



Supramolecular carbohydrate scaffold-catalyzed synthesis of tetrahydroquinolines

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ABSTRACT

Natural supramolecular carbohydrate scaffold-catalyzed synthesis of tetrahydroquinoline derivatives by the reaction of aromatic amine and cyclic enol ether in excellent yield with high diastereoselectivity has been developed. Carbohydrates, cellulose, and starch were converted into their sulfonic acid derivative and these scaffolds exhibit efficient catalytic properties, along with excellent cost effectivity and recyclability.

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Recently due to environmental and social pressure on industry, there has been a strong shift towards green technology.¹ Chemists have to dedicate numerous efforts to the development of clean technologies either by replacing a conventional solvent with an ecofriendly solvent or by developing a new ecofriendly catalyst.² The major challenge in this area is the development of lucrative, highly active, and stable solid acid catalyst as a substitute of homogeneous catalysts, such as HF, AlCl₃, and H₂SO₄. Even though these homogeneous catalysts are very successful, they produce highly corrosive media with chemically reactive waste streams. Indeed, the solid catalysts have many advantages; they are noncorrosive and environmentally benign, presenting fewer disposal problems. Their reuse is possible and their separation from liquid products is much easier. Furthermore, they can be designed to give higher activity, selectivity, and longer catalytic life. In this regard natural

biopolymers are attractive candidates as new solid support catalysts.^{3,4}

As a part of our continual efforts toward the development of environmentally benign synthetic procedures for multicomponent reactions,⁵ we have initiated exploration of ecofriendly natural supramolecular carbohydrates as catalyst for the synthesis of bioactive tricyclic tetrahydroquinoline scaffolds.

The tricyclic tetrahydroquinoline moieties are widely distributed in nature and reveal a broad range of biological activities. Tricyclic tetrahydroquinoline moieties are found in many alkaloids (Fig. 1) such as flindersine, oricine, veprisine, and skimmianine.^{6,7} These alkaloids possess important biological activities such as anti-allergic,⁸ psychotropic,⁹ anti-inflammatory,¹⁰ and estrogenic.¹¹

A plethora of procedures for the formation of tetrahydroquinoline is preceded in the literature, catalyzed by Lewis acid,^{12–17}

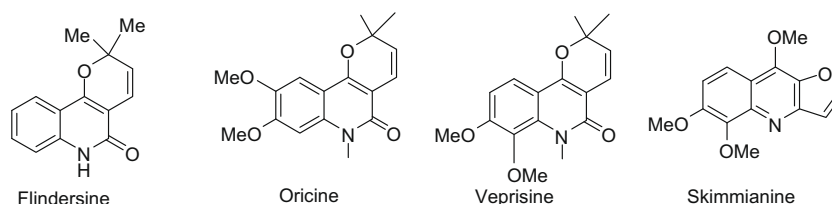


Figure 1. Bioactive tricyclic tetrahydroquinoline.

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metal triflates,^{18–20} and protonic acids, such as HCl and trifluoroacetic acid. Also Chao-Jun Li et al. have reported that indium(III) chloride catalyzed pyranoquinoline in water.²¹ The *aza*-Diels–Alder reaction catalyzed by Lewis acid is the most explored method for the synthesis of pyrano-/furan-quinoline derivatives. All these methodologies involve costly and hazardous catalyst as well as cumbersome work-up procedure.

We wish to report here an efficient synthesis of tricyclic tetrahydroquinoline using natural supramolecular carbohydrates as catalyst via cycloaddition of aromatic amine and cyclic enol ether. Carbohydrates are considered as the most abundant molecules of the biomass and we have selected two most generous supramolecular carbohydrates: cellulose and starch molecules, for catalytic activity, because these are very cost-effective, biodegradable, and are obtained from renewable resources. In order to achieve effective catalytic properties, cellulose and starch were converted to their sulfonic acid derivatives (Fig. 2).

We herein describe the diastereoselective synthesis of tricyclic tetrahydroquinoline by cellulose sulfuric acid (CellSA) or starch sulfuric acid (StarSA) as catalyst from aromatic amine and cyclic enol ether.

The reaction of aromatic amine with 2 equiv of cyclic enol ether in the presence of CellSA or StarSA in acetonitrile at room temperature furnished the corresponding pyranoquinoline and furanoquinoline in good to excellent yields. The *cis* and *trans* isomers are formed in almost all the cases. However *cis*-isomer is preferentially formed with a high diastereoselectivity. Furanquinolines showed a better diastereoselectivity than pyranoquinolines²² (Scheme 1). This reaction is categorized as ABB' type multicomponent reaction because cyclic enol ether (B) component is chemodif-

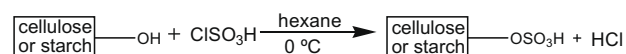
ferentially incorporated in two distinct manners (B and B').²³ The cyclic enol ether serves a dual role: as an aldehyde and as a cyclic enol ether.

CellSA or StarSA can be easily prepared by the reaction of an inexpensive cellulose or starch with chlorosulfonic acid²⁴ (Scheme 2).

This white homogeneous solid acid is very stable and is not affected by air, water, or light. Sulfur content of the samples by conventional elemental analysis was 0.55 and 0.12 mmol/g for cellulose sulfuric acid and starch sulfuric acid, respectively. The number of H⁺ sites of cellulose–SO₃H and starch–SO₃H determined by acid–base titration was 0.50 and 0.10 mequiv/g, respectively. This value corresponds to about 90% and 83% of the sulfur content, indicating that most of the sulfur species on both the samples are in the form of the sulfonic acid group.

The cellulose–SO₃H catalyst has an excellent catalytic property which is attributed to the high hydrothermal stability and strong acid sites of sulfo functional groups. Due to low solubility and high stability, cellulose is more suitable as a support relative to starch.

We explored the 1:2 coupling of substituted anilines with electron-rich alkene under different conditions and found that cellulose sulfuric acid (cellSA) was the most efficient catalyst for tetrahydroquinoline synthesis in CH₃CN at room temperature.



Scheme 2. The preparation of a catalyst.

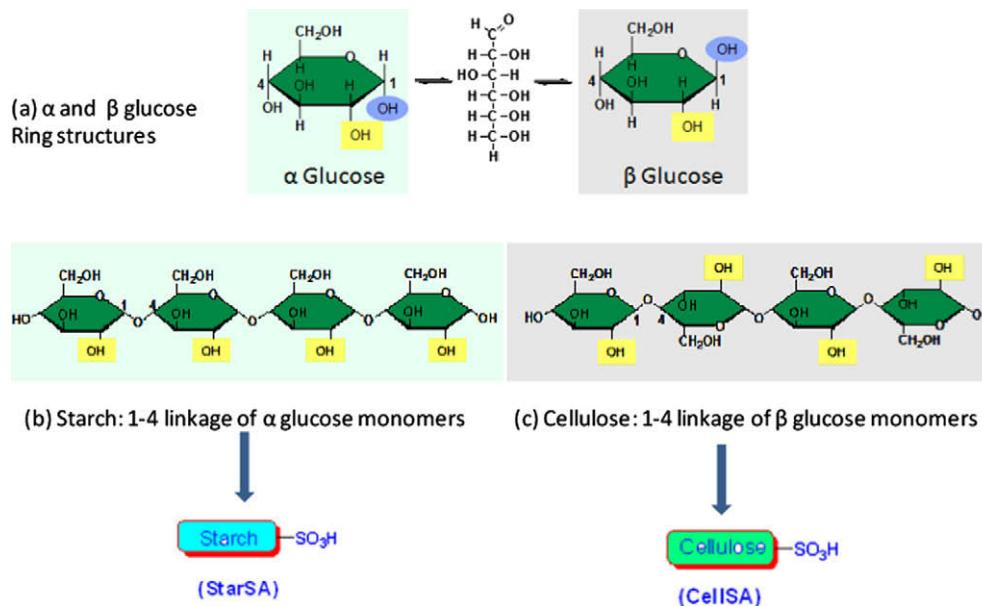
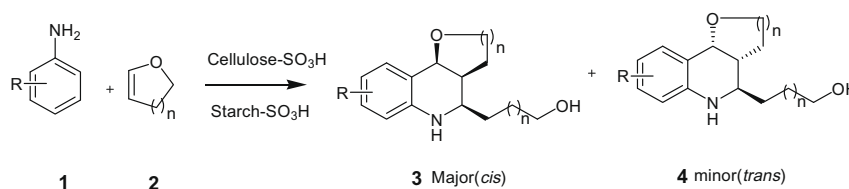


Figure 2. Natural supramolecular carbohydrate catalyst.



Scheme 1. Synthesis of pyranoquinoline and furanoquinoline.

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