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Synthesis of 6-endo-hydroxy norphos, a potential ligand for construction of chiral bimetallic catalysts

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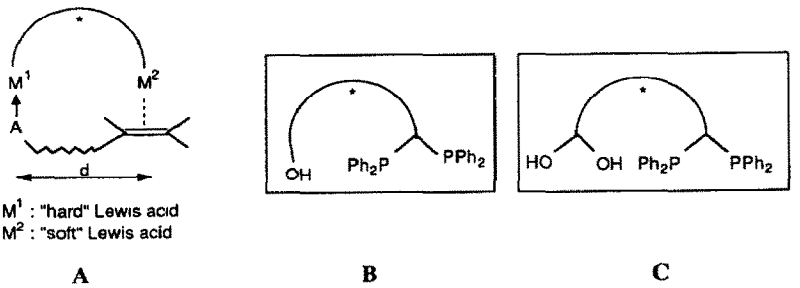
Abstract: 6-endo-hydroxy norphos has been synthesized in two steps from norphos dioxide. The key step involves hydroxymercuration with the participation of the endo P=O group. The hydroxy diphosphine is expected to be a good candidate for the synthesis of a bimetallic system where the diphosphine moiety will bind a soft metal (such as rhodium) while the OH group will provide a hard center by its transformation into an OM group (M = Ti, Al, B etc). The fixed geometry of the system should be adapted to stereoselective catalytic transformations on bifunctional substrates of defined structures.

Asymmetric catalysis has developed considerably in the last two decades, reaching the point where it is considered as a useful synthetic tool, even able to give rise to some industrial applications[1-6]. However many reactions remain which need to be improved, because either enantioselectivity or catalytic activity is too low to be of synthetic use. Apart recent results obtained in asymmetric dihydroxylation and asymmetric epoxidation of isolated double bonds[7], most of the high ee's in asymmetric catalysis involving double bonds are obtained when functional groups (OH, esters or amides) are directly connected or are in close vicinity of the double bond. We wish to consider the cases of asymmetric reactions on non-functionalized double bonds where a remote functional group is able to interact with a Lewis acid center localised on the chiral ligand at a defined distance (see **A** in Figure 1). We hope, in the cases of a good fit between chiral catalyst and the prochiral substrate, to improve both the enantioselectivity and the reactivity in hydrogenations or other typical transformations of C = C double bonds[8]. For that purpose we are currently devising relatively rigid chiral ligands, such as hydroxy diphosphine **B** or dihydroxy diphosphine **C**, able to bind two different metals at distances avoiding direct interactions between the two coordination spheres.



A B C

Figure 1

In this note we intend to present our first results in the elaboration of a ligand of class **B**, namely hydroxy norphos **10** (Figure 2).

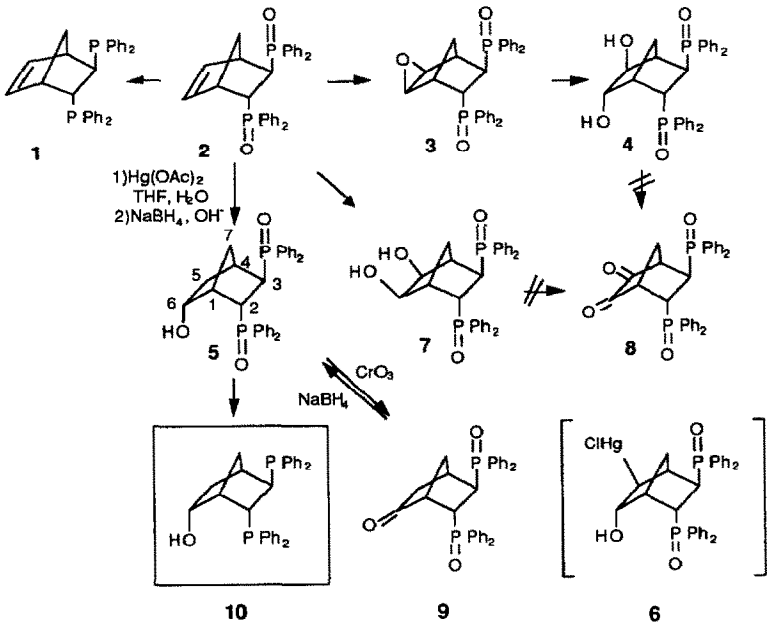


Figure 2

The bicyclo [2.2.1] heptane has a rigid skeleton which could be one of the candidates to orientate by respect to each other the two binding sites in **B** or **C**. Norphos **1** is a chelating chiral diphosphine prepared by H. Brunner et al. in 1979 which gave excellent results in asymmetric hydrogenation[13]. Racemic diphosphine dioxide **2** has been synthesized by a Diels-Alder reaction and has been subsequently resolved by dibenzoyl tartaric acid. We choose to use the double bond of norphos dioxide **2** for the introduction of one or two endo hydroxyl groups. Trans diol **4** or cis exo diol **7** are easily obtained, however we were unable to prepare diketone **8** (whose reduction should give rise to the desired endo diol). Attempts to oxidise directly **2** into **8** by the MnO_4K / Cu(II) reagent[14] were unsuccessful. We then decided to prepare the endo alcohol **10**. Treatment of norphos dioxide **2** by $Hg(OAc)_2$ in aqueous THF followed by addition of $NaBH_4$ and NaOH 3M gave in 95% yield an alcohol to which we assigned structure **5**. The compound is devoid of any epimeric or

regioisomeric alcohol as shown by ^{1}H, ^{13}C and ^{31}P nmr and thin layer chromatography of the crude compound. C_5 was identified by its coupling constant with the exo P=O ($^{3}J_{C\text{-}P}$ = 13.8 Hz) while C_6 gave $^{3}J_{C\text{-}P}$ = 5 Hz with the endo P=O[15]. The endo stereochemistry of the hydroxyl was derived from the detection of a small coupling $^{3}J_{H1\text{-}H6}$ < 5Hz (one expects $^{3}J_{H1\text{-}H6}$ = 0 for exo OH group), since it is known that $J_{H\text{-}H}$ between a bridged H and an endo H is zero[17]. Similarly $^{3}J_{H1\text{-}H2}$ = 4.7 Hz while $^{3}J_{H3\text{-}H4}$ = 0. Another proof of endo stereochemistry of OH (cis by respect to an endo P=O) is clearly shown by a sharp doublet (J = 12.4 Hz) at 5.95 ppm for the hydroxyl proton. This occurs because of intramolecular hydrogen bonding between the endo OH of **5**, **4** and **6** while exo OH in **4** and **7** gave ill defined signals. Oxidation of alcohol **5** by the Jones reagent led to ketone **9**. Reduction of the later gave the endo alcohol (without trace of its epimer) by an exo attack as usually found in [2.2.1] bicycloheptane systems. It is interesting that the hydrolysis of epoxide **3** produces only one of the two possible trans diols. The structure of **4** is well supported by ^{1}H and ^{13}C nmr. The surprisingly high regioselectivity is indicative of participation by the P=O group during the epoxide opening, either directly or indirectly by binding a water molecule. The hydroxymercuration of norphos dioxide **2** is also unexpected. Only compound **5** had been formed, to the exclusion of the alternate trans derivative (OH at C_5 position). Moreover the trans stereochemisty is unusual, since it has been shown that norbornene leads to cis exo chloromercuri alcohol[18,19]. Participation of the endo P=O group would explain both the regioselectivity and the stereoselectivity of the hydroxymercuration of norphos dioxide **2**. We did not find any reports in the literature on vicinal phosphinyl participation in electrophilic reactions, we are currently looking at this problem. All the transformations in figure 2 were performed starting from racemic norphos dioxide **2**. Moreover the sequences **2** -> **5** -> **10** were also realized from (-)-(2R,3R) norphos dioxide **2**[20], after resolution of racemic **2** by dibenzoyl tartaric acid[13]. The deoxygenation reaction at phosphorus (**5** -> **10**) was achieved in 50 % yield using $HSiCl_3$ and triethylamine at 80°C.

We compared the behaviour of endo hydroxy norphos **10** to norphos **1** itself in asymmetric hydrogenation of (Z)-N-acetyl dehydrophenylalanine. This ligand gives an *in situ* rhodium complex (by mixing with $(RhClCOD)_2$ in ethanol) which catalyzes asymmetric hydrogenation under 1 atm hydrogen, leading to (S) N-acetylphenylalanine with 98 % ee, in the range of the results obtained with norphos[13]. The catalyst with **10** is much more active than the catalyst with norphos itself (reaction time 4 h and 10 h respectively). We are currently investigating the introduction of a Lewis acid center in hydroxy norphos **10** attached to the hydroxyl group in order to realise the project described in Figure 1, where M^1 is titanium, aluminum or boron and where M^2 is rhodium.

Acknowledgments

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20) (-)-(2R,3R,6R) **5** : $[\alpha]_D$= -29 (c= 1, $CHCl_3$), mp >250°C.

(-)-(2R,3R,6R) **10** : $[\alpha]_D$= -43 (c= 1, $CHCl_3$), mp = 147-149°C.