Pure & Appl. Chem., Vol. 70, No. 2, pp. 415–418, 1998.
Printed in Great Britain.

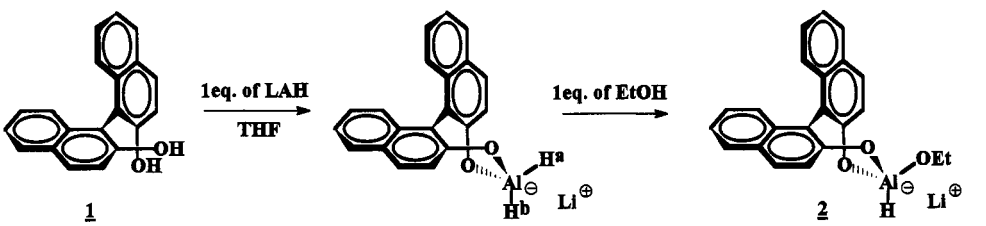
Chiral tridentate ligands based on 3-substituted binaphthols and derived complex hydrides of aluminium

M.Hovorka, I.Smíšková, R.Holakovský, J.Beran and I.Stibor

Department of Organic Chemistry, Prague Institute of Chemical Technology, 166 28 Prague 6, Czech Republic

Abstract: 2,2′-Dihydroxy-1,1′-binaphthalene-3-carboxylic acid 7, easily accessible by oxidative cross-coupling of methyl 3-hydroxy-2-naphthoate with β-naphthol followed by saponification, was successfully resolved and both enantiomers were reduced to 3-hydroxymethyl-1,1′-binaphthalene-2,2′-diol 9. Triol 9 served as a common chiral building block for the synthesis of two new types of axially chiral tridentate ligands (4a-b and 5a-h). When treated with 1eq. of LAH in THF, (*S*)-4a formed a hydride species exhibiting one quadrupole-broadened singlet in ^{27}Al-NMR and reducing acetophenone at room temperature within 5 minutes with 84%ee.

Enantioselective synthesis of chiral organic compounds represents a rapidly growing field which discloses fascinating new perspectives almost every day. A need for obtaining the structures with different degree of complexity in high optical purities set the challenge for hundreds of organic laboratories throughout the world. Enormous efforts in this branch bring constantly large amount of information helping thus to complete gradually the mosaic of stereoselective approaches to almost every class of chiral targets. Nevertheless, there is still much to be explored either in the development of new chiral auxiliaries (reagents, catalysts) or in fine tuning already known systems so that they are better able to fulfill desired requirements. Enantioselective reduction of prochiral carbonyl group is one of the most common and at the same time the most important problems in stereoselective synthesis. Efficient differentiation of enantiotopic carbonyl faces can be achieved using different approaches - methods based on complex hydrides being the most popular ones. Prior to the reduction step, lithium aluminium hydride ($LiAlH_4$), sodium borohydride ($NaBH_4$) and borane-THF complex (BH_3-THF) were modified by hundreds of chiral modifiers with varying degree of success depending on substrate structure and reaction variables (ref.1).
Binal-H 2, a complex hydride of aluminium modified by axially chiral 1,1′-binaphthalene-2,2′-diol 1, was introduced by Noyori in 1979 and since then it has been attracting remarkable attention in enantioselective reduction of carbonyl compounds (ref.2). This interest has several reasons: (*i*) the reagent is easily prepared *in situ* by successive treatment of LAH with binaphthol and 1eq. of ethanol (Scheme 1), (*ii*) both configurations are available due to ready accessibility of both enantiomers of binaphthol, and (*iii*) Binal-H exhibits exceptionally high enantioface-differentiating abilities toward diverse unsaturated carbonyl compounds.

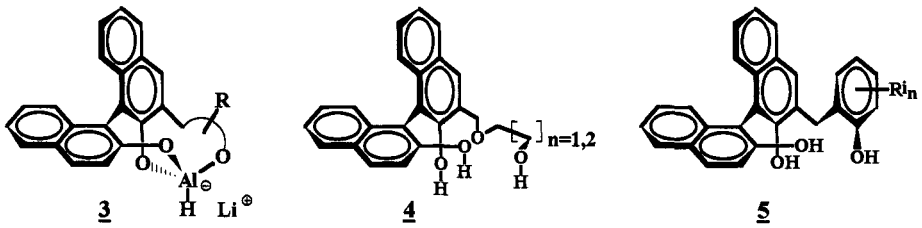


Scheme 1: *In situ* preparation of Binal-H

THE DESIGN OF NEW TRIDENTATE BINAPHTHOL-DERIVED LIGANDS

Few years ago our group has started a research directed to the exploitation of **unsymmetrically** substituted binaphthols (BINOLs) as chiral modifiers for LAH. We have concentrated on the design and construction

of tridentate ligands where the third oxygen bound to aluminium is covalently connected to position 3 of BINOL skeleton (general formula 3, Fig.1). We felt that the structure (*i.e.* length and stereochemistry) of this "connection" can play decisive role in reduction abilities of derived hydride species. From the inspection of general structure (3) it immediately becomes apparent that the intramolecular triple coordination of aluminium by three oxygens of unsymmetrical binaphthol-derived ligand imposes central chirality to aluminium atom. It is therefore necessary to tune the length and rigidity of a bridging chain so that only one configuration of aluminium is possible. Herein, we describe the synthesis of new ligands of general formulae (4) and (5) together with some preliminary results obtained in stereoselective reduction of carbonyl compounds.



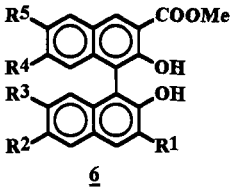
3 4 5

Fig.1: The design of new tridentate binaphthol-based ligands for LAH modification

SYNTHETIC PROBLEMS AND THEIR SOLUTION

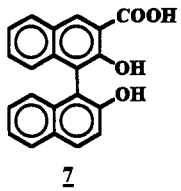
Unsymmetrically substituted binaphthol derivatives

In 1991 we have described a new, highly selective method for the preparation of unsymmetrically substituted BINOLs (ref.3). This approach, based on the oxidative cross-coupling of substituted β-naphthols mediated by Cu(II) salts in alkaline media, allows for the synthesis of diverse binaphthol building blocks generalized as (6) in very simple and straightforward manner. In following text we will focus on the simplest structure - 2,2′-dihydroxy-1,1′-binaphthalene-3-carboxylic acid (7).



6

R1 = H, Me, OMe
R2 = H, *tert*-Bu, adamanthyl, Br
R3 = H, OMe, OH
R4 = H, OMe
R5 = H, *tert*-Bu, adamanthyl



7

Fig.2: Available unsymmetrically substituted BINOLs

Resolution of starting material

Although we have already successfully resolved methyl 2,2′-dihydroxy-1,1′-binaphthalene-3-carboxylate (8) using low pressure LC on triacetylcellulose (ref. 3c), this method is not applicable on sufficiently large scale. Fortunately, simple method using sequential crystallization of racemic (7) with cinchonidine and cinchonine, respectively, from toluene-EtOAc mixtures was developed allowing to obtain optically active 7 in multigram quantities (ref.4). Advantageously, both enantiomers of 7 are accessible and resolving alkaloids can be recovered in high yields (Fig.3). HPLC analysis of corresponding methyl esters (*R*) and (*S*)-8 on Chiralpak OP+ chiral column was used to verify the enantiomeric purity (Fig.4).

Synthetic approach to tridentate ligands of type (4)

Simple and high-yield synthesis of ligands 4a (n=1) and 4b (n=2) was developed and reported by us very recently (ref.5). This process involves acid-mediated ionization of alcoholic group of 3-hydroxymethyl-

2,2′-dihydroxy-1,1′-binaphthalene 9 (easily obtained by the reduction of 8) in the presence of ethylene glycol or 1,3-propane diol as solvents. Chlorinated silica gel was advantageously used towards this purpose

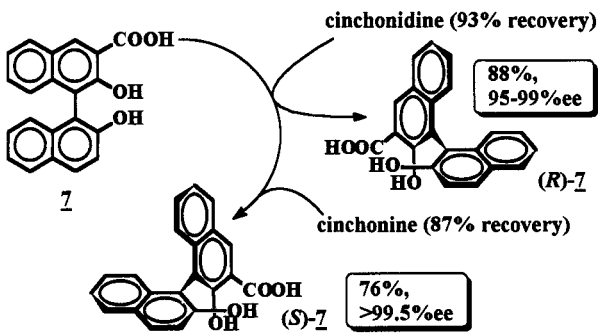


Fig.3: Resolution of racemic (7) into enantiomers

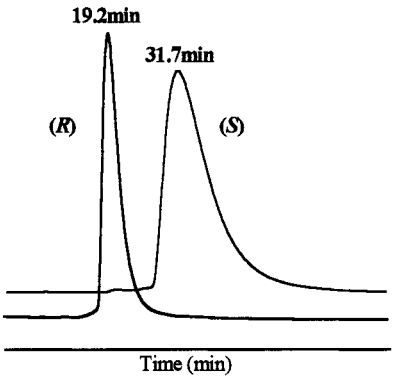
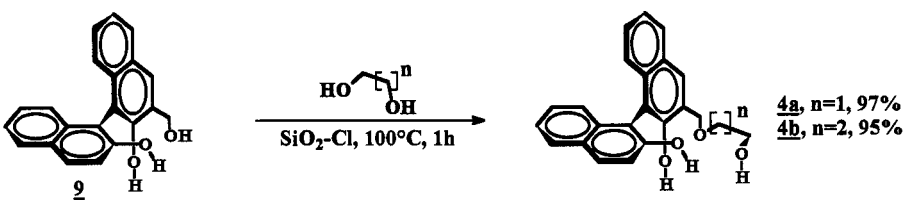


Fig.4: HPLC analysis of methyl esters derived from (*R*) and (*S*)-7 on CHIRALPAK OP+ column, elution with MeOH

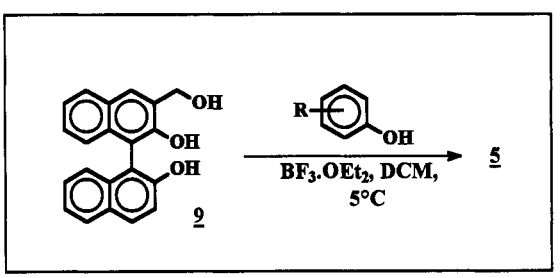
and no racemisation was observed during the reaction (Scheme 2).



Scheme 2: Synthesis of ligands 4a and 4b by acid-mediated etherification of 9

Synthetic approach to tridentate ligands of type (5)

A synthetic protocol was developed in our laboratories allowing to prepare ligands 5a - h in good yields and sufficient amounts (ref.6). This methodology is based on Friedel-Crafts alkylation of substituted phenols by binaphthalene benzylic alcohol 9 in the presence of BF_3 etherate. Ligands 5a and 5f were also prepared in optically pure form as (*S*)-enantiomers (Scheme 3).



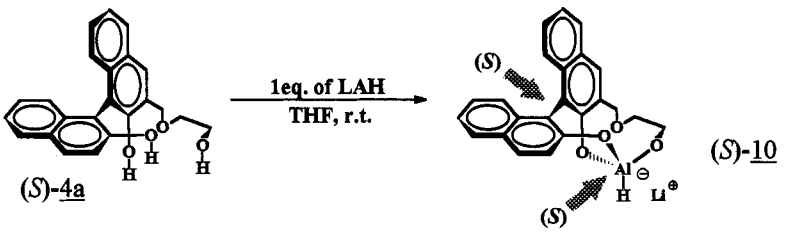
Starting phenol	Product
3,5-di-*tert*-butylphenol	(*rac.* 5a), 71%, (*S*-5a) 70%, >99.5%ee
2,4-di-*tert*-butylphenol	(*rac.* 5b), 43%
3,5-diphenylphenol	(*rac.* 5c), 78%
4-*tert*-butylphenol	(*rac.* 5d), 66%
4-phenylphenol	(*rac.* 5e), 72%
4-methylphenol	(*rac.* 5f), 66%, (*S*-5f) 65%, >99.5%ee
4-nonylphenol	(*rac.* 5g), 62%
6-*tert*-butyl-2-naphthol	(*rac.* 5h), 80%

Scheme 3: Synthesis of tridentate ligands 5a - h by Friedel-Crafts alkylation of phenols

Optical purity of 5a and 5f can easily be checked by their conversion to tri-O-methyl derivatives and subsequent measurement of ^{1}H-NMR spectra in the presence of (*R*)-(-)-1-(9-anthryl)-2,2,2-trifluoroethanol as a chiral solvating agent.

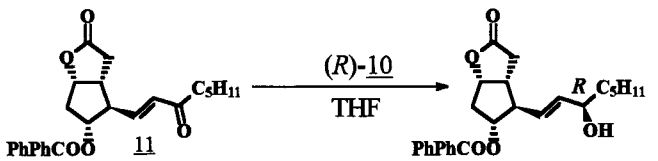
PRELIMINARY RESULTS OBTAINED WITH LIGAND 4a MODIFIED $LiAlH_4$

In a preliminary study, LAH was treated with 1eq. of optically pure 4a in THF at room temperature. Resulting homogeneous solution showed one quadrupole-broadened singlet in ^{27}Al-NMR spectrum positioned at 72ppm (ref.7). This observation seems to be in accordance with the structure (*S*)-10 (Scheme 4) which we propose for the complex hydride species.



Scheme 4: Generation of complex aluminium hydride in THF solution

The investigation of reducing abilities of complex hydride (*S*)-10 as well as similar species derived from other available ligands is just at the beginning at the moment, nevertheless, some promising results were already obtained. For instance, acetophenone is reduced by (*S*)-10 within 5 minutes at room temperature giving 92:8 mixture of enantiomeric 1-phenylethanols in almost quantitative yield.
Interesting results were also obtained in the reduction of prostaglandin intermediate 11. Diastereoselectivity of the reduction by (*R*)-10 is improving with decreasing temperature and affords product with predominating unnatural configuration 15*R*.



Temp.	(15*R*):(15*S*)
20°C	50 : 50
-20°C	60 : 40
-78°C	92 : 8

Scheme 5: The reduction of prostaglandin intermediate by (*R*)-10

Acknowledgement

Financial support of Grant Agency of Czech Republic (Grant No.203/94/0951) is gratefully acknowledged.

REFERENCES

1. See for example: V.K.Sing. *Synlett* **1991**, 605; K.Matsuki, H.Inoue and M.Takeda. *Tetrahedron Lett.***34**,1167 (1993); H.Haubenstock. *Top.Stereochemistry* **14**, 231 (1983).
2. R.Noyori, I.Tomino and Y.Tanimoto. *J.Am.Chem.Soc.* **101**, 3129 (1979); R.Noyori, I.Tomino, Y.Tanimoto and M.Nishizawa. *ibid.* **106**, 6709 (1984); R.Noyori, I.Tomino, M.Yamada and M.Nishizawa. *ibid.* **106**, 6717 (1984); R.Noyori. *Pure & Appl.Chem.* **53**, 2315 (1981); R.Noyori, I.Tomino and M.Nishizawa. *J.Am.Chem.Soc.* **101**, 5843 (1979); R.Noyori, M.Nishizawa and M.Yamada. *Tetrahedron Lett.* **22**, 247 (1981); R.Noyori and M.Nishizawa: *ibid.* **21**, 2821 (1980).
3. (a) M.Hovorka, J.Závada and J.Günterová. *Tetrahedron Lett.* **31**, 413 (1990); (b) M.Hovorka and J.Závada. *Org.Prep. & Proc.Int.* **23**, 200 (1991); (c) M.Hovorka, J.Závada, J.Günterová, M.Tichý and R.Ščigel. *Tetrahedron* **48**, 9503 (1992); (d) M.Hovorka and J.Závada: *Tetrahedron* **48**, 9517 (1992).
4. M.Hovorka, I.Stibor, I.Smíšková, V.Stružka and R.Holakovský. Czech Patent Application (*Reg.No.* PV 64-96).
5. M.Hovorka, I.Stibor, R.Ščigel and I.Smíšková. *Synlett* **1995**, 251; Czech Patent Application (*Reg.No.* PV 3347-94).
6. M.Hovorka, I.Stibor and I.Smíšková. Publication in preparation; Czech Patent Application (*Reg.No.* PV 1410-95).
7. Referenced externally to $Al(H_2O)_6^{3+}$, see D.A.Horne. *J.Am.Chem.Soc.* **102**, 6011 (1980).