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CONDENSATION OF CHIRAL 1,3-OXAZOLIDINES WITH CATHECOL AND 4,4'-DIBROMOBIPHENOL: NEW ENANTIOPURE POLYDENTATE LIGANDS WITH C_2-SYMMETRY

Fabrizio Fabris,* Ottorino De Lucchi

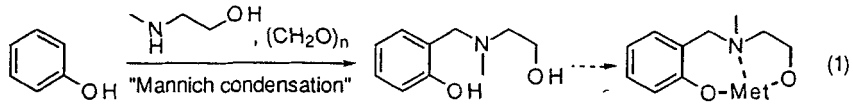
Dipartimento di Chimica, Università Ca' Foscari di Venezia, Dorsoduro 2137
I-30123 Venezia, Italy. E-mail: fabrisfa@unive.it

Giovanna Delogu and Davide Fabbri
Istituto per l'Applicazione delle Tecniche Chimiche Avanzate ai Problemi Agrobiologici del C.N.R., via Vienna 2, I-07100 Sassari, Italy

Abstract: The new enantiopure polydentate ligands **3a,c** and **4a-c** have been synthesized via Mannich condensation of 1,3-oxazolidines **1a-c** with 5,5'-dibromobiphenol and cathecol. The products are enantiopure C_2 chiral ligands of potential use in asymmetric synthesis as well as bioactive compounds.

The demand for new and diversified chiral ligands possessing more than two heteroatoms is warranted by the number of applications where they can be put to use. The Mannich condensation of an aminoalcohol to a phenol, as exemplified in Eq (1), allows for the introduction of two new heteroatoms at a proper distance from the phenolic hydroxy function as to permit, in principle, bond formation of all three heteroatoms with a metal centre.

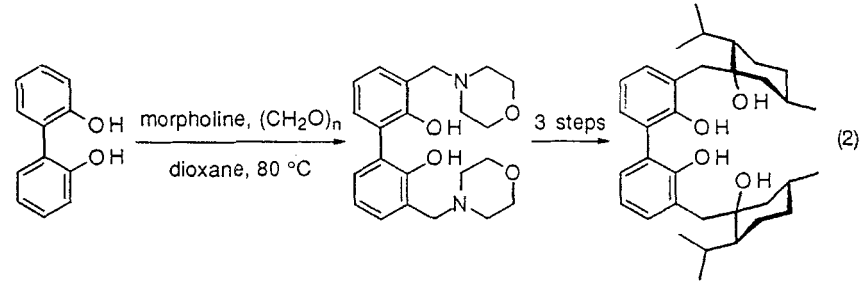
*To whom correspondence should be addressed.



(1)

This procedure, that has been applied in several instances to simple phenols,[1] has recently found useful utilization in the preparation of aminomethylated calixarenes[2] and in the development of a method for the generation of *o*-quinone methides as potential DNA alkylating or cross-linking agents.[3] We were interested in the preparation of C_2-symmetric chiral ligands derived from cathecol and 2,2'-biphenol for preparation of chiral catalysts for asymmetric synthesis. The doubling of the number of heteroatoms in a single polyfunctionalized ligand obtainable with these substrates, leads to systems with increased geometrical restrictions and possibly to a higher stereoselection and a better efficiency in the transmission of the chirality.[4] This is especially the case of lanthanides[5] that are used in an increasing number of applications in organic synthesis and are able to perform with up to 12 coordination sites. In other fields, these ligands are of interest as dinucleating ligands for multimetal or two centre catalysts and in bioinorganic chemistry.[4]

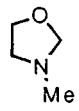
We have recently reported on the synthesis of new chiral tetrols composed by 2,2'-dihydroxybiphenyls substituted in the 3,3' positions by menthone (Eq 2) or camphor and observed chiral transfer from the terpenes to the atropisomeric bond of the biphenyl.[6] These tetrols were obtained in good yields in four step, the first of which was a Mannich reaction between biphenol, morpholine and paraformaldehyde.



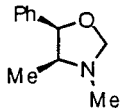
(2)

As a logical extension of this work, we thought to replace the symmetrical morpholine in the Mannich condensation with a secondary amine containing a hydroxy function such as *N*-methylhydroxylamine, and also containing

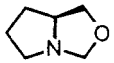
stereogenic centers such as (−)-ephedrine and (+)-prolinol. Under the same reaction conditions employed in the methylenomorpholination of 2,2'-biphenol,[1] *N*-methylhydroxylamine and paraformaldehyde gave complex mixture of products and the 1,3-oxazolidine **1a**. (−)-Ephedrine proved less reactive and more selective affording the oxazolidine **1b** and the monosubstituted derivative **2**.



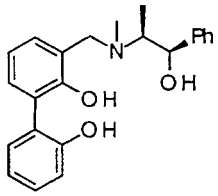
1a



1b



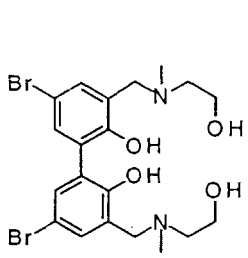
1c



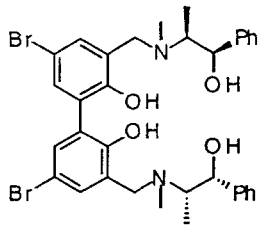
2

On forcing the reaction conditions and using directly the preformed 1,3-oxazolidines **1a,b** in place of the aminoalcohol and formaldehyde,[7] 2,2'-biphenol was observed to give complex reaction mixtures that were not further processed for the production of the desired ligands. With the aim of producing a 3,3'-substituted 2,2'-biphenol, circumventing the use of 2,2'-biphenol itself, it was thought to use the 5,5'-dibromo derivative that, having both the *para* positions occupied by the bromine atoms, should limit the products to the desired *ortho* derivatives only. Even if the reactivity seems to be lowered with respect to the parent 2,2'-biphenol, 5,5'-dibromo-2,2'-dihydroxybiphenyl succesfully added two molecules of the parent oxazolidine **1a** to afford the C_2 symmetrical aminoalcohols **3a** in 70% yield. The reaction occurs on heating the diol and the 1,3-oxazolidine in the minimum amount of dioxane (*ca.* 5 M solutions) in closed vials. On need, it is possible to stop the reaction at the stage of the monoaddition product, although tries were not accomplished toward this-aim. The reaction with the oxazolidine derived from (−)-ephedrine **1b** gives complex mixtures of products that are difficult to separate and that decompose on heating and on column chromatography. At variance, the (+)-prolinol derivative **1c** reacted smoothly with 5,5'-dibromo-2,2'-dihydroxybiphenyl to afford **3c** in good yield.

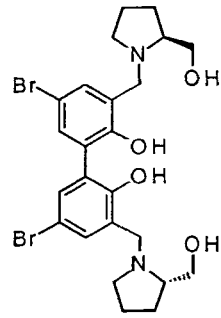
The cleaner reactivity of **1c** with respect to **1b** might be due to the conformational restrictions and strain of its bicyclic structure.



3a



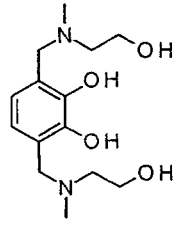
3b (not obtained)



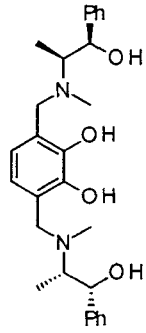
3c

It should be noticed that under the reaction conditions employed, 1,1'-binaphthol proved unreactive to either **1a-c**. This result might be expected on the basis that the Mannich reaction on a 2-naphthol requires the temporary suppression of the aromaticity in both rings of the naphthyl moiety. For this substrate, other reagents and conditions should be used.[8]

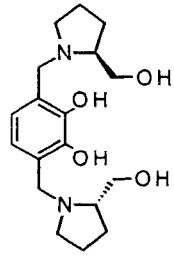
Turning to other reagents, it was observed that cathecol reacts under rather mild conditions with **1a-c** to afford the double Mannich product **4a-c**.



4a



4b



4c

The results of our screening on the reactivity of these substrates is summarised in the following table.

The aminoalcohols **4a-c** are representative of the class of chiral C_2-symmetric cathecols, a class of reagents that by virtue of the well-known complexing ability of cathecol to chelate metals should present wide applicability.[9] It shoud be

Table. Reaction conditions, yields and physical constants for products **2-4.**

Compound	Temperature (°C)	Time (hours)	Yield (%)	m.p. (°C)
2	80	12	14	151-153
3a	110	4	70	135 (dec)
3b[a]	110	12	/	/
3c	50	5	88	140-142
4b	110	24	70[b]	oil
4c	50	4	23	oil

[a]:The product was not observed. [b]: The product was not isolated

noticed that the reaction with cathecol occurs at lower temperature and that raising of the temperature causes decomposition of the products and a drammatic lowering in yields. The relative poor stability of these products can be attributed to retro-Mannich as well as photoinduced generation of the very reactive *o*-quinone methide.[2]

These tetrols will be employed in asymmetric catalysis, but they may also find application in biochemistry in analogy with siderophores[10] or for the incorporation of metals into protein for labeling purposes.[11]

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