, and hence catalyst, dissociation. Thioctic acid, a naturally occuring disulfide, is known to strongly bind to the exterior surface of Au nanoparticles.[6b]

As part of a long-term investigation[7] into the coordination chemistry of oxazoline ligands (*i.e.* **A**: Figure 1), we report herein a simple synthetic methodology for the synthesis of agents which are capable of attaching to both Au nanoparticles (*via* a disulfide) and to transition metal fragments (by coordination of an oxazoline group).[8] In addition, this methodology provides access to inherently chiral linker fragments by the use of oxazolines derived from enantiopure amino-indanols.

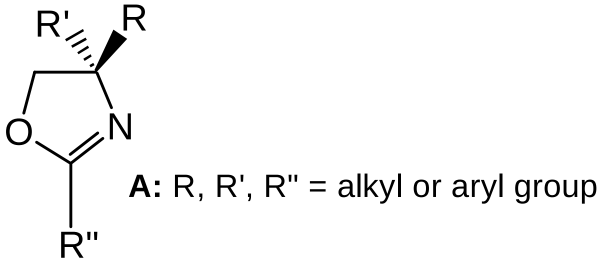
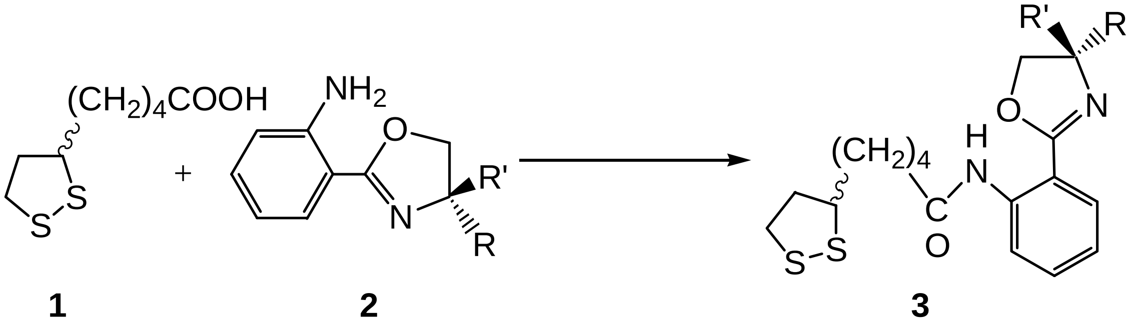


Figure 1

RESULTS AND DISCUSSION

Our synthetic methodology involves the coupling of commercially available thioctic acid (**1**: *i.e.*, rac-α-lipoic acid) and an appropriate 2-anilinyl-2-oxazoline (*i.e.* **2**)[9] to produce the required amide (**3**: Scheme1).

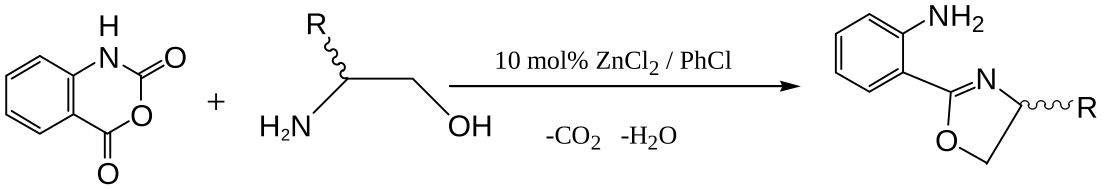


1 **2** **3**

Scheme 1

Oxazolines such as (**A**) are well known to coordinate with a large number of early and late transition metals to form stable complexes (R" = aryl).[8] We have chosen a simple aryl oxazoline (**2a**: R, R' = Me; *i.e.*, 2-[4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl]aniline[9a,b]) because of its ease of synthesis and demonstrated ligating potential.[9a] **2a** is readily synthesised (85%[9a]; recry. CH_2Cl_2/pet. ether) by boiling

(24 h) a PhCl or PhMe solution of isatoic anhydride (**4**), 10 mol% anhyd. $ZnCl_2$ and a slight excess of 2-methyl-2-amino-1-propanol (Scheme 2).[9a-c] Similarly, **[+]-5** is accessible (63%: Figure 2)[10] using similar synthetic protocols employing (*1S, 2R*)-(-)-*cis*-1-amino-2-indanol as the reactive amino-alcohol.[11]



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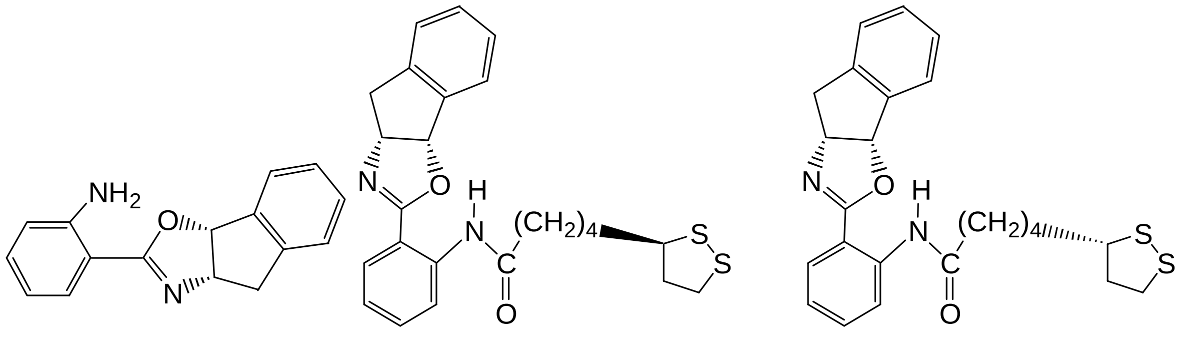
Scheme 2

Oxazolines (**2a**) and **[+]-5** are then used as shown in Scheme 1 to give the desired racemic derivative (**3**: R, R' = Me) and a diastereoisomeric mixture (Figure 2) of **6a** and **6b**.[10] For compounds (**3**) and (**6**), coupling was performed using the *in situ* derived acid chloride derivative of **1** (obtained *via* treatment of **1** with oxalyl chloride in CH_2Cl_2) and treating it with a solution of the desired aminooxazoline dissolved in CH_2Cl_2 containing excess NEt_3. In both cases, the crude mixture was subjected to flash chromatography (EtOAc/pet. ether, 1/10 [v/v]). This procedure led to the isolation of the pure racemate (**3**: 41%) and the diastereoisomeric mixture of **6a**/**6b**: 58%.



(+)-5 **6a** **6b**

Figure 2

We then tested one of these thioctic acid appended oxazolines in a nanoparticle forming reaction. Compound (**3**: R = R' = Me) readily forms stable Au nanoparticles in toluene solution[12] under standard reaction conditions.[13] We are currently investigating the binding properties of these new ligands in addition to developing separation protocols for the **6a**/**6b** mixture. In this regard, an enantioselective synthesis of natural (*R*)-(+)-α-lipoic acid has recently appeared.[14]

CONCLUSIONS

Racemic (**3**) and diastereoisomeric oxazoline ligands (**6a/b**) have been produced which are designed for simultaneous attachment to Au nanoparticles and for coordination to transition metal ions. Ligand (**3**) has been shown to readily form stable Au nanoparticles in toluene solution under standard conditions.

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†Oxazoline Chemistry Part II. For Part I, see reference 7.

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10. All new compounds show satisfactory spectroscopic purity (250 MHz ^{1}H NMR [$CDCl_3$/TMS], IR, and GC-MS). **rac-3**: orange oil; R_f (EtOAc/pet. ether: 1/10) = 0.49; IR: 1650 cm^{-1}; ^{1}H NMR: δ = 12.23 (s, 2H), 8.72 (d, *J* = 8.0 Hz, 2H), 7.83 (m, 2H), 7.45 (m, 2H), 7.03 (m, 2H), 4.06 (s, 4H), 4.02 (s, 4H), 3.58-1.49 (m, 24H), 1.40 (s, 6H, $C\underline{H}_3$, isomer 1), 1.39 (s, 6H, $C\underline{H}_3$, isomer 2). **(+)-5**: white solid; mp 140-141 ºC; R_f (EtOAc/pet. ether: 1/10) = 0.64; $[\alpha]_D$) = +127 (±7)° (*c* 0.011, 299 K, EtOAc); IR: 1650 cm^{-1}; ^{1}H NMR: δ = 7.67 (d, *J* = 7.9 Hz, 1H), 7.50 (br d, *J* = 3 Hz, 1H), 7.16 (m, 2H), 6.62 (m, 2H), 6.05 (br s, 3H), 5.77 (m, 1H), 5.36 (m, 1H), 3.44 (m, 3H). **6a/b**: light yellow solid; mp 80-81 ºC; R_f (EtOAc/pet. ether: 1/10) = 0.38; IR: 1650 cm^{-1}; ^{1}H NMR: δ = 12.20 (s, 1H), 8.67 (d, *J* = 8.6 Hz, 1H), 7.83 (m, 1H), 7.49-7.00 (m, 5H), 5.83 (d, *J* = 7.3 Hz, 1H), 5.42 (m, 1H), 3.64-1.23 (complex m, 15H). We were unable to determine the %de of this mixture by NMR spectroscopy; details of the separation of these two isomers will be reported elsewhere. Full spectroscopic details and assignments of all of the above compounds will be reported in a forthcoming full paper.
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12. Using an analogous method to that of Brust *et al.*,[13] an aqueous solution of sodium tetrachloroaurate is added to a toluene solution containing **3** and tetraoctylammonium bromide (as phase transfer reagent), followed by slow addition of excess $NaBH_4$. A dramatic colour change from red to dark purple/black is noted and a black powder is isolated from the organic layer. This material is entirely consistent with the known properties (*i.e.*, UV/Vis, *etc.*) of thiol-derivatised (*i.e.* **3** containing) Au nanoparticles. Full details of this reaction and the resulting Au materials will be reported shortly.

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