



New chiral 1,2-aminoalcohols derived from biomass and their application in diethyl zinc additions



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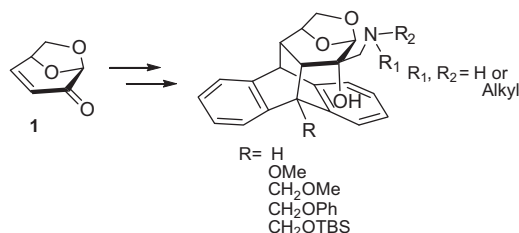
ABSTRACT

A convenient procedure for the preparation of chiral 1,2-aminoalcohols starting from levoglucosenone, a biomass derivative, is described. The 1,2-aminoalcohols, bearing primary, secondary, and tertiary amino groups, were tested as chiral catalysts in the asymmetric addition of diethyl zinc to benzaldehyde.

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Introduction

Chiral 1,2-aminoalcohols are versatile synthons for the preparation of a wide range of biologically active compounds as well as catalysts for asymmetric synthesis.¹ One of the most extensively studied methodologies for asymmetric carbon–carbon bond formation is the nucleophilic addition of organometallic reagents to carbonyl compounds.² Despite the variety of chiral ligands that have been synthesized and tested, mostly bearing a 1,2-aminoalcohol moiety, the development of cost-effective catalysts exhibiting high reactivity and enantioselectivity remains an active research topic. In the context of our ongoing interest in the development of new tools for asymmetric synthesis derived from biomass we synthesized new and efficient chiral auxiliaries and organocatalysts starting from levoglucosenone (**1**) (1,6-anhydro-3,4-dideoxy-β-D-glycero-hex-3-enopyranos-2-ulose) which is the major product of the pyrolysis of acid-pretreated waste paper.^{3,4} This bicyclic enone has been intensively used as chiral synthon in the synthesis of a wide variety of compounds.⁵ In order to explore new applications, we envisaged the use of this easily available member of the carbohydrate pool for the development of new chiral 1,2-aminoalcohols (Scheme 1) and their applications in the enantioselective carbon–carbon bond forming reactions.



Scheme 1.

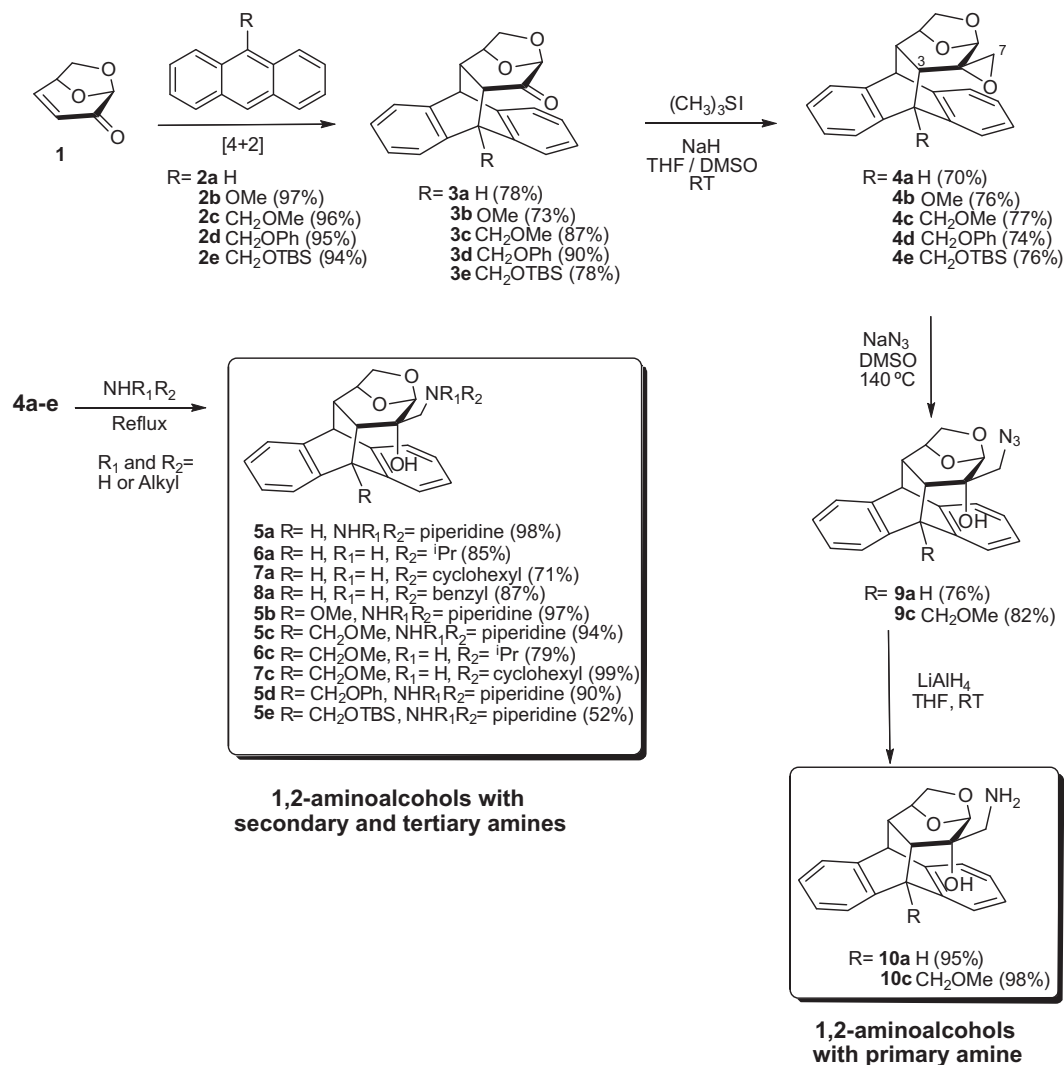
Results and discussion

The strategy toward the preparation of the new chiral aminoalcohols derived from levoglucosenone was envisaged by functionalizing the double bond of **1**, using a general procedure which involves a Diels–Alder reaction between **1** and anthracene or 9-substituted anthracenes **2** to afford the cycloadducts **3**, Scheme 2. The chemical transformation of the ketone functionality of **3** into an oxirane ring group would allow to produce epoxides **4**, which are key intermediates to generate the desired 1,2-aminoalcohols.

Levoglucosenone was obtained through a conventional or microwave assisted pyrolysis of pre-treated microcrystalline cellulose.⁴ With a convenient access to large amounts of **1** as the chiral starting material, cycloadducts **3a–e** were prepared through the reaction of **1** with anthracene or 9-anthracene derivatives. The introduction of a substituent at the benzylic position would allow

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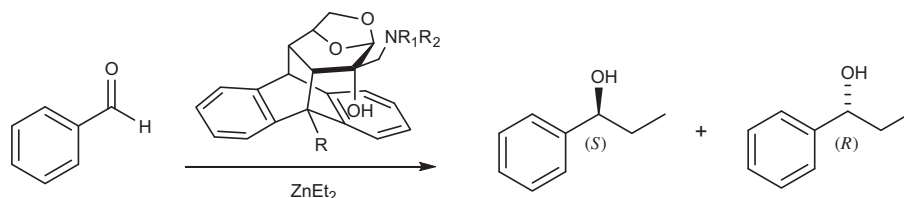


to place different groups as another element of steric control. Previously results demonstrated that structurally related chiral auxiliaries which contain this kind of substitution showed to be more efficient in the asymmetric reaction tested.³ We considered the preparation of 9-derived anthracenes **2b–e** with a methoxy, methoxymethyl, phenoxyethyl, and *tert*-butyldimethylsilyloxymethyl (OTBS) substituent groups. The 9-derived anthracenes **2c–d** were synthesized in a simple and efficient way from commercially available 9-anthracenemethanol.⁶ 9-Methoxyanthracene (**2b**) was obtained in 97% yield from anthrone by refluxing with trimethylorthoformate and sulfuric acid for seven days.⁷ The Diels–Alder reaction between **1** and **2a–b** with catalytic amounts of FeCl_3 produced the desired cycloadducts **3a–b** in good yields. Cycloadducts **3c–e** were prepared through a Diels–Alder reaction using thermal conditions, as described in previous reports.⁶

There are precedents in the literature about the functionalization of the keto group of levoglucosone derivatives.^{8,9} It was reported that the generation of the oxirane ring was carried out employing the Corey–Chaykovsky reaction,^{9,10} for this reason, we chose this methodology in order to obtain the *spiro*-epoxide **4**. The reaction proceeds through the addition of a sulfur ylide to the keto group of the cycloadduct **3a–e** to produce the corresponding epoxide derivatives **4a–e**. The diastereoselective conversion of **3** relies mainly on the competitive steric hindrance exerted by the

1,6-andrydro bridge above the plane of the pyranose ring and the aromatic rings below it. The epoxides were isolated as a single isomer in good yields and identified as the product derived from the attack of the ylide to the carbonyl group from the same face of the 1,6-anhydro bridge. This is in contrast to the reported results where the ylide attack occurred exclusively from the α face of the keto group of **1**, only due to the steric encumbrance exerted by the 1,6-anhydro bridge.⁹ There are precedents which demonstrated that the aromatic rings below the pyranose ring favor the approach of the reagent from the opposite face.^{3,6} The stereochemical assignments were made possible by the use of ^1H NMR spin decoupling and NOE data. The NOE observed between H-3 and H-7 indicated the proximity of these nuclei through the space suggesting the configuration at C-2 in compounds **4a–e**.

We next studied the synthesis of chiral 1,2-aminoalcohols with primary, secondary, and tertiary amino groups. Our purpose was to determine if the amino substitution could exert any influence on the enantioselective capacity of these chiral ligands, as it was reported for other catalysts.¹¹ To achieve this goal, a toluene solution of epoxides **4a–e** was refluxed with piperidine, isopropylamine, cyclohexylamine, or benzylamine to produce the corresponding 1,2-aminoalcohols with secondary and tertiary amino group **5–8**, in moderate to excellent yields. The ring opening reaction of **4a** and **4c** with isopropylamine to give aminoalcohols

Table 1Evaluation of the inductive capability of 1,2-aminoalcohols in the ZnEt₂ addition reaction to benzaldehyde at room temperature^a

Entry	Ligand	Yield (%)	ee ^b (%)	Config. ^c
1	5a	95	34	S
2	5b	98	24	R
3	5c	84	50	R
4	5d	70	0	—
5	5e	92	30	R
6	6a	76	4	R
7	7a	94	14	R
8	8a	83	6	S
9	10a	81	44	S
10	6c	97	20	R
11	7c	84	26	R
12	10c	70	4	S

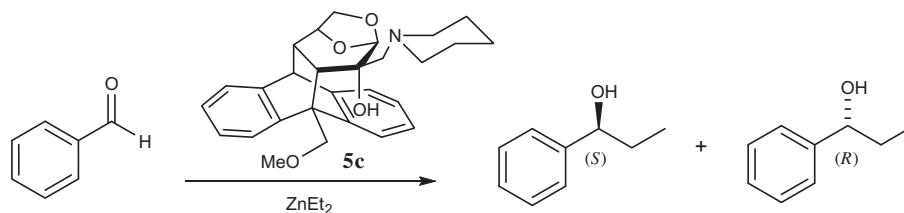
^a 1.1 M in hexane, 2 equiv regarding to benzaldehyde.^b Determined by HPLC with Chiralcel OD-H column.^c Main enantiomer of 1-phenyl-1-propanol assigned by the literature data¹³ and confirmed by polarimetry through [α]_D measurements.

6a and **6c** were too slow under conventional thermal reaction condition. In order to reduce the reaction time, we assayed the use of microwave assisted methodology and we obtained the desired compounds **6a** and **6c** in higher yields with the concomitant reduction in reaction times.¹² In order to synthesize 1,2-aminoalcohols with the primary amino group, the oxirane ring of **4a** and **4c** was converted to azidoalcohols **9a** and **9c** by the reaction with sodium azide followed by the reduction with LiAlH₄ to afford the 1,2-aminoalcohols **10a** and **10c**.

Once the syntheses of 1,2-aminoalcohols were achieved in enantiomeric pure form, they were evaluated as chiral ligands in the enantioselective addition of diethylzinc to benzaldehyde. The reactions were performed using standard conditions² with 2 equiv of Et₂Zn in the presence of 20% of the chiral ligand, **Table 1**.

The 1,2-aminoalcohols **5a–e** containing the tertiary amino group were the first ligands to be tested (entries 1–5). The outcome

of the nucleophilic addition demonstrated that the 1-phenyl-1-propanol was obtained in good to excellent yields. The best enantioselectivities were observed with ligands **5a** and **5c**, having a hydrogen or a methoxymethyl substituent at the benzylic position. These experimental results suggested that there was no correlation between the substitution at the benzylic position with the efficiency of the enantiomeric induction. We then turned our attention to evaluate the effect of the substitution at the amino group. For this reason, we evaluated aminoalcohols **6–8a,c** and **10a,c** with secondary and primary amino groups, structurally related to the most efficient catalysts **5a** and **5c** containing a tertiary amino group. The reactions catalyzed by these 1,2-aminoalcohols (entries 6–12) afforded the addition product in good to excellent yields. The induction capacities observed were from moderate to low. The comparison of the inductive capacity between all chiral ligands evaluated demonstrates that the most efficient one was **5c**, having

Table 2Study of the ZnEt₂ addition to benzaldehyde catalyzed by **5c** under different reaction conditions^a

Entry	5c (mol %)	Additive (equiv)	Yield (%)	ee ^b (%)
1	5	—	86	26
2	10	—	82	32
3	20	—	84	50
4	30	—	77	66
5	40	—	78	48
6	20	LiCl (0.6)	51	24
7	10	N ¹ ,N ² -ditosyl-1,2-ethanediamine (0.1)	85	40
8	10	Ni(acac) (0.05)	78	16
9	20	Ti(O ⁱ Pr) ₄ (1.2)	60	6

^a 1.1 M in hexane, 2 equiv regarding to benzaldehyde.^b Determined by HPLC with Chiralcel OD-H column.

a tertiary amino group which is in agreement with the tendency observed in other systems.¹¹

In as much as **5c** proved to be the most selective 1,2-aminoalcohol in the chemical reaction tested, we considered this aminoalcohol to study the different reaction conditions that may have influence on the induction capacity. Ethylation of benzaldehyde does not occur without the addition of an aminoalcohol; however the presence of 100 mol % of catalyst does not cause the reaction to proceed either. Only the addition of a small amount of ligand accelerates the organometallic reaction efficiently.¹⁴ On the other hand, the addition of different types of substances, such as bis-sulfonamides or inorganic salts which can act as Lewis acid like Ti(O^{*i*}Pr)₄, Ni(acac), or LiCl, have proved to affect the enantioselectivities of other aminoalcohols reported in the literature.^{15–20} For this reason, we tested the effect of the catalyst amount and the presence of additives. The results are summarized in Table 2.

All the reactions tested gave the *R*-1-phenyl-1-propanol as major enantiomer. We could observe that the increment of the amount of **5c** (from 5 to 30 mol %, entries 1–4) increased the enantioselectivity (from 26 to 66%). However, the ee decreased with the use of more than 30 mol % of chiral ligand (entry 5). This is in good agreement with the literature reports^{14,19} where it was found that the stoichiometry of the aldehyde, dialkylzinc, and catalyst strongly affects the reactivity and selectivity.¹⁴ All the reactions performed in the presence of additives (entries 6–9) did not increase the enantioselectivity; moreover it had a deleterious effect. The reactions performed at lower temperature, as 0 °C with 30 mol % of **5c** were less selective (ee 52%) than the reaction carried out in the same experimental condition at room temperature (entry 4). From all the reactions assayed the only condition that allows to improve the enantioselectivity obtained with **5c** was to increase the catalytic amount of ligand up to 30 mol %, in this condition we obtained the benzylalcohol with an ee of 66%.

In summary, this is the first report of the preparation of 1,2-aminoalcohols with primary, secondary, and tertiary amino groups derived from levoglucosenone and their application in the enantioselective diethylzinc addition to benzaldehyde. It is important to point out that all 1,2-aminoalcohols tested in this study were recovered and could be reused. The syntheses of the aminoalcohols were simple and effective, allowing to obtain the desired compounds in three or four steps (depending on the substitution of the amino group) from levoglucosenone. The wide variety of amino groups present in this new family of aminoalcohols, show the adequate functionalization for further transformation into other chiral derivatives. The level of induction obtained, in addition to the fact that the starting material is easily obtained from biomass, makes this system an excellent model to be exploited in other asymmetric reactions and a starting point for the development of new chiral catalysts.

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Supplementary data

Supplementary data (experimental procedures for the synthesis of all compounds, characterization data, and copies of ¹H and ¹³C NMR spectra of new products) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2014.08.124>.

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