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Development of polymer-supported chiral aminoalcohols derived from biomass and their application to asymmetric alkylation

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ABSTRACT

A synthetic strategy has been developed for the preparation of immobilized 1,2-aminoalcohols starting from easily available and renewable chiral building blocks. They were tested as chiral ligands for the asymmetric diethylzinc addition to carbonyl compounds. Enantioselectivities were comparable to those observed for non-immobilized analogs. These results provide strong evidence for the flexibility of our approach to generate highly valuable supported chiral ligands derived from cellulose-rich materials.

Introduction

Asymmetric catalysis remains one of the most explored alternatives for the efficient production of enantiomerically pure organic compounds whose demand in agricultural, pharmaceutical, cosmetic, and food industries have increased progressively during last decades.[1] This methodology offers several advantages for big-scale applications, such as high enantioselectivity, low catalyst loadings and the prospect for catalyst recycling, contributing to the economic sustainability of the synthetic route. In this regard, polymer-supported chiral catalysts offer additional benefits compared to their soluble counterparts,[2] since catalyst could be recovered by simple filtration, therefore avoiding expensive chromatographic purifications and simplifying the recycling with the concomitant reduction of costs, process timeline, and environmental impact. Moreover, immobilized catalysts open the prospect for their use in continuous-flow systems during automated asymmetric organic synthesis.[3]

Affordable chiral catalysts for industrial applications can only be rendered from readily available enantiopure sources, such as carbohydrates or amino acids. For quite some time already, our group has been working on the generation of asymmetric auxiliaries, catalysts and organocatalysts by manipulation of the chiral pool available in the biomass.[4,5] Particularly, we have used levoglucosenone (1,6-anhydro-3,4-dideoxy-β-D-glycero-hex-3-enopyranos-2-ulose) (**1**) (Scheme 1) as starting material to obtain chiral auxiliaries for stereoselective Diels–Alder reactions[6] as well as the generation of chiral 1,2-aminoalcohols for catalytic additions of diethylzinc to carbonyl compounds,[7] both in homogenous conditions. Aminoalcohols are among the most versatile chemical structures that could be employed as chiral inducers for asymmetric catalysis.[8] Levoglucosenone can be produced in acceptable quantities by thermal or microwave-assisted[9] treatment of cellulose-rich sources, such as waste paper and other common inexpensive materials, and constitutes therefore a great supply for chirality.

Results and discussion

With the aim of improving the environmental and economical sustainability of our previously reported chiral 1,2-aminoalcohols, we decided to explore their performance after immobilization on a solid support for the heterogeneous enantioselective diethylzinc addition to aldehydes. To the best of our knowledge, this is the first report of the development of immobilized, carbohydrate-derived aminoalcohols and their application as chiral ligands in the asymmetric addition of diethylzinc to carbonyl compounds. For this purpose, a set of primary, secondary, and tertiary immobilized aminoalcohols derived from **1**, were synthesized and their properties as chiral ligands were evaluated. 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

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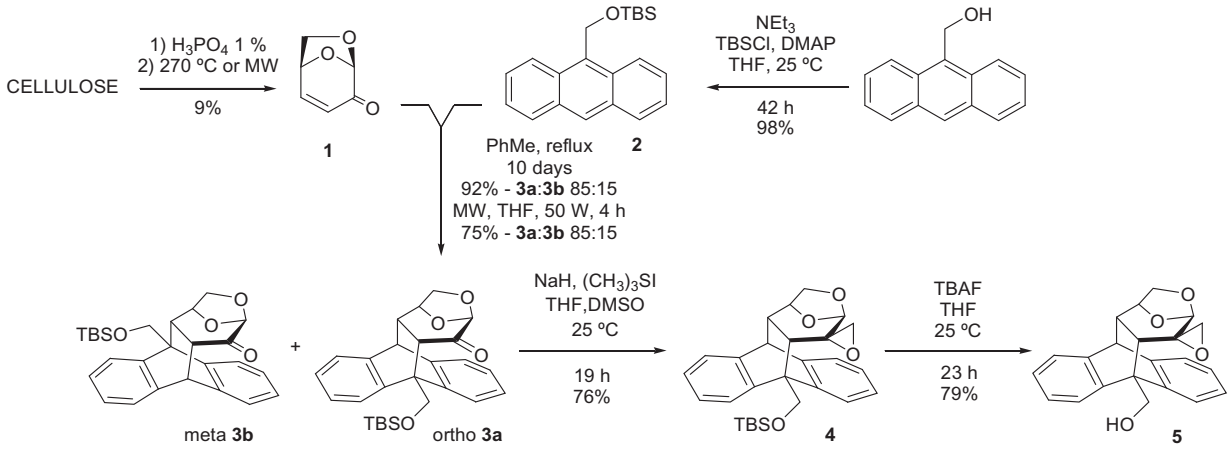


Scheme 1. Synthesis of epoxide **5**.

between **1** and 9-substituted anthracene **2** to afford the cycloadducts **3a**–**b** (Scheme 1). The chemical transformation of the ketone moiety of **3a** into an oxirane ring group would allow to obtain epoxide **4**, which is a key intermediate to generate the desired 1,2-aminoalcohols. Additionally, epoxide **4** constitutes a versatile structure that could be further functionalized through reactions with thiols, amines, hydroxyl groups, and other nucleophiles.

With a convenient access to large amounts of **1** as the chiral starting material, cycloadducts **3a**–**b** were prepared through the reaction of **1** with 9-*tert*-butyldimethylsilyloxymethyl (TBSO) anthracene (**2**). Diene **2** was chosen since attachment of the resulting cycloadduct **3a**–**b** to the solid support could be achieved in a straightforward manner. Furthermore, the presence of a substituent at the benzylic position would allow another element of steric control. Previous results demonstrated that structurally related chiral auxiliaries which contain this kind of substitution can perform asymmetric reactions more efficiently.[6c,10] The 9-substituted anthracene **2** was synthesized in a simple and efficient way from commercially available 9-anthracenemethanol. We have previously reported that *ortho*/*meta* stereochemistry for the Diels–Alder cycloadducts derived from reaction between **1** and **2** play a crucial role in their asymmetric induction capacity.[6] Although we made several attempts to determine the role of the solid support in influencing the regioselectivity of the Diels–Alder reaction between a solid-supported 9-substituted anthracene and **1**, the resulting adducts were not sufficiently stable to resist the harsh conditions for resin cleavage, hampering the elucidation of the product stereochemistry.

Therefore, we decided to synthesize epoxide **4** (Scheme 1) starting from the cycloadduct **3a** (major Diels–Alder stereoisomer),[11] followed by removal of TBSO protecting group to obtain the adduct **5**, as precursor for the attachment to the polymeric support. This synthetic approach allowed us to gain fully stereochemical control of the immobilized molecule used for heterogeneous chiral induction and the outcomes could then be directly compared to their counterparts in solution.[6c] There are a number of precedents in the literature about the functionalization of the keto group of levoglucosenone derivatives.[12,13] Generation of the oxirane ring has been carried out employing the Corey–Chaykovsky reaction.[13,14] Using this methodology, the spiro-epoxide **4** was isolated in good yield as a single isomer; its stereochemistry was the result of the ylide attack to the carbonyl group from the same face of the 1,6-anhydro-bridged of the levoglucosenone fragment. Finally, deprotection of **4** with TBAF gave the key intermediate **5** in very good yield.

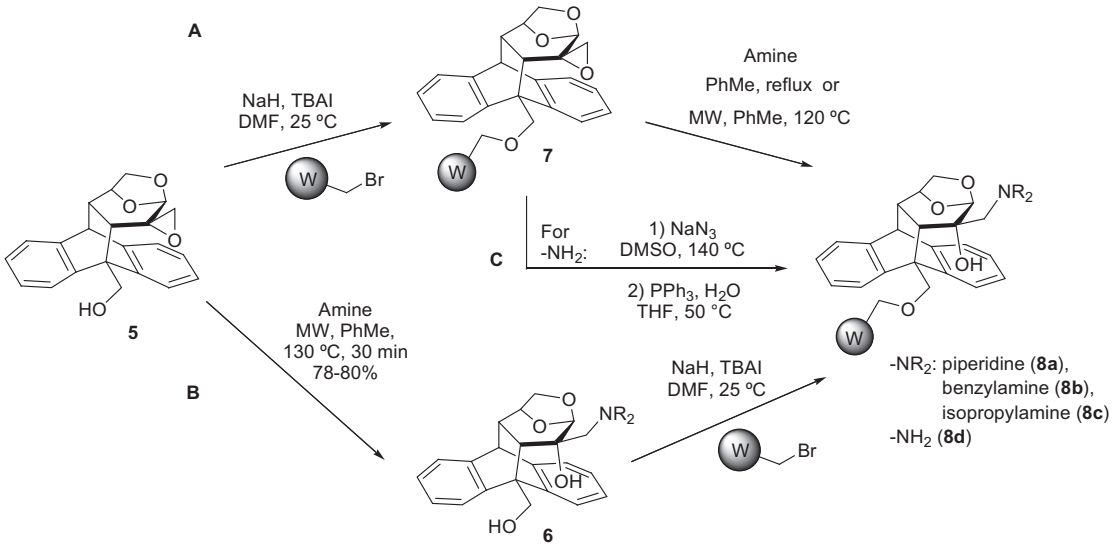
At this point, two alternative synthetic methodologies were explored for the generation of resin-bound 1,2-aminoalcohols (Scheme 2). In a first strategy, epoxide **5** was attached to Br-Wang resin to give **7**, with the subsequent nucleophilic attack by several amines to generate different 1,2-aminoalcohols (**8a**–**c**), with primary, secondary, and tertiary amine groups (Scheme 2, path A). In an alternative approach, desired 1,2-aminoalcohols were previously synthesized in solution and ultimately anchored to the resin (Scheme 2, path B).[7] Full characterization (gel-phase ^{13}C NMR, IR, elemental analysis) of the final immobilized 1,2-aminoalcohols obtained by both methodologies, showed no significant differences, providing strong evidence of the synthetic versatility of our procedure.

For the generation of 1,2-aminoalcohol with a primary amino group (**8d**), opening of the oxirane ring on the immobilized epoxide **7** was performed by means of sodium azide as nucleophile to give the corresponding azidoalcohol, which was subsequently reduced employing PPh_3 and H_2O[15] to give the amine **8d** (Scheme 2, path C).

Once the syntheses of the immobilized 1,2-aminoalcohols were achieved in enantiomeric pure form, they were evaluated as chiral ligands in the enantioselective addition of diethylzinc to benzaldehyde under heterogeneous conditions. This procedure constitutes a standard method to assess inductive capacity for such chiral organic molecules.[8b] Simultaneously, this reaction leads to the generation of optically active secondary alcohols with relevant industrial application such as drug candidates, agrochemicals, perfumes, and several other high added value intermediates.[16]

To perform the reaction, the solid-supported aminoalcohol **8a**–**d** was suspended in a minimum amount of dry toluene at 0 °C and a 1.1 M solution of $ZnEt_2$ in toluene was added. After stirring for 30 min, the mixture is allowed to reach room temperature, the corresponding aldehyde (1 mmol) was added and stirring of the reaction was continued for 22–66 h. The suspension was filtered to recover the immobilized ligand, the solution obtained was passed through a pad of silica gel or celite and the filtrate evaporated under reduced pressure to give the corresponding 1-aryl-1-propanol.

The outcome of the nucleophilic addition revealed that the 1-aryl-1-propanols were obtained in good to excellent yields (Table 1). In some cases, benzyl alcohol was obtained as a by-product. The formation of benzyl alcohol has been observed by others and is attributed to a secondary process in which benzaldehyde is reduced by the zinc alkoxide of the ethylation product, 1-phenyl-1-propanoxide.[16] All the reactions tested gave the (*R*)-1-aryl-1-propanol as major enantiomer. Comparison of the inductive capacity between all evaluated chiral ligands indicates that **8a**, bearing a tertiary amino group, is the most efficient (entry 3, Table 1). This is in agreement with the tendency observed in other systems reported.[17]



Scheme 2. Synthesis of polymer-supported aminoalcohols **8a–d**.

Table 1
Asymmetric addition of diethylzinc to aromatic aldehydes

Entry	Aldehyde	PS ligand[a] (mol %)	Time (h)	Product yield[b] (%)	Benzyl alcohol[b] (%)	Product ratio *R*:*S*
1	PhCHO	**8a**, 40	48	95	5	51:49
2	PhCHO	**8a**, 50	48	87	9	72:28
3	PhCHO	**8a**, 80	48	90	5	82:18
4	PhCHO	**8a**, 90	36	88	9	66:34
5	PhCHO	**8b**, 50	48	57	39	58:42
6	PhCHO	**8c**, 50	66	95	5	51:49
7	PhCHO	**8d**, 80	24	50	43	54:46
8	4-Cl-PhCHO	**8a**, 80	18	100	—	68:32
9	4-OMe-PhCHO	**8a**, 80	22	100	—	60:40

[a] With respect to the added moles of aldehyde.
[b] As calculated from the ^{1}H NMR spectra.[1,2,19b]

Taking these results into account, we considered this aminoalcohol **8a** for studying the different reaction conditions that may influence the chiral induction capacity. It is well known that ethylation of aldehyde does not occur without addition of the aminoalcohol; however, it is crucial to determine the quantity of ligand that accelerates the organometallic reaction efficiently.[18] We could observe that an increment of the amount of **8a** (from 40 to 80 mol %, entries 1–3) increased the enantioselectivity from 2% to 64%. However, the ee decreased when more than 80 mol % of chiral ligand was used (entry 4). This is in line with other literature reports[18,19] where it was found that the stoichiometry of the aldehyde, dialkylzinc, and ligand strongly affects reactivity and selectivity.[18] Based on results shown in Table 1, we could determinate that a considerable enantioselectivity was observed when 50 mol % of the ligand was employed, and the best chiral induction could be attained with 80% mol of the immobilized aminoalcohol present in the heterogeneous reaction mixture. It is important to point out that the immobilized ligand is easily recovered by filtration at the end of the experience.[20]

Conclusions

In summary, we report an efficient solid-supported protocol toward the generation of 1,2-aminoalcohols derived from a renewable and easily accessible source of chirality. Newly generated resin-bound 1,2-aminoalcohols were successfully employed as asymmetric ligands for the addition of $ZnEt_2$ to aromatic aldehydes with moderate enantioselectivities, comparable to those previously observed for analogous 1,2-aminoalcohols in solution. These polymer-supported 1,2-aminoalcohols could be easily recovered, broadening the sustainability of our approach. In fact, this is the first report on immobilized, carbohydrate-derived aminoalcohols and their use as chiral ligands in the asymmetric addition of diethylzinc to carbonyl moieties. Further studies are required to investigate the prospective of such solid-supported 1,2-aminoalcohols in other asymmetric organic transformation.

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Supplementary data

Supplementary data (experimental procedures for the synthesis of all compounds, characterization data, 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.2016.04.021.

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20. The experiment to reuse the supported catalyst in a second run demonstrated that the yield of the product was similar to the first run, however, the enantioselective capacity decreased.