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Nitrogen-functionalized Isohexides in Asymmetric Induction

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Abstract: Biosourced isohexides have attracted the considerable attention of both the academic and industrial chemistry communities over the last 50 years. This highlight focuses on the synthesis of nitrogen-containing isohexides and their applications in asymmetric catalysis.

Keywords: Asymmetric catalysis · Isohexides

For the past few decades, the academic landscape has been strongly modified due to the concepts issuing from 'green chemistry'. Even if some terminology was finally established by Trost,[1] Sheldon[2] and Anastas,[3] for their contribution to the atom economy principle, the E factor definition and the twelve principles of green chemistry, pioneering work in this field should be acknowledged as originating from Giacomo Ciamician in 1908. As a confirmation of his thoughts, the use of renewable materials or reagents is now clearly indexed as Principle 7.[4]

Isosorbide **1** is a chiral dianhydrohexitol and a major product of the starch industry produced by Roquette Frères (Lestrem, France)[5] that expanded its production to several thousand tons in 2011. The industrial process is initiated by double dehydration of sorbitol. The hydroxyl group on the C_6 position has an *exo* configuration (pointing out from the cycle) whereas the one on C_3 has an *endo* configuration (pointing into the cycle) (Fig. 1). As a consequence, two pivotal parameters have been highlighted to influence the native reactivity: i) hydrogen bonding between the *endo*-hydroxyl group and the endocyclic oxygen; ii) steric hindrance of the *endo*-hydroxyl group compared to the *exo* one.

Along with isosorbide, the family of 1,4:3,6-dianhydrohexitols is completed with two other symmetrical diastereomers: isomannide **2** (*endo*/*endo* isomer) and isoidide **3** (*exo*/*exo* isomer) (Fig. 1). Double dehydration of D-mannitol and D-glucitol have afforded isomannide and isosorbide in a wide range of acidic conditions such as formic acid/HF,[6] pyridinium chloride,[7] H_2SO_4,[8] Amberlyst or Dowex resins,[9] metal phosphates (of tin, zirconium, titanium, niobium),[10] zeolites,[11] silicotungstic acid[12] and so on. Simple metallic or bifunctional catalysts also efficiently performed the dehydration of these polyols.[13] Cellulose[14] could be directly converted by combining acidic and hydrogenation catalysts. Isoidide is the sole diastereomer that is not produced on industrial scale by double dehydration of L-iditol barely present in nature. Conformations of these bicyclic derivatives have been evaluated by NMR studies to be a combination of C_S and C_2 classical forms associated with cyclopentanes.[15]

Beyond the valorization of isohexides as chiral diols from renewable resources, most of all in polymer applications,[16] the corresponding diamino-dideoxy isohexides **4**–**6** have recently attracted increased interest (Scheme 1).[17] The importance of diamines as building blocks in the chemical industry and a growing aim to increase the sustainability and biocompatibility of the large-scale production of intermediates in the synthesis of polyamides and polyurethanes are highly motivating this research.[18] Asymmetric induction is also another field of interest for valuable valorization of mono- and diamines, largely used as chiral auxiliaries and ligands.[19] As a consequence, from the early 2000s, isosorbide derivatives have been investigated in asymmetric catalysis. A few examples of enantioselective induction in the presence of nitrogen-containing isohexide derivatives have already been reported and will be presented in this contribution.[20]

1. Synthesis of Nitrogen-containing Isohexide Derivatives

1.1 *Preparation of Diamines*

Starting from dianhydrohexitols **1**–**3**, primary diamines **4**–**6** were obtained by a classical three-step sequence of tosylation, azoturation (in DMF or in [bmim]BF_4[21]) and hydrogenolysis (Scheme 1).[22] Replacement of sodium azide by benzylamine and subsequent high-pressure hydrogenation allowed the access to diamines **4** and **5** with 50% and 61% global yield.[23] Unfortunately, when reacting isoidide ditosylate with ammonia[24] or benzylamine,[17b] a tricyclic adduct **7** was isolated due to intramolecular nucleophilic substitution. Despite a poor atom-economy factor, the displacement by phthalimide,[17a] followed by acidic hydrolysis, was proposed as a more efficient scalable strategy to obtain **5**

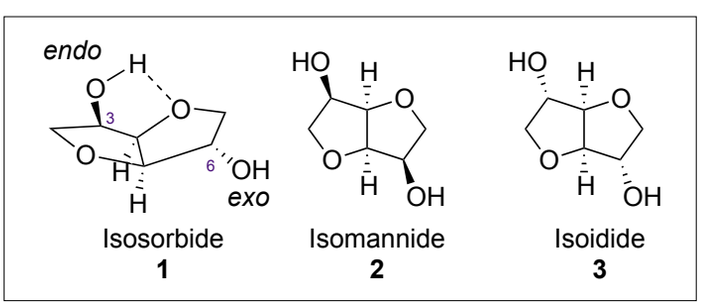

Fig. 1. Diastereomeric isohexides.

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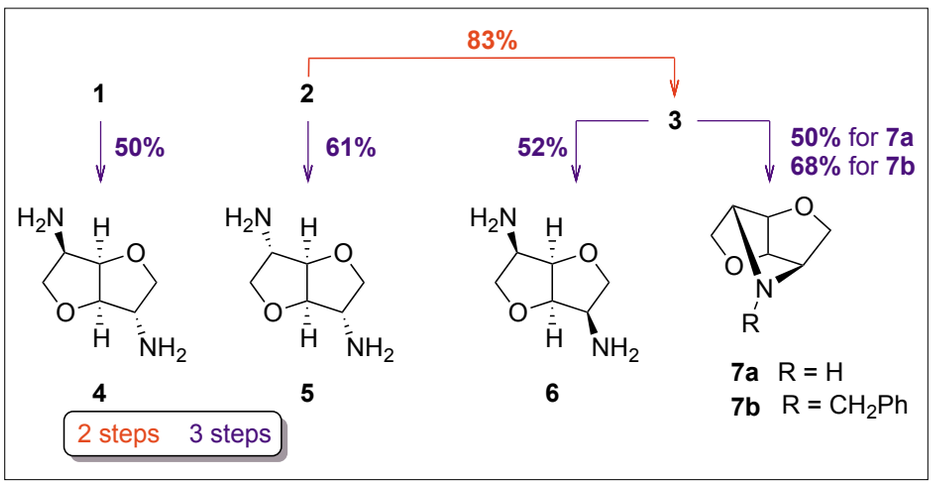


Scheme 1. Primary diamines arising from isohexides and side product.

on a multi-gram scale with high purity for step-growth polymerization.

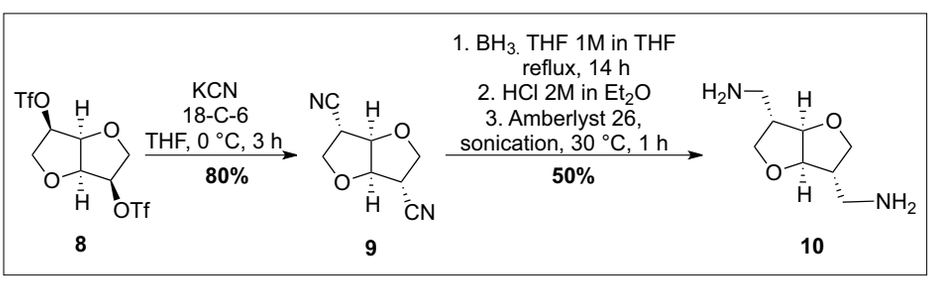
To date, the least accessible diamine **6** is synthesized in five steps from isomannide **2** in 43% yield *via* a diazide intermediate[25] which breaks the defined safety rules.[26] More recently, Beller reported a ruthenium-catalyzed amination of isosorbide through a borrowing hydrogen reaction leading to an inseparable diastereomeric mixture of diamines **4**–**6** in an excellent 96% yield.[27] As an alternative to metal-catalyzed amination, biocatalysis promoted by an enzymatic couple of transaminase/dehydrogenase only afforded isosorbide monoamine with 7% yield.[28] These recent proofs of concepts opened the way to original sustainable and safer approaches, with, so far, no significant breakthrough regarding the synergistic efficiency and diastereoselectivity.

Nucleophilic substitution of ditriflated isomannide **8** by KCN (2.2 equiv.) in THF in the presence of crown-ether 18-C-6 (2.2 equiv.) provided dinitrile **9,** which under reduction with an excess of borane, afforded homologated diamine **10** (Scheme 2).[29]

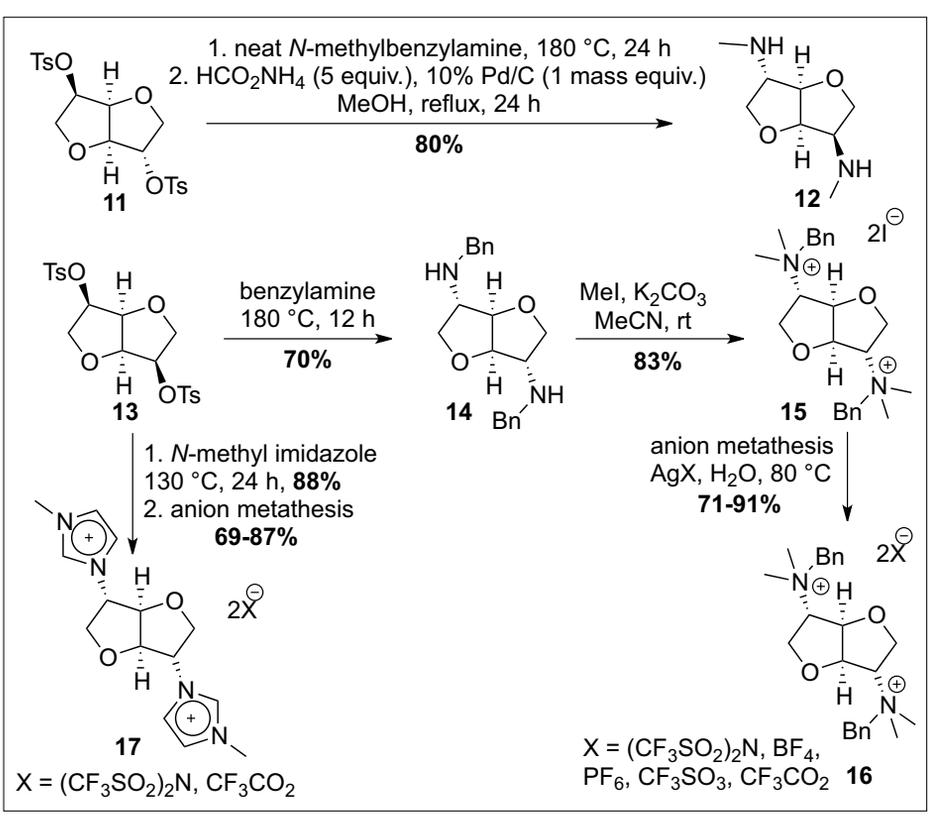
Depending on the nature of the nucleophilic species, secondary diamines (*e.g.* **12** and **14**) as well as tertiary diamines could be prepared (Scheme 3). In our hands, initial substitution by *N*-methylbenzylamine of isosorbide ditosylate **11** afforded an intermediate, easily isolable, tertiary amine. Upon treatment with ammonium formate, in the presence of 1 mass equivalent of palladium, bis-secondary methyl amine **12** was obtained in 80% yield (Scheme 3). Nevertheless, direct substitution with low boiling point amines (methylamine, allylamine, diallylamine) failed resulting in complete recovery of the starting material.

Subsequent quaternization of secondary amine **14** provided biosourced ionic liquids (bis-ammonium **15**, **16**[30] or bis-imidazolium **17**[31]). Ammonium and imidazolium ionic liquids were investigated for their physical and chemical properties such as low vapor pressure, high thermal stability, ionic conductivity, offering new organic media for reactions with a high potential of recyclability as an alternative to classical solvents. Task-specific ionic liquids were also considered for their dual combination both as catalyst and solvent. As an example, chiral ionic liquids specially have shown promising applications in asymmetric synthesis, chiral chromatography or resolution.[32] Concerns about the feedstock source, the toxicity and the poor biodegradability have also encouraged the synthesis of novel ionic liquids from bio-renewable resources,[33] like isohexides, to investigate their physico-chemical properties and applications.[34]

The synthetic sequence to provide ionic liquids **15** and **16** was generally described from isomannide ditosylate **13**, reacting at 140–160°C in pure benzylamine, followed by quaternization with methyl iodide and/or tuning the anion counterpart *via* metathesis. Compound **17** was prepared by direct substitution of **13** by *N*-methyl imidazole, followed by anion metathesis.



Scheme 2. Synthesis of homologated primary diamine **10**.



Scheme 3. Access to secondary diamines **12** and **14** followed by quaternization to ammonium and imidazolium salts **15**–**17**.

1.2 *Preparation of Mono-amine Derivatives*

1.2.1 *Monofunctionalization of Isohexides*

The access to mono-amine derivatives is a more challenging exercise, relying on an initial single functionalization of isosorbide (or isomannide) with more or less success in the selective discrimination of hydroxyl groups. The di-functionalization is also a serious limitation to tackle.

An overview of different related substrates (**18**–**20**) available for single nucleophilic substitution is depicted in Fig. 2.

As an example, after selective monotosylation of isomannide affording **18a** in 44–68% yield (side product: bis-tosylate isolated in 26% yield), the displacement of tosylate provided the amine in the *exo* position. If necessary, the remaining hydroxyl group could be protected as an ether **18b** (R = Me, Et, allyl, Bn)[35] or as a *tert*-butyl dimethylsilyl ether **18c**.[31]

Given the intrinsic difference of reactivity between *endo* and *exo* positions, isosorbide was the most investigated as a starting material for monofunctionalization selectively directed on the C_3 (compounds **19**) or C_6 position (compounds **20**). Initial studies reported direct tosylation in the early sixties: a solution of isosorbide, tosyl chloride (1 equiv.) stirred in pyridine at 5 °C for 46 h provided *endo* tosylate **19a** (45% yield), its *exo* regioisomer **20c** (12% yield) and di-tosylate **11** (5% yield).[36] Direct esterification[37] and alkylation[38] of isosorbide were also performed with moderate to excellent regioselectivity. In particular, the most advanced academic work concentrated on selective acetylation or benzylation of isosorbide with mechanistic propositions on the influence of the base, solvent and interactions with both hydroxyl groups determining the preferred position between C_3 and C_6. A large panel of experimental conditions was adjusted to turn either in favor of the *exo* regioisomer or the *endo* regioisomer (Scheme 4). Acetylation (or benzoylation) in the *endo* position can be carried out with PbO at room temperature in up to 92% yield to give **21**.[37b,39] The *exo* regioisomer **22** was obtained under relatively harsh conditions with Ac_2O (or Bz_2O) at 120 °C in 1 h followed by selective hydrolysis[37b] or *via* DCC activation.[37c] Loupy and Quéguiner also described, in 1994, the regioselective mono-benzylation (and to a general extent mono-alkylation), tuned by the nature of the solvent and the base (Scheme 4).[38a] Thereafter, derivatives **21**–**25** were widely reported as valuable intermediates allowing the introduction of phenylsulfonate (**20a**),[40] *p*-toluene sulfonate (**19b**, **19c**, **20b**),[35a,41] or triflate (**20d**)[40a] as an activating group.

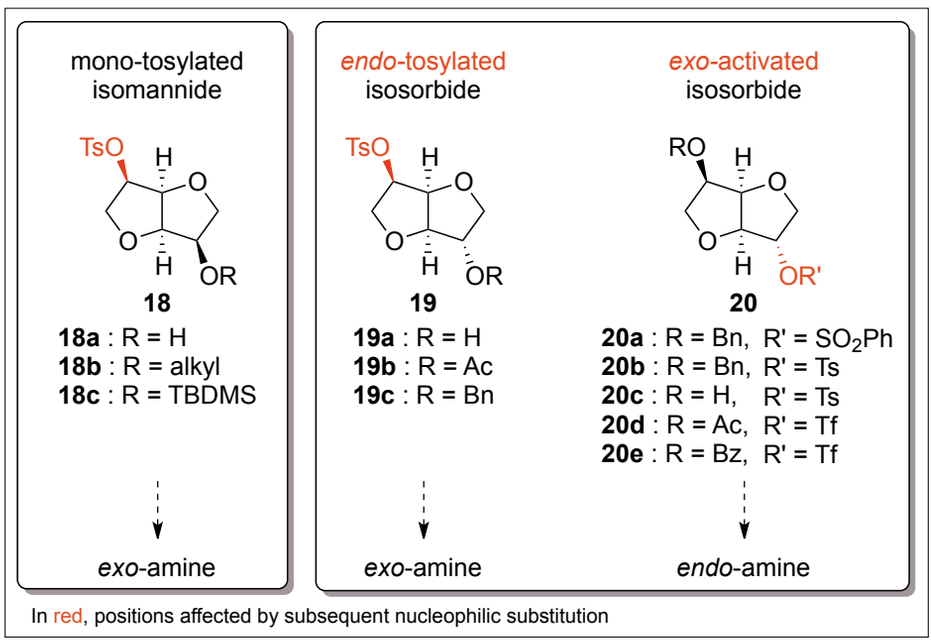
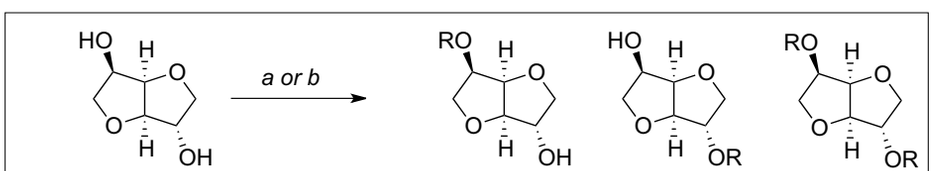


Fig. 2. Main precursors of amino isohexides arising from monofunctionalization of isomannide and isosorbide.

1.2.2 *Nucleophilic Substitution of Activated Isohexides*

Nitrogen nucleophiles used in S_{N2} reactions on substrates shown in Fig. 2 were nearly identical to the ones used for double displacement producing diamines, with only slight changes in the reaction conditions. For the displacement of *endo*-tosylated molecules, compounds **18** or **19** (or their phenylsulfonate analogue[34a]) were reacted with primary alkyl amines, including benzylamine.[35a,41] Sodium azide was handled in different solvents: DMF,[42] [bmim]BF_4,[21,35c] leading to azido derivatives with moderate to very good yields. From derivative **20a**, primary alkyl amines (benzylamine, cyclohexylamine, cyclohexylmethylamine, isopropylamine, *tert*-butylamine) could be introduced in *endo* position with 56–85% yield under classical heating or microwave irradiation. Lower yields (45 and 31%) and epimerization were observed with aniline and *N*-ethylaniline.[41] *N*-Methylimidazole reacted with phenylsulfonate **20a** in 50% yield after 4 h at 130 °C. In the case of triflates **20d** and **20e**, the substitution took place at room temperature for 2 days but without any yield improvement due to significant competitive elimination (30%) as a negative counterpart.[40a] The introduction of azide in *endo* configuration from derivatives **20** proved to be more difficult as an optimized 25% yield was several times reported and confirmed in our hands even using triflate as a leaving group.[43] Free amines were obtained after hydrogenation of benzylamino derivatives or azides.[40b,c] Methylation was performed either *via* an Eschweiler-Clark reaction followed by quaternization[34] or *via* a phase-transfer catalyzed reaction in a biphasic medium with Me_2SO_4, to lead to mono ammonium or imidazolium derivatives.[35a]



R = Ac	**21**	**22**	**23**
Conditions a : Ac_2O, PbO, DCM	92%	0%	8%
Conditions b : AcOH, DCC, DMAP, DCM	0%	68%	12%
R = Bn	**24**	**25**	**26**
Conditions a : BnCl, LiH, LiCl, DMSO	63%	0%	11%
Conditions b : BnCl, CsOH, H_2O	15%	40%	4%

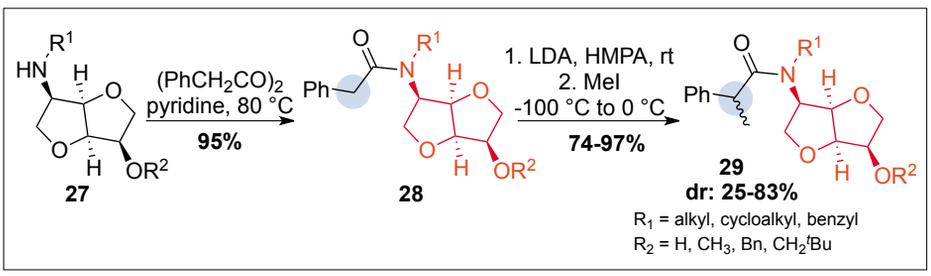
Scheme 4. Optimized conditions for regioselective acetylation/benzylation of isosorbide.

2. Application to Asymmetric Induction

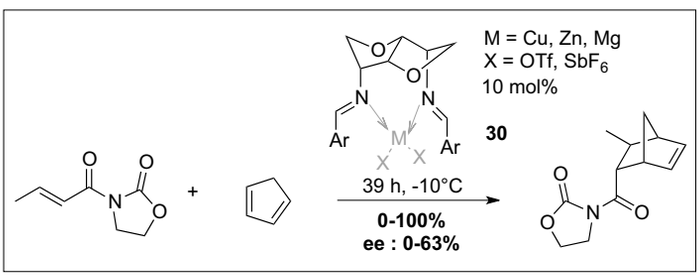
The potential of highly functionalized isosorbide derivatives in asymmetric catalysis as chiral auxiliaries,[44] or ligands,[45] has only been investigated in the last 15 years.[46]

To our knowledge, there is only one example using nitrogen-containing isohexide as a chiral auxiliary. In 1993, Quéguiner reported for the first time the synthesis of chiral aminoethers **27**[41] and their use in the asymmetric alkylation of phenylacet amides **28** (Scheme 5). The best diastereomeric ratio was evaluated at 83% when running the reaction at –100 °C with R_1 = cyclohexyl.[47]

With the above exception, most of the disclosed reports over the last 15 years on the use of nitrogen-based isohexides for asymmetric synthesis (or chiral resolution) dealt with their role as chiral ligands or as precursors of organocatalysts.



Scheme 5. Diastereoselective alkylation in α-position of isohexide amides.



Scheme 6. Bis-imine copper-catalyzed Diels-Alder reaction.

2.1 *Organometallic Catalysis*

Enantioselective organometallic catalysis was studied with nitrogen-based ligands from isohexides especially with Diels-Alder and transfer hydrogenation reactions, which we designate model reactions.

Endo/*endo* diamine **6**, prepared in five steps (overall yield 45%) from isomannide **2**, was then converted into a set of di-imines **30** by reaction with substituted benzaldehydes. These di-imines were evaluated as ligands, in association with copper, zinc or magnesium in Diels-Alder reactions of cyclopentadiene and *N*-crotonyl-oxazolidinone (Scheme 6). Best enantioselectivity (*ee* 63%) was reached by complexation of copper (II) triflate and bidentate ligands issued from coupling with 2,6-dichlorobenzaldehyde.[25]

In contrast to the Diels-Alder reaction, asymmetric transfer hydrogenation in the presence of amino isohexides ligands, was investigated in more depth, mainly for the reduction of C=O bonds. The Ru-catalyzed enantioselective reduction of acetophenone was reported with different sets of ligands and then followed by other aromatic ketones (Scheme 7). The conversion of acetophenone into 1-phenylethanol proved to be efficient (*ee* 80%) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (1.25 mol%) with *endo*/*endo* ligand **31a** (5 mol%).[40b,c] Diamine **31b** turned out to be active but not selective (*ee* <23%) while its *N*-tosylated counterpart **31c** gave better conversion or selectivity depending on the Ir or Ru catalyst. In comparison, ligand **32**, obtained from isosorbide after ring opening of one THF moiety, preserving the 1,2-amino alcohol sequence required for complexation with Ru^{II} catalyst, afforded almost a quantitative conversion but a lower enantiomeric excess of 60%.[48] The presence of the chiral isosorbide part proved to be necessary, a very poor enantioselectivity (*ee* <30%) being obtained with *(S)*-2-amino-2-phenylethanol or *(S)*-2-amino-3-methylbutan-1ol.[40c]

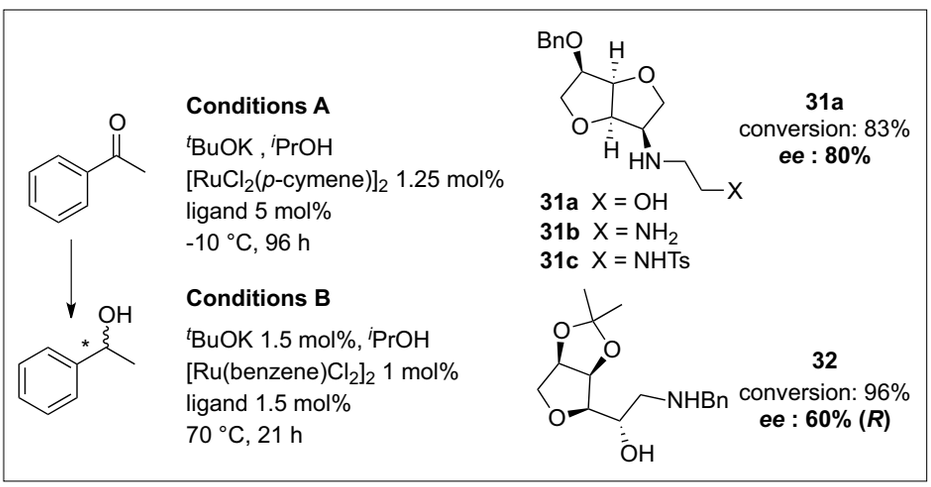
2.2 *Organocatalysis*

Organocatalysis relies on two different types of mechanism: i) *covalent catalysis* implying the formation of covalent intermediates between the organocatalyst and the substrate; ii) *non-covalent catalysis* relying on non-covalent interaction(s) such as hydrogen bonding or intermediate ionic species pairs. So far, only a few articles describe isohexide organocatalysts, the asymmetric induction being promoted either by chiral ionic liquids (or phase transfer catalysts) or thiourea derivatives, *via* a non-covalent mechanism.

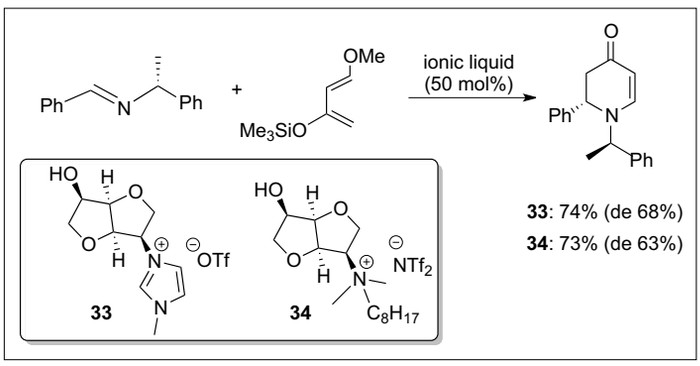
2.2.1 *Chiral Ammonium or Imidazolium Salts*[34]

Imidazolium derivative **33** and its ammonium congener **34** have been prepared and used in aza Diels-Alder reactions as chiral ionic liquids (IL). The screening of various derivatives showed that the presence of the free hydroxyl group and the non-substitution of the imidazolium nucleus were important for both reactivity and asymmetric induction (Scheme 8). Best results were obtained with IL **33** (74% yield and 68% *de*).[34a,49]

Mono and bis-ammonium ionic liquids have also been successfully used in chiral discrimination. The diastereomeric interaction between the chiral ammonium IL and the racemic Mosher's acid silver salt was investigated (Fig. 3).[30,35b] A significant enhancement in the splitting of the CF_3 signals could be observed with ^{19}F NMR spectroscopy of the salt in the presence of an excess of the ionic liquid **16'** or **35**. The influence of the anion and of the



Scheme 7. Asymmetric transfer hydrogenation of acetophenone.



Scheme 8. Aza Diels-Alder reaction in chiral isohexides IL.

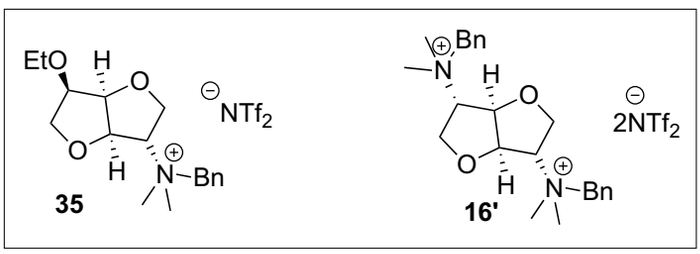
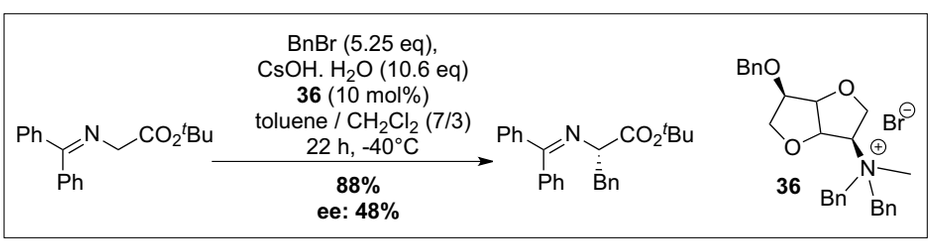


Fig. 3. Mono and bis-ammonium ILs for chiral resolution.

concentration in IL resulted in $\Delta\delta$ varying from 5 to 23 Hz.

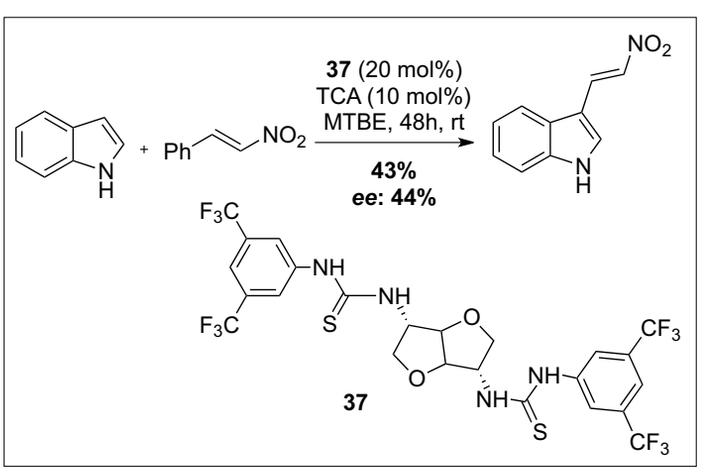
Some of these quaternary salts were used as phase transfer catalysts (PTC) leading to intermediate chiral ion pairs. Alkylation of *N*-(diphenylmethylene) glycine *tert*-butyl ester in the presence of benzyl bromide and PTC **36** afforded a moderate 48% *ee* in favor of the product with *S*-configuration (Scheme 9).[35a]



Scheme 9. Alkylation of *N*-(diphenylmethylene)glycine *t*-Bu ester.

2.2.2 *Thiourea Derivatives*

Recently, Saluzzo and colleagues focused on the design of thioureas isohexide-based compounds, and their evaluation in the asymmetric Friedel-Crafts alkylation of indole with nitrostyrene.[50] Mono and di-thioureas were prepared by tuning the stoichiometric amount of the appropriate isocyanate reacting with diamine **5** or **6**. Despite a modest 44% enantiomeric excess, di-thiourea **37** was to date the first example of the potential of isohexide derivatives in asymmetric induction mediated by non-covalent interactions, and, in this case, *via* hydrogen bond (Scheme 10).

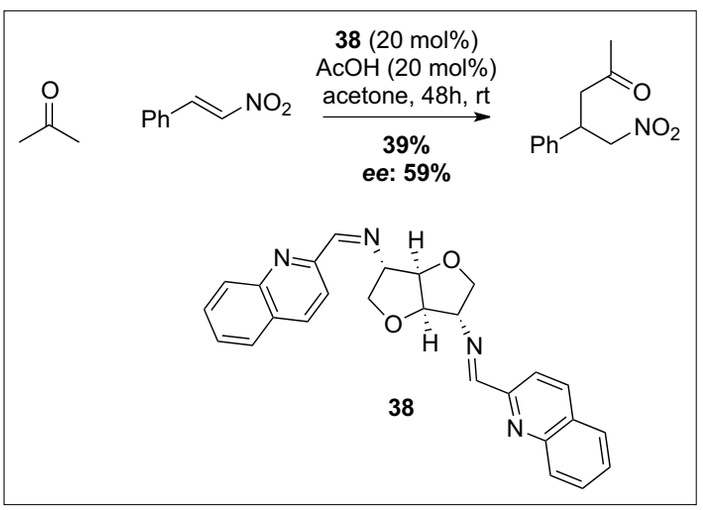


Scheme 10. Asymmetric Friedel-Crafts alkylation with thiourea **37**.

2.2.3 *Amines and Imines*

The same group reported the use of imines in the 1,4-addition of acetone on nitrostyrene. Organocatalyst **38** provided a low yield of 39% but a promising enantioselectivity of 59% (Scheme 11). A mechanistic model involving **38** in equilibrium with the corresponding amines was proposed involving both covalent and non-covalent interactions.[51]

Our group is currently involved in research projects exploring synthetic applications using Michael addition, for example in the synthesis of indolizidine alkaloid 167B,[52] or for the addition of activated methylenes to non-protected nitrovinylindole in mild conditions.[53] Due to recent contributions on the 4-hydroxycoumarin nucleus,[54] Warfarin, prepared by Michael addition of 4-hydroxycoumarin on benzalacetone, attracted logically our attention. Imidazolidine-catalyzed Michael addition was the first example reported for the asymmetric synthesis of Warfarin with an *ee* better than 80%.[55] Simple vicinal primary diamines (1,2-diaminocyclohexane, diphenyl- or dinaphthylethylenediamine)[56] or cinchonine derivatives (9-amino-9-deoxyepicinchona)[57] also contributed efficiently to the formation of an iminium intermediate. Following this strategy, simple bulky aminoalcohols derived from phenylglycine represent an alternative to other chiral diamines.[58] For a combined mechanism based on covalent/non-covalent activation, bifunctional catalysts have been developed from previously described vicinal diamines.[59]



Scheme 11. Michael addition of acetone on nitrostyrene catalyzed by di-imine **38**.

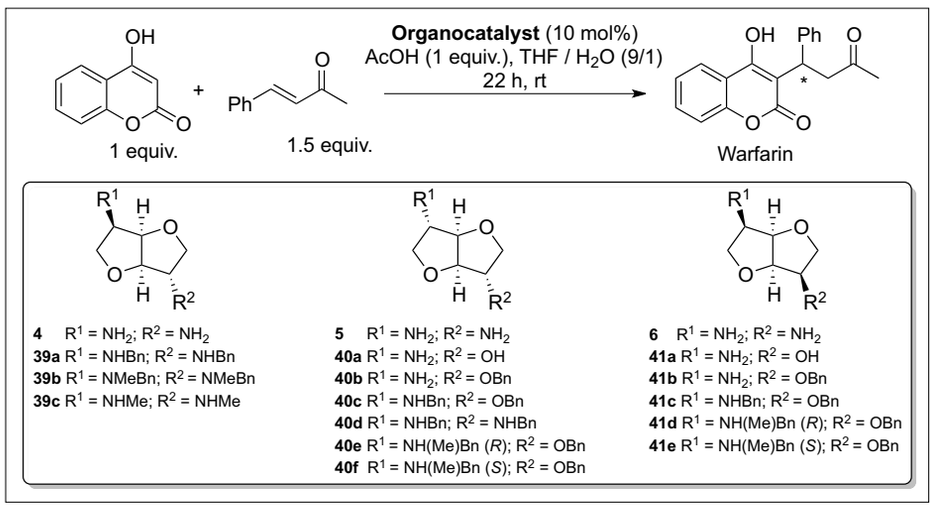
In this context, our group decided to exploit the potential of biosourced carbohydrates arising from both commercially available isosorbide and isomannide and lab-made isoidide.[25,60] Their functionalization into suitable amino alcohols, aminoethers and diamines, could provide a different option for organocatalysis. A first generation of chiral aminoalcohols, aminoethers, primary/secondary diamines were prepared following the classical synthetic pathways described in section 1 of this contribution leading to 17 potential organocatalysts (Scheme 12).

Those molecules were then screened in the asymmetric synthesis of Warfarin. Preliminary results confirmed the induction of enantioselectivity with diamine **5**, but neither in a satisfying yield nor enantioselectivity (yield 20%, *ee* 29%).[61]

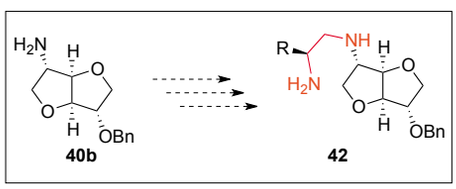
As chiral vicinal diamines derivatives are recognized as robust organocatalysts in 1,4-addition reactions, we contemplated introducing the 1,2-diamine pattern as suggested in structure **42**. A three-step sequence (peptidic coupling, reduction of amide, Boc deprotection) should provide the second generation of organocatalysts (Scheme 13).

A survey of the literature pointed out the lack of synthetic tools for the formation of amide on isohexide derivatives, only briefly reporting the use of β-aminoacids (*via* DCC, DMAP or EDCI, HOBt),[62] acid chloride (with triethylamine, DMAP),[60] or oxazolone (*via* a ring opening by an Erlenmeyer–Plöchl reaction).[21,35c] Most of the well-established methods for their formation are relatively inefficient, with large quantities of potentially hazardous waste products, leading to difficult purification of the desired amides. Our laboratory recently developed a simpler method using catalytic amounts of boric acid and affording the expected amides with excellent yields.[63] After optimization of the methodology, the coupling between amino-ether **40b** and a variety of carboxylic acids was performed with good to excellent yields regardless of the nature of the carboxylic acid: benzoic acids (76–97%), aliphatic carboxylic acids (90–96%) and amino acids (71–85%) (Scheme 14). A large scope of carboxylic acids and amino acids could thus be introduced leading to a diversity of new functionalized isohexide derivatives.

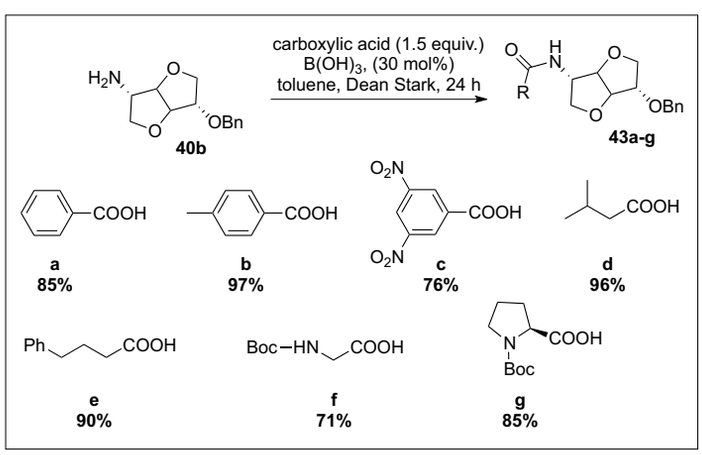
Perspectives of this study will specially focus on the synthetic potential of coupled derivatives with amino acids. Specifically, compound **43g** and analogs will be applied in a reduction/deprotection sequence to provide corresponding vicinal diamines **42** that will be evaluated for the asymmetric synthesis of Warfarin.



Scheme 12. Overview of the first generation of organocatalysts screened for the stereoselective synthesis of Warfarin.



Scheme 13. Second generation organocatalysts **42.**



Scheme 14. Boric acid catalyzed amidation.

3. Conclusion

Isohexide derivatives have displayed their potential through different industrial applications. POLYSORB® ID37 (isosorbide diester monomer), registered in compliance with REACH regulations, represents an alternative to traditional plasticizers. ISORDIL® (isosorbide dinitrate) is sold as a vasodilatator, and ARLASOLVE™ DMI (dimethylisosorbide) as a new solvent. Eco-conception of molecules of high-added value is nowadays of great concern in industrial and academic laboratories. Our global strategy is to promote isohexide derivatives, that albeit known for more than 50 years, have been used only recently as a chiral platform. The attraction of isosorbide especially relies on the bio-based access to this skeleton, in accordance with the twelve fundamental principles of green chemistry. Less attention has been paid to its applications as a chiral catalyst, which probably will be developed in the next years, considering the recent publications in this field.

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