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.

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. One of the most extensively studied methodologies for asymmetric carbon–carbon bond formation is the nucleophilic addition of organometallic reagents to carbonyl compounds. 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-3,4-L-glycero-hex-3-enopyranos-2-ulose) which is the major product of the pyrolysis of acid-pretreated waste paper. This bicyclic enone has been intensively used as chiral synthon in the synthesis of a wide variety of compounds. 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.

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 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. 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...
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. We considered the preparation of 9-derived anthracenes with a methoxy, methoxymethyl, phenoxyethyl, and tert-butyldimethylsilyloxymethyl (OTBS) substituent groups. The 9-derived anthracenes and d were synthesized in a simple and efficient way from commercially available 9-anthracenemethanol. 2c The preparation of 9-derived anthracenes employing the Corey–Chaykovsky reaction, was reported that the generation of the oxirane ring was carried out using thermal conditions, as described in previous reports.

There are precedents in the literature about the functionalization of the keto group of levoglucosenone derivatives. There are precedents which demonstrated the configuration at C-2 in compounds 4a–e. There are precedents which demonstrated that the aromatic rings below the pyrane ring favor the approach of the reagent from the opposite face. 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 amines. Our purpose was to determine if the amino substitution could exert any influence on the 1,6-andrydro bridge above the plane of the pyrane 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-andrydro 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-andrydro bridge. There are precedents which demonstrated that the aromatic rings below the pyrane ring favor the approach of the reagent from the opposite face. 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.

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 pyrane 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-andrydro 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-andrydro bridge. There are precedents which demonstrated that the aromatic rings below the pyrane ring favor the approach of the reagent from the opposite face. 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.

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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.

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

### Table 1
Evaluating the inductive capability of 1,2-aminoalcohols in the ZnEt₂ addition reaction to benzaldehyde at room temperature

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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>5c (mol %)</th>
<th>Additive (equiv)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>—</td>
<td>86</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>—</td>
<td>82</td>
<td>32</td>
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<td>3</td>
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<td>—</td>
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<td>50</td>
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<tr>
<td>4</td>
<td>30</td>
<td>—</td>
<td>77</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>—</td>
<td>78</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>LiCl (0.6)</td>
<td>51</td>
<td>24</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>N,N'-ditosyl-1,2-ethanediylamine (0.1)</td>
<td>85</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>N,N'-dicysteine (0.05)</td>
<td>78</td>
<td>16</td>
</tr>
<tr>
<td>9</td>
<td>20</td>
<td>Ti(OPr)₄ (1.2)</td>
<td>60</td>
<td>6</td>
</tr>
</tbody>
</table>

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*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.

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efficient one was 5c, having a tertiary amino group which is in agreement with the tendency observed in other systems.\textsuperscript{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.\textsuperscript{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\textsubscript{2}Pr\textsubscript{4}), Ni(acac), or LiCl, have proved to affect the enantioselectivities of other aminoalcohols reported in the literature.\textsuperscript{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\textsuperscript{14,19} where it was found that the stoichiometry of the aldehyde, diethylzinc, and catalyst strongly affects the reactivity and selectivity.\textsuperscript{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.

Acknowledgments
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Supplementary data
Supplementary data (experimental procedures for the synthesis of all compounds, characterization data, and copies of $^1$H and $^{13}$C 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.

References and notes
12. See Supporting Information.

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