Tetrahedron: *Asymmetry* xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

Enantioselective alkylation of aromatic aldehydes with (+)-camphoric acid derived chiral 1,3-diamine ligands

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A R T I C L E I N F O

Article history:
Received 3 January 2017
Revised 12 January 2017
Accepted 19 January 2017
Available online xxxx

A B S T R A C T

A series of chiral 1,3-diamine ligands derived from (+)-camphoric acid were prepared from the reaction of 1,3-diamino-1,2,2-trimethylcyclopentane with aromatic aldehydes, followed by reduction of the corresponding diimines. These newly synthesized ligands were tested in the enantioselective alkylation of benzaldehyde with diethylzinc, giving 1-phenyl-1-propanol with enantiomeric ratios of up to 86:14. Our most selective ligand, derived from 2-methoxybenzaldehyde, was also tested in the alkylation of several aromatic aldehydes and product alcohols with enantiomeric ratios of up to 93.5:6.5 being observed in 2 h at room temperature in the presence of 5 mol % ligand.

1. Introduction

Chiral secondary alcohols have found widespread application in many areas such as fine chemistry, pharmaceuticals, perfumes, herbicides and pesticides, among others, because they incorporate many structures with biological activity. Thus, reactions which allow the efficient synthesis of these compounds are of major importance in organic chemistry. The direct synthetic utility of chiral alcohols is no less significant, since the hydroxyl group is an excellent precursor for many other functional groups. Among the methods for obtaining optically active secondary alcohols, special interest has been placed upon the enantioselective alkylation of aldehydes with organozinc reagents in the presence of chiral ligands. This reaction allows the creation of a new stereogenic center from the carbonyl carbon atom and, simultaneously, a lengthening of the carbon chain in the alcohol product relatively to the parent aldehyde.[1–9] Additionally, the use of organozinc reagents with different alkyl or aryl groups allows obtaining a wide variety of optically active products to be obtained.

While many types of structurally diverse ligands have been used in enantioselective alkylations,[10–15] those with two *N*-donor atoms have not received widespread attention, although there are several examples of efficient ligands of this type. It should also be noted that 1,3- and 1,4-bidentate ligands have been relatively less studied than 1,2-bidentate ligands.[16–25]

Our continued interest in the use of (+)-camphoric acid derived (1*R*,3*S*)-1,3-diamino-1,2,2-timethylcyclopentane, a 1,3-diamino chiral backbone,[26–29] led us to prepare some new chiral secondary diamine ligands to test in the enantioselective alkylation of aldehydes with diethylzinc.

2. Results and discussion

2.1. Ligand synthesis

Scheme 1 illustrates the synthetic sequence used for obtaining the camphoric acid derived secondary diamines **3**: the reaction of (1*R*,3*S*)-1,3-diamino-1,2,2-trimethylcyclopentane **1**, prepared according to our previously described procedure,[26] with aromatic aldehydes, originates from diimines **2**, which are subsequently reduced to the chiral secondary diamines.

For the synthesis of diimines **2**, we initially carried out the reaction with benzaldehyde, using various reaction conditions (reflux in ethanol or toluene, acid and base catalysis, the use of water sponges, ultrasound irradiation, microwave irradiation). Microwave irradiation has been described for the synthesis of imines under different reaction conditions, so we decided to try this technique in the synthesis of our diimines.[30–33]

From the different methods tested, we found that the most favorable one was using microwave irradiation. Using this method, the products were formed in short reaction times and tedious work-up was not necessary, since the products precipitated directly from the reaction medium upon cooling. Our studies led to the following optimized conditions: the reaction of the diamine with 2 equivalents of aldehyde, in ethanol and in the presence of a

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http://dx.doi.org/10.1016/j.tetasy.2017.01.013
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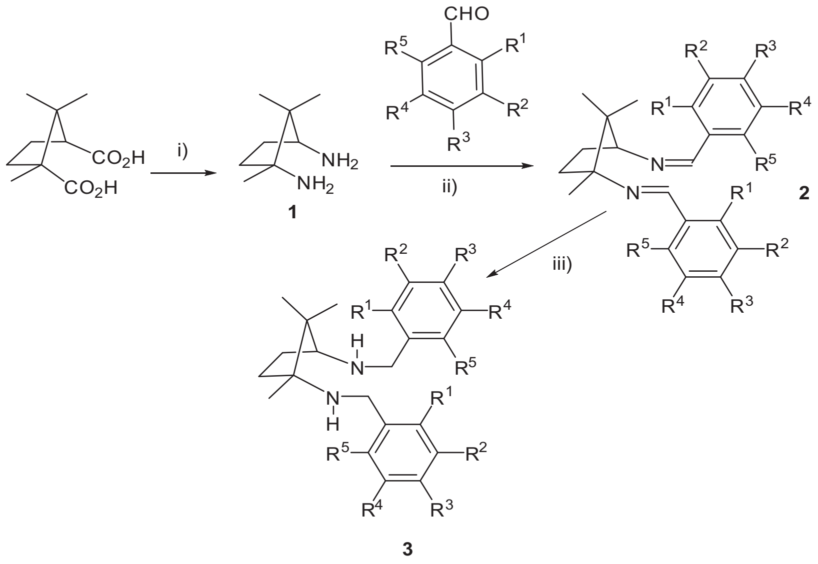


Scheme 1. Synthesis of the chiral diamine ligands. Reagents and conditions: (i) H_2SO_4, NaN_3, $CHCl_3$, 55–65 °C, overnight; (ii) ethanol, microwave radiation, 30 min. (iii) $NaBH_4$, MeOH/$CHCl_3$ 1:1, rt.

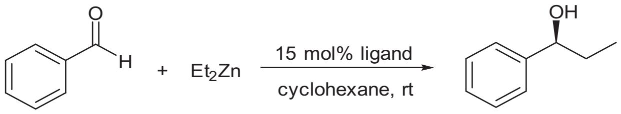
catalytic amount of *p*-toluenesulfonic acid monohydrate. The reaction was irradiated for 15 min. at 250 W (the reaction temperature reached 85–150 °C and the pressure 1–8 bar). Using these conditions, we synthesized the series of diimines **2a**–**2h**, (Table 1) with moderate yields.

In order to obtain the diamines, the corresponding diimines **2a**–**2h** were subjected to reduction with sodium borohydride, in a 1:1 mixture of MeOH/$CHCl_3$, at room temperature. In this way, diamines **3a**–**3h** were isolated, mostly in very good yields (Table 2).

2.2. Enantioselective alkylation reactions

Using benzaldehyde as the model substrate, diamine ligands **2a**–**2h** were tested in the enantioselective alkylation with diethylzinc. The reactions were initially carried out in dry cyclohexane at room temperature for 24 h, in the presence of 15 mol % of chiral ligand, our previously optimized conditions in Scheme 2.[26] The results obtained are presented in Table 3.

All of ligands tested were very efficient, with almost complete conversion in the alkylations. Moderate to good selectivity was observed, and the highest enantiomeric ratio (*er*), 86:14, was obtained in the presence of ligand **3b**. In order to analyze the effect of the reaction temperature, the most selective ligands **3b** and **3h** were additionally tested at 0 °C and −10 °C. Only a slight



Scheme 2. Asymmetric addition of diethylzinc to benzaldehyde.

Table 1
Diimines derived from camphoric acid

Ligand	R^1	R^2	R^3	R^4	R^5	Yield (%)
2a	H	H	H	H	H	52
2b	OCH_3	H	H	H	H	49
2c	CH_3	H	H	H	H	19
2d	Cl	H	H	H	H	49
2e	H	OCH_3	H	H	H	53
2f	H	H	OCH_3	H	H	52
2g	Cl	H	H	H	Cl	52
2h	CH_3	H	CH_3	H	CH_3	36

Table 2
Diamines derived from diimines **2a**–**2h**

Ligand	R^1	R^2	R^3	R^4	R^5	Yield (%)
3a	H	H	H	H	H	96
3b	OCH_3	H	H	H	H	65
3c	CH_3	H	H	H	H	97
3d	Cl	H	H	H	H	80
3e	H	OCH_3	H	H	H	88
3f	H	H	OCH_3	H	H	99
3g	Cl	H	H	H	Cl	65
3h	CH_3	H	CH_3	H	CH_3	47

Please cite this article in press as: Serra, M. E. S.; et al. *Tetrahedron: Asymmetry* (2017), http://dx.doi.org/10.1016/j.tetasy.2017.01.013