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Abstract: The development of new and more efficient catalytic systems is the subject of increasing attention from both academic and industrial research. Moreover, biomass is an endless supply of hydrocarbon materials that can be used as renewable raw materials for the development of new organic compounds. In this context, many research groups have devoted their works to products with a natural chirality source, non-toxic, biodegradable and usually cost effective for the development of new chiral catalysts.

Some new chiral molecules derived from biomass such as carbohydrates and natural amino acids have been synthesized and used as chiral ligands or organocatalysts for asymmetric transformations leading to the formation of expected products in good yields with high enantioselectivities

Key-words: Asymmetric transfer hydrogenation, asymmetric allylic substitution, [4+2] annulation reaction, isosorbide, isomannide, L-proline.

Introduction

Nowadays, science and technology are growing strongly and serve better for human life. In the midst of scientific disciplines, chemistry contributes a considerable part in the development of human. However, besides the great achievements, chemists have to face with a lot of new challenges, health issues, food safety, environment... Hence, sustainable development is really a target to be achieved for the chemists today.

In 1998, Paul Anastas and John C. Warner published a set of 12 principles to guide the practice of green chemistry. The twelve principles give a range of ways to reduce the environmental and health impacts of chemical production, and also indicate research priorities for the development of green chemistry technologies.[1] Remarkable among the principles is the catalysis. Indeed, catalysts could reduce the energy consumption which presents an economic and environmental interest, increase yields by limiting the formation of by-products or could improve selectivity of reaction.

Ongoing use of petroleum for chemical feedstocks and energy is not sustainable. It is imperative that new catalysts for existing processes and new products are developed based on renewable sources.

The development of available, inexpensive, modular and innovative ligands and catalysts from biomass products such as carbohydrates and natural amino acids is expected to be one of the key procedures for expanding the reaction scope and the synthetic potential of metal-catalyzed enantioselective catalysis.

Besides metal complexes and biocatalysis, small organic molecules may promote chemical transformations. Organocatalysis could accelerate the reactions with a sub-stoichiometric amount of organic molecules, which do not contain any metal element. Advantages of organocatalysts include their lack of sensitivity to moisture and oxygen, their ready availability, low cost, and low toxicity, which confers a huge direct benefit in the production of pharmaceutical intermediates when compared with (transition) metal catalysts. Organocatalysis is a 'metal-free method' and therefore the metal pollution can be prevent. Due to all these features, organocatalysis appears as a very attractive area in modern organic synthesis.

The conversion of biomass and its derivatives to chemicals has been the subject of intense research efforts during the past decade.[2]Many chemical transformations on biomasssuch as carbohydrates,[3]glycerol,[4] triglycerides,[5]cellulose,[6]lignin[7], etc into high-added value products have been reported so far.However, the design and synthesis of novel chiral catalysts starting from biomass still presents a challenge and an opportunity to researchers.

This mini-review focus on our works dealing with the synthesis of chiral ligands and organocatalysts derived from carbohydrates and natural amino acids and their applications in asymmetric catalysis.

Design and synthesis of novel chiral ligands derived from carbohydrates.Applications to asymmetric metal catalysis

We report herein the synthesis of a new class of chiral β-amino alcohol, diamine and monophosphine ligands startingfrom isosorbide and isomannide as chiral renewable sources. The efficiency of these ligands has been evaluated for the ruthenium-catalyzed enantioselective reduction of aromatic ketones by transfer hydrogenation as well as for the rhodium-catalyzed enantioselective hydrogenation of olefins.

Isosorbide **1**and its diastereoisomer, isomannide **2**, also known as (3*R*,3*aR*,6*S*,6*aR*)-hexahydrofuro[3,2-b]furan-3,6-diol and 3*R*,3*aR*,6*R*,6*aR*)-hexahydrofuro[3,2-b]furan-3,6-diol, are renewable, and commercially available chiral carbohydrates. Isosorbide is basically giving a wedge-shaped molecule with two fused tetrahydrofuran rings having the *cis*-arrangement at the ring junction.[8]The compound possesses two hydroxyl groups, one at C6 having the *exo*-orientation with respect to the wedge-shaped molecule, and the other at C3 having the *endo*-orientation, which

makes possible the intramolecular hydrogen bonding with the oxygen atom of the neighboring tetrahydrofuran ring. In the case of isomannide, the two hydroxyl groups at C6 and C3 have both the *endo*-orientation (Figure 1).

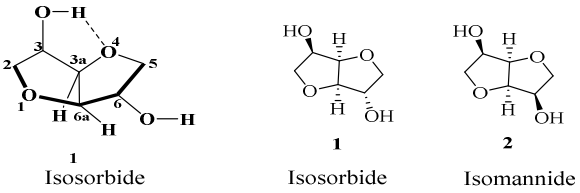
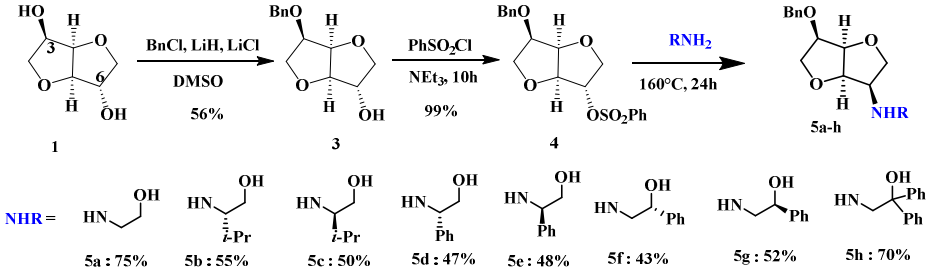


Figure 1: Structure of isosorbide **1**and isomannide **2**



Scheme 1: Synthesis of amino alcohols **5a-h**.

The complete inversion of configuration in the substitution reaction of **4** with an amine was confirmed by ^{1}H NMR analysis based on the observation of the H_a, H_b coupling constant of products **5a-h**. For compounds **4**, the proton H_a appears as doublet corresponding to *trans*-coupling $J_{Ha\text{-}Hb}$ = 0 Hz. The signal turns to a doublet of doublet for compounds **5a-h** corresponding to a *cis*-coupling $J_{Ha\text{-}Hb}$ = 5 Hz (
Figure).

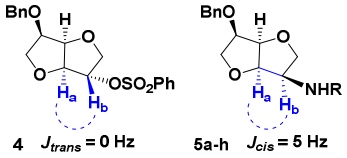
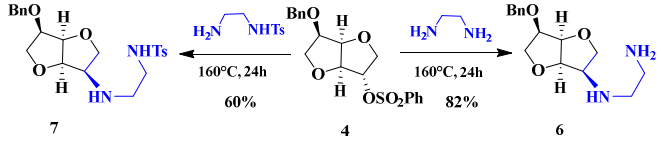


Figure 2: ^{1}H NMR studies for **3** and **4a-h**

Using the similar reaction conditions previously described for the synthesis of amino alcohol ligands **5**, sulfonate **4**afforded diamine **6** and *N*-tosylated amine **7**with yields ò 82% and 60%,respectively (Scheme 2).



Scheme 2: Synthesis of diamine **6** and *N*-tosylated amine **7**.

Asymmetric reduction of aromatic ketones by transfer hydrogenation reaction.

The reduction of carbonyl compounds to the corresponding alcohols is one of the most fundamental and useful reactions that are important in the pharmaceutical and chemical industry.

Isosorbide and isomannide, industrially obtained by dehydration of D-sorbitol and D-mannitol, represent commercially available and low cost chiral starting materials for the synthesis of sophisticated molecules including chiral ionic liquids,[9] phase-transfer catalysts[10]and ligands (amino alcohols, amines, diphosphines, diphosphites, bis diaminophosphites, diamidophosphites).[11,12]

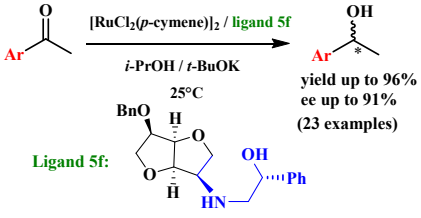
Synthesis of chiral amino alcohols and diamines

Starting from isosorbide **1**, a series of eight amino alcohols **5** was synthesized and isolated in moderate to good overall yields using classical organic transformations (Scheme 1).

The asymmetric transfer hydrogenation (ATH) of ketones has recently emerged as a highly efficient method for the synthesis of enantiomerically enriched secondary alcohols that are key intermediates for the manufacture of a variety of molecules and molecular scaffolds of biological and therapeutic interest.[13]Transition metal-catalyzed asymmetric transfer hydrogenation of prochiral ketones provides a powerful alternative to asymmetric hydrogenation owing to its ease of handling, the easy availability of hydrogen sources, lower cost and safety.[14] Many chiral ligands and transition metals have been developed and applied to this reaction. The common catalysts are rhodium, ruthenium and iridium complexes with chiral phosphine and chiral diamine ligands.[15]

ATH reaction offers an interesting and common tool to evaluate the activity of these new chiral ligands. At this point of our investigation, we decided to study the reduction of acetophenone by ATH as a model reaction to explore the catalytic behavior of our complexes.

After optimization of reaction conditions by screening many parameters including hydride sources, catalysts precursors, base nature, base/ligand/metal ratio, solvent, reaction temperature, reaction time, substrate concentration, and structure of ligands, the reduction of aromatic ketones by ATH reaction with ligand **5f** led to the formation of expected product in excellent yields and with good enantioselectivities up to 91% ee as shown in Scheme 3.[16]

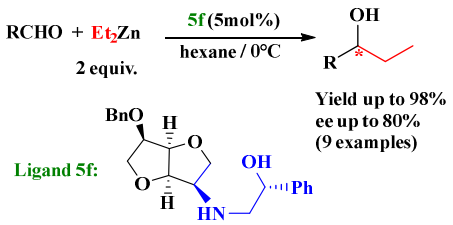


Scheme 3: Asymmetric transfer hydrogenation of aromatic ketones with ligand **5f.**

These results clearly indicated the efficiency of the isosorbide structure for the preparation of chiral ligands and encouraged us to evaluate our amino alcohol ligands**5a-h** in the addition of diethylzinc to aldehydes. This reaction has been extensively studied and offers an excellent tool for evaluating of new chiral ligands.[17]

Asymmetric addition reaction of diethylzinc to aldehydes with amino alcohol ligands.

Based on these chiral amino alcohols **5a-h**as well as the ATH reaction of aromatic ketones, we decided to study the zinc-catalyzed ethylation of aliphatic and aromatic aldehydes.
In the same way, after examining many reaction parameters, the addition of diethylzinc to a selection of aldehydes bearing electron-withdrawing or -donating groups, under optimized reaction conditions, afforded the corresponding products in very good yield and with high enantioselectivity.[18]

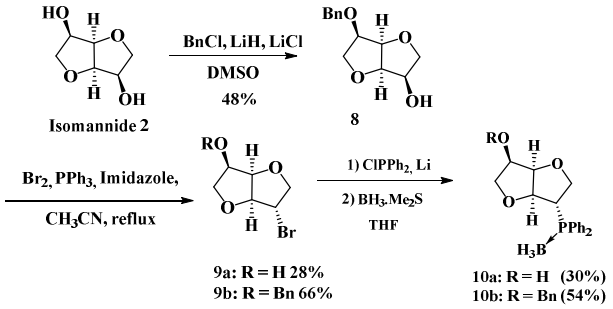


Scheme 4: Asymmetric addition reaction of diethylzinc to aldehyde with ligand **5f**.

In all cases, amino alcohol **5f** was found to be the best ligand in all two studied reactions. The presence of phenyl group at the α position of the hydroxyl function was crucial for improving the enantioselectivity. The use of diamine ligands **6** or **7**led to the formation of the expected product in good yield but with low enantioselective excess.

Synthesis of chiral monophosphine ligands derived from isomannide and isosorbide.

Starting from isomannide **2**, two monophosphine-borane complexes **10a** and **10b** were respectively synthesizedfrom bromide derivatives **9a** and **9b** by nucleophilic substitution with diphenylphosphine anion, followed by a protection with borane dimethylsulfide complex (Scheme 5). It should be noted that the substitution of sulfonate **4** with the same diphenylphosphine anion did not work at all, and produced only the alcohol **3** (see Scheme 1).



Scheme 5: Synthesis of chiral monophosphine-borane **10a** and **10b**.

Surprisingly, X-ray single-crystal diffraction analysis of **10b** and **10a** confirms an *exo* position of phosphine group due to a total retention of configuration during the substitution step (Figure 3).

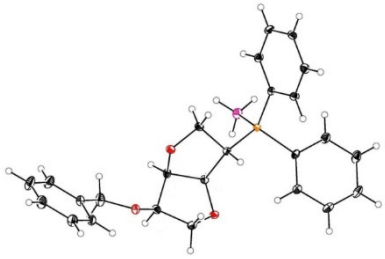
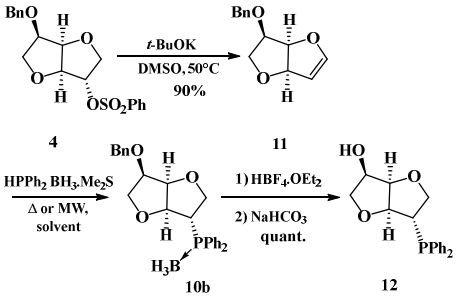


Figure 3*:* ORTEP drawing of **10b**. Ellipsoids are drawn at the 50 % probability level

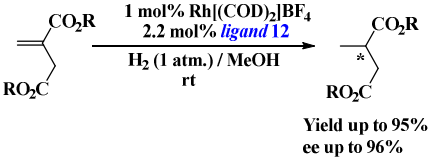
On the other hand, hydrophosphination of the olefin **11,** easily obtained in some steps from isosorbide **1**, conducted to monophosphine-borane **10b** in 47% yield using microwave heating (Scheme 6). Almost no conversion was observed when performing hydrophosphination using classical heating conditions even for several days.

Treatment of the phosphine-borane **10b** with an excess of tetrafluoroboric acid dimethylether complex resulted in a quantitatively formation of the phosphines **12** (Scheme 6).



Scheme 6: Synthesis of chiral monophosphine **12**.

Complexes formed *in situ* from Rh[$(COD)_2$]BF_4 and ligand **12** were examined as catalysts for the enantioselective hydrogenation of itaconic acid derivatives, leading to the formation of expected products in excellent yield and enantioselectivety up to 96% ee (Scheme 7).[19]



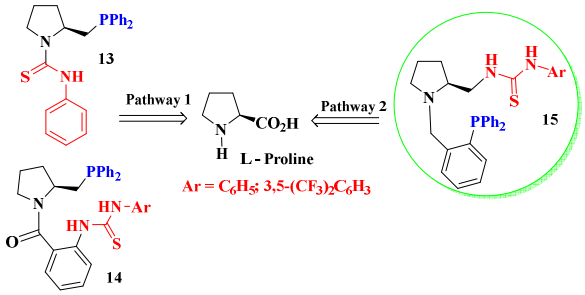
Scheme 7: Hydrogenation of itaconic acid derivatives.

These results indicated clearly the efficiency of the isosorbide and isomannide structure for the synthesis of new chiral ligands for asymmetric catalysis applications. Development of new chiral compounds derived from this carbohydrate family as ligands or organocatalysts and their applications in asymmetric catalysis is currently underway in our laboratory.

Design and synthesis of bifunctional chiral organocatalysts.Applications to asymmetric organocatalysis.

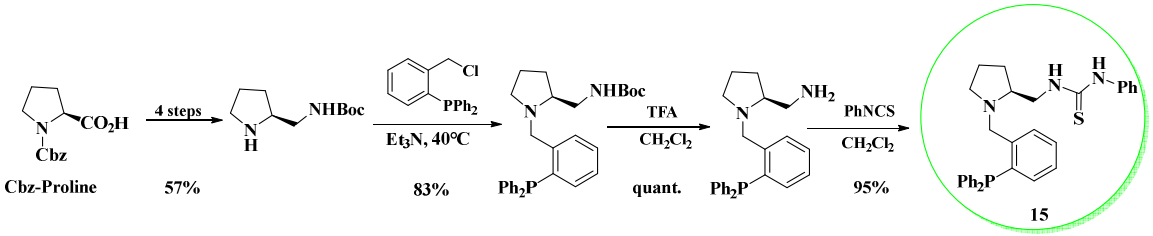
The development of suitable, inexpensive, modular chiral organocatalysts has attracted considerable interest in recent years. Many chiral thiourea-phosphine compounds derived from natural or unnatural products have been reported in literature.[20,21]Moreover, the potentiality and effectiveness of L-proline derivatives as organocatalysts have demonstrated very broad applications.[22]Thus, in the course of our study to promote the use of natural and inexpensive compounds to elaborate catalytic systems, we focus on the use of simple and well-known L-proline as a chiral renewable resource for the synthesis of a new class of chiral thiourea-phosphines. The original structure of the chiral framework offers an interesting potential to the construction of bifunctional organocatalysts for asymmetric transformations.

Starting from L-proline, a new family of bifunctional chiral thiourea-phosphine organocatalysts was designed and synthesized. Our design of modular catalyst involves: 1) a urea function for interaction between catalyst and substrates; 2) a phosphorus center that is responsible for catalytic activity; 3) a stereogenic center that is ensured by the natural chirality of L-proline; 4) a chiral carbon framework which offers potential modularity of a catalyst (Scheme 8).



Scheme 8: Retrosynthetic pathway to thiourea-phosphines **13**, **14**, **15**.

Thus, a series of 5 chiral thiourea-phosphine organocatalysts derived from L-proline was isolated in good overall yields.[23] The synthesis is quite short, flexible and could be carried out in large gram scale. An example of the synthesis of **15** was presented in Scheme 9.



Scheme 9: Synthesis of thiourea-phosphine **15** from CBz-proline.

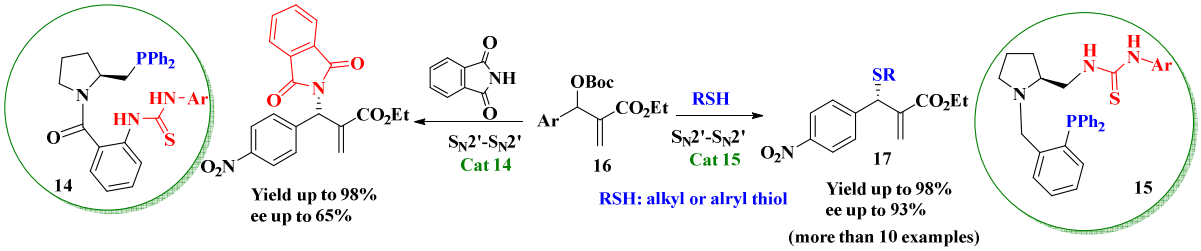
Thiourea-phosphine-organocatalyzed asymmetric C-N and C-S bond formation reaction

After achieving the synthesis of these chiral thiourea-phosphines, we were interested in testing their potential as organocatalysts for asymmetric organocatalyzed transformations.

Asymmetric allylic substitution reactions catalyzed by a chiral amine or phosphine have been powerful and versatile tools for the C–C, C–N, C–O and C–P bond construction.[24] However, if several organocatalytic procedures exist for the C–S bond formation,[25] examples including the allylic substitution of modified Morita-Baylis-Hillman (MBH) adducts are very scarce.[26]To the best of our knowledge, only one example of asymmetric allylic substitution of alkyl thiols with MBH carbonate adducts catalyzed by a chiral amine has been described.[27] No example of phosphine-catalyzed allylic substitution of MBH acetate or carbonate adducts for C–S bond creation has been reported so far.

We report hereafter the use of chiral thiourea-phosphine as organocatalysts in the asymmetric allylic substitution of modifiedMBH adducts with phthalimide or alkyl thiols for the C–N or C–S bond formation.

After screening many reaction parameters including solvent, catalyst structure, additive, reaction time and temperature, the asymmetric allylic substitution reaction of tert-butoxycarbonyloxy-MBH adduct**16**with phthalimide using thiourea-phosphine based-organocatalysts derived from L-proline worked smoothly leading to the formation of expected product in very good yields and moderate to good enantioselectivities. We have also described the first example of thiourea-phosphine organocatalyzed C–S bond formation affording enantioenrichied α-methylene-β-mercapto esters in excellent yields and with very high enantiomeric excess up to 93% ee (Scheme 10).[28]



Scheme 10: Asymmetric allylic substitution of *tert*-butoxycarbonyloxy-MBH adduct **16.**

Reaction of **16a** (Ar = *p*-$NO_2C_6H_4$)with trityl thiol conducted to optically pure **17a** (R = Ph_3C) as a single crystals after recrystallization. Its absolute configuration was determined by X-ray single-crystal diffraction analysis (Figure 4).

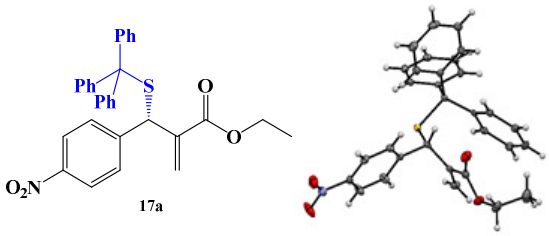
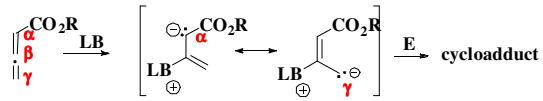


Figure 4*:* ORTEP drawing representation of the molecular structure of **17a**. Ellipsoids are drawn at the 30 % probability level.

Synthesis of functionalized 2*H*- and 4*H*-pyran derivatives *via* organocatalyzed [4+2] annulation of tetrasubstituted alkenes with allenoates.

Allenoates are interesting substrates for the Lewis base-catalyzed reactions because of their high reactivity to give access to the structurally divergent molecules. The addition of a Lewis base (LB) to the *sp*-hybridized *β*-carbon of allenoate generates the zwitterionic intermediates (Scheme 11) which participate in various annulation reactions for the synthesis of carbocyclic and heterocyclic compounds.[29]



Scheme 11: Lewis base (LB)-catalyzed reactions of allenoates with electrophiles (E).

Among them, the [4+2] and [2+2] annulations of allenoates catalyzed by a tertiary amine bring potentialities for preparation of six and four membered ring structures towards the synthesis of natural products and biologically active molecules (Figure 5).[30,31] However, to the best of our knowledge, the annulation of all-carbon tetrasubstituted alkenes with allenoates has not been reported so far.

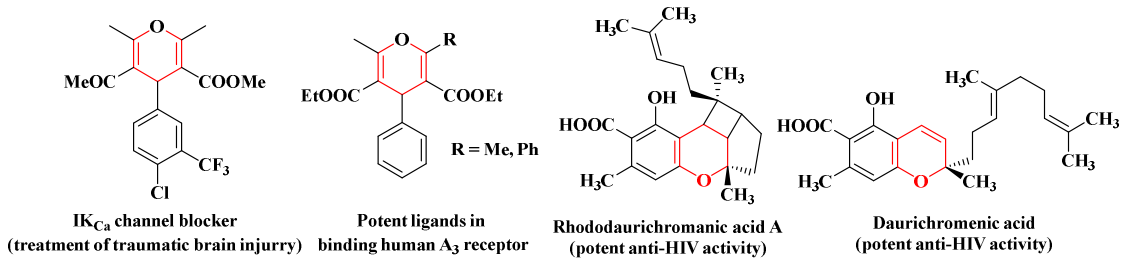
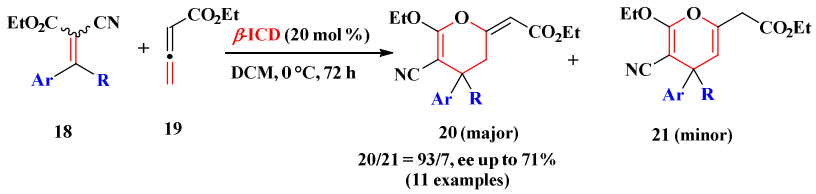


Figure 5*:* Some bioactive *4H*-pyran and *2H*-pyran compounds.

We have recently reported the first amine-organocatalyzed [4+2] annulation of allenoate **19**and all-carbon tetrasubstituted alkenes **18**for the synthesis of highly functionalized *2H*-and 4*H*-pyran **20** and **21**derivatives. Different chiral amines including quinidine, cinchonidine, quinine, *α*-ICPNwere tested for this reaction (Figure 6). Only *β*-ICD, conducted to the formation of expected enantioenrichied 2*H*-pyran **20**bearing a chiral all-carbon quaternary center with enantiomeric excess up to 71% (Scheme 12).[32]The results obtained will open the opportunities in synthesis of bioactive heterocyclic products and other pharmaceutical products.



Scheme 12: β-ICD catalyzed [4+2] annulation reaction of allenoate **19**with alkene **18**

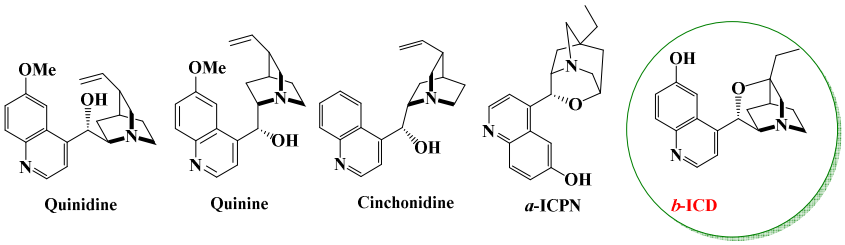


Figure 6: Structure of chiral amine catalystsfor [4+2] annulation reaction.

Based on these results obtained, the design of novel multifunctional organocatalysts, which are expected to afford higher levels of enantioselectivities, is currently underway in our laboratory.

Conclusion

We have designed and synthesized a new family of chiral amino alcohols, diamines and monophosphines derived from isosorbide and isomannide. These chiral ligands were obtained in moderate to good overall yields. The procedures for the preparation of these compounds were quite simple and practical and could be performed in large scale thanks to the inexpensive available starting materials. These ligands were successfully used in the metal-catalyzed enantioselective hydrogenation of ketones or activated olefins leading to the formation of expected products in excellent yields and enantioselectivities.We have recently reported the synthesis of new chiral thiourea-phosphines starting from L-proline. These molecules catalyzed efficiently the asymmetric allylic substitution of modified MBH adducts. Moreover, the synthesis of enantioenrichied 2*H*-pyran derivatives bearing a chiral all-carbon quaternary center was also descried, for the first time, using β-ICD catalyzed [4+2] annulation reaction.
Although, a number of chiral organocatalysts were designed and synthesized, their applications in asymmetric organocatalysis are still limited in catalyst loading and in asymmetric reaction scope. The concern of finding out an advanced and 'perfect' organocatalytic system always inspires chemists. We hope that this work would bring a promising way in the construction of chiral molecules with high enantiomeric purity which will be used as precursors for the synthesis of molecules or molecular scaffolds of biological and therapeutic interest.

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