Tetrahedron 67 (2011) 334–338

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Acetyl-BINOL as mimic for chiral β-diketonates: a building block for new modular ligands

Robert von Rönn, Jens Christoffers *

Institut für Reine und Angewandte Chemie, Carl von Ossietzky-Universität Oldenburg, D-26111 Oldenburg, Germany

ARTICLE INFO

Article history:
Received 5 October 2010
Received in revised form 5 November 2010
Accepted 8 November 2010
Available online 13 November 2010

Keywords:
Homogeneous catalysis
Chiral ligands
BINOL derivatives
Asymmetric catalysis
Titanium
Amino acid derivatives

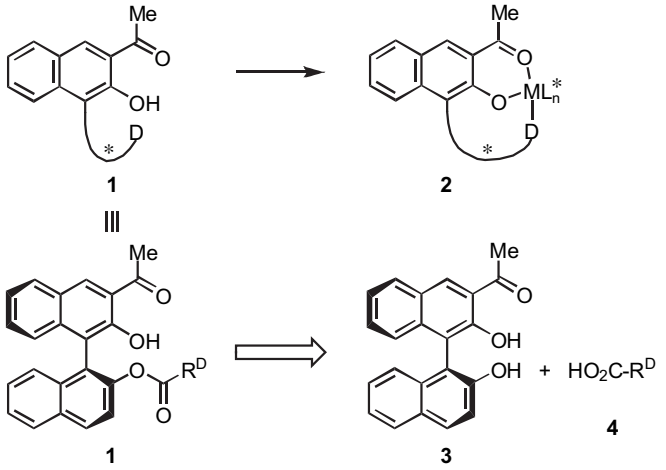
ABSTRACT

α-Acetyl-(*S*)-BINOL was prepared by *ortho*-lithiation and subsequent acetylation of acetal-protected (*S*)-BINOL. The β-hydroxyketone moiety of this compound is herein a structural mimic for a β-diketonate and forms six-membered chelates with transition metal ions. The second hydroxy-function was submitted to esterification with several carboxylic acids bearing another donor function, thus, new tridentate chiral ligands were obtained. Out of this library the L-proline-α-acetyl-(*S*)-BINOL-ester was identified to be most effective for the titanium-mediated addition of Et_2Zn to PhCHO yielding the respective secondary alcohol with up to 93% ee, which is better than with using (*S*)-BINOL itself. Besides a solvent dependency (use of MeCN is optimal), the proper choice of the counter-ion is crucial: anion exchange of bromide by trifluoroacetate gave a significant increase of enantioselectivity.

1. Introduction

Transition metal β-diketonato complexes are an important class of compounds in homogeneous catalysis.[1] However, chiral cogeners were extraordinarily seldom reported,[2] although they might be of great interest for asymmetric catalysis. The reason for rare reports on such chiral ligands might be, that stereogenic elements can only be implemented at the periphery of the planar six-membered chelates, making effective stereoinduction close to the catalytically active metal center difficult. We envisioned the α-carbonyl phenolate motif to be a reasonable structural mimic for β-diketonate ligands. With an additional donor function D another chelate ring could form and such a ligand **1** would become tridentate and capable of coordination to one face in an octahedral or tetrahedral metal complex **2** (Scheme 1). While the initial stereogenic element is the chiral axis, this second chelate ring would transfer the stereoinformation from the periphery of the acylphenol **1** to the metal fragment ML_n, thus, the metal center itself is becoming a stereocenter. With additional coordination sites L_n, the stereogenic metal center might be able to catalyze suitable C–C bond forming reactions in an asymmetric fashion.

We considered 3-acetyl-2,2′-dihydroxy-1,1′-binaphthyl (**3**) to be a suitable scaffold for such tripodal ligands **1**, since it combines all three key features of our new ligand concept: first, the 2-OH and the 3-acetyl group are a perfect mimic of a β-diketone, as already indicated by intramolecular H-bonding. Secondly, the other 2′-OH group is suitable for esterification with various carboxylic acids **4**, which carry the additional donor function D. Third, the chiral axis directs the chelating group D above the planar β-hydroxycarbonyl moiety of this scaffold, thus, providing the prerequisite for facial coordination to an octahedral or tetrahedral metal center. Since the



Scheme 1. A library of modular α-acetyl-BINOL derivatives **1** with additional donor functions D as mimetics of chiral β-diketonato complexes **2** and their synthesis from (*S*)-α-acetyl-BINOL (**3**) and carboxylic acids **4**.

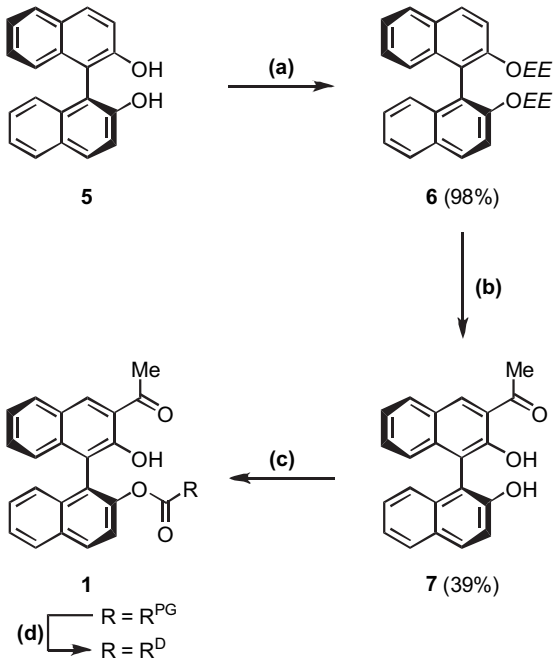
* Corresponding author. Tel.: +49 441 798 4744; fax: +49 441 798 3873; e-mail address: jens.christoffers@uni-oldenburg.de (J. Christoffers).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.11.037

BINOL moiety is a leading structure in asymmetric catalysis,[3] it is not surprising that tridentate BINOL derivatives have been successfully prepared and applied before.[4] However, respective compounds with a β-diketone mimicking motif have never been reported. For this reason, we wish to report herein on the synthesis of ligands **1** with a different range of donor groups D. We moreover report on the application of these ligands in a well investigated model reaction:[5] the titanium catalyzed nucleophilic addition of Et_2Zn to benzaldehyde. This process can be realized with BINOL itself with high yields and selectivities.[6]

2. Results and discussion

For the synthesis of ligand library **1** we envisioned introduction of the acetyl group after *ortho*-metalation. For this purpose, the ethoxyethyl (EE) protective group seemed to be a suitable acetal function for directing the metalation.[7] Twofold EE-protection of (*S*)-BINOL (**5**) proceeded as reported earlier by others (Scheme 2, 98% yield).[8] *ortho*-Deprotonation of bisacetal **6** underwent smoothly with a small excess of *n*-BuLi, however, conversion with different acetylating reagents turned out to be very tedious. For example, methyl acetate gave only traces of product **7**, although we had good experience with it in another project.[9] The application of AcCl, $AcNMe_2$, AcCN or MeCHO (with subsequent oxidation) neither gave significant amounts of compound **7**. Finally, the application of excess Ac_2O followed by acidic workup in order to cleave the acetal protective groups furnished α-acetyl-BINOL **7** as a yellow solid. The esterification as diversifying synthetic step was performed with carboxylic acids **4** and DCC as coupling reagent in the presence of catalytic amounts of DMAP. This esterification was first of all explored with the conversion of $PhCO_2H$ (**4a**). To our delight, it proceeded completely regioselective, as it is indicated by the chemical shifts of OH groups in the NMR spectra: compound **7** has the signal of the 2-OH-proton at 12 ppm, because it is involved in H-bonding to the 3-acetyl group. The phenolic 2′-OH appears at 5 ppm. The signal of the acidic proton of compound **1a** (and later on in all other examples **1b**–**1w**) shows up at 12 ppm, again clearly indicating H-bonding to the adjacent carbonyl group. Table 1 lists carboxylic acids **4** as well as yields of corresponding esters **1**. Several benzoic acid derivatives (**4b**–**4h**, entries 2–8) as well as picolinic (**4i**, entry 9) and nicotinic acids (**4j**, entry 10) were applied. Moreover, derivatives of L- and D-proline (**4k**–**4l**, entries 11 and 12) and L-valine (**4m**, entry 13) were submitted to esterification. In these and some other cases the donor function D of residues R^D needed protection in order to perform the esterification step. Other carboxylic acids with protected residues R^{PG} were compounds **4c**, **4d**, **4f**, and **4g**, which were debenzylated subsequently to the esterification step. Table 2 lists deprotection conditions and yields. For anthranilic acid **4e** and valine **4m** the *N*-Boc protective group was used, whose cleavage was unproblematic when performed with TFA (entries 3 and 10). Actually, we used *N*-Boc-L-proline instead of **4k** in initial experiments. It however turned out that Boc-deprotection with TFA did not give the corresponding ester **1t**. For unknown reasons, decomposition under formation of compound **7** occurred. Therefore, Cbz was chosen as the protective group for proline. The Cbz-group was then cleaved with HBr[10] and the hydrobromides **1s** and **1u** (entries 6 and 8) were formed. In subsequent studies a significant anion dependence of enantioselectivities was observed (vide infra). For this reason, the bromide was exchanged by trifluoroacetate (ligands **1t** and **1v**, entries 7 and 9). This anion change was achieved by evaporating the pyrrolidinium bromide with TFA. Conversion was monitored by ESI-MS (negative mode); it was complete when no more bromide was detectable.



Scheme 2. Synthesis of library of modular α-acetyl-BINOL derivatives **1** with additional donor functions D. Reagents and conditions: (a) 4 equiv EVE, 0.1 equiv PPTS, CH_2Cl_2, 23 °C, 16 h; (b) 1. 1.2 equiv *n*-BuLi, THF, 0 °C, 15 min; 2. 10 equiv Ac_2O, 0 °C, 15 min, 23 °C, 15 min; 3. HCl–H_2O, 23 °C, 30 min; (c) 1 equiv RCO_2H **4**, 1.2 equiv DCC, 0.1 equiv DMAP, CH_2Cl_2, 60 °C, 16 h; for residues R (R^D or R^{PG}) and yields see Table 1; (d) for deprotection details and conditions see Table 2; EVE=ethylvinylether, PPTS=pyridinium *para*-toluenesulfonate, DCC=dicyclohexylcarbodiimide, DMAP=4-(dimethylamino)pyridine, EE=1-ethoxyethyl.

Table 1
Esterification of acetyl-BINOL **7** with carboxylic acids **4**. Compounds **1c**–**1g** and **1k**–**1m** were subsequently deprotected (see Table 2)

Entry	RCO_2H	Product	Yield (%)
1	$PhCO_2H$ **4a**	**1a**	74
2	2-$MeOC_6H_4CO_2H$ **4b**	**1b**	53
3	2-$BnOC_6H_4CO_2H$ **4c**	**1c**	61
4	3-$BnOC_6H_4CO_2H$ **4d**	**1d**	51
5	2-$BocHNC_6H_4CO_2H$ **4e**	**1e**	41
6	2-$BnO_2CC_6H_4CO_2H$ **4f**	**1f**	49
7	3-$BnO_2CC_6H_4CO_2H$ **4g**	**1g**	68
8	2-$Ph_2PC_6H_4CO_2H$ **4h**	**1h**	64
9	2-Pyridyl-CO_2H **4i**	**1i**	65
10	3-Pyridyl-CO_2H **4j**	**1j**	64
11	(*S*)-*N*-Cbz-proline **4k**	**1k**	83
12	(*R*)-*N*-Cbz-proline **4l**	**1l**	49
13	(*S*)-*N*-Boc-valine **4m**	**1m**	64

In order to establish the feasibility of our new ligand library, we adopted a procedure for a titanium-mediated asymmetric addition of Et_2Zn to benzaldehyde as reported by Mori and Nakai,[6] who converted PhCHO with Et_2Zn in the presence of 1.2 equiv $Ti(O\textit{i}\text{-}Pr)_4$ and 0.1 equiv (*S*)-BINOL and achieved 85% ee of (*S*)-1-phenyl-1-propanol (Scheme 3). First of all, we used (*S*)-BINOL (**5**) itself in order to check our procedure and to compare it with Mori's results. With this experiment, we furthermore established a reference for the absolute configuration of the product. Conversion as well as enantiopurity of the product was determined by GLC on a chiral phase after quenching a sample of the reaction mixture with aqueous NH_4Cl. In order to compare reaction rates with different ligands, we stopped every batch after 1 h stirring at 0 °C and listed the respective conversion in the Tables 3–5. Quantitative conversions could of course be achieved in all cases when running the reactions over night. The control experiment with (*S*)-BINOL (**5**) resulted in 78% conversion and 81% ee (Table 3, entry 1). Next we checked the effect of acetyl-BINOL **7**, which gave lower ee than BINOL (entry 2). Furthermore, benzoic ester **1a** without a third