

New organic solvents based on Carbohydrates

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Ionic green solvents from renewable resources^{*}

Abstract: Nature provides a vast new vista of opportunities for the preparation of new recyclable solvents. Natural compounds have been recently used to prepare the cationic or anionic moiety of room temperature ionic liquids. In many cases, these new solvents based on modification of natural products contain chiral centres and/or specific functional groups. This paper is an overview in an area of research that is destined to a rapid development and expansion.

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Introduction

In recent years the choice of the solvent for performing a reaction has become an increasingly important task; selective reagents are used for chemical transformations and the choice of the solvent may determine high reaction rates and high selectivities. At the same time, as response to increasing legislative and social pressure and an increasingly “green”-conscious industrial community, researchers have started to examine more eco-friendly and sustainable chemical processes. Toxicity and recycling considerations are influencing the choice of the solvent to use for industrial reactions. Ionic liquids (figure 1), represent a class of alternative solvents receiving currently serious consideration with the promise of benefits both environmental and technological. The development of reactions in ionic liquids is not only important on the laboratory scale but also for industrial applications and although very few have come to execution, several are at pilot scale.¹ The main processes that use an ionic liquid are BASF’s BASIL process and the Dimerosol process,² whereas the biphasic hydrosilylation in ionic liquids is actually set for industrial implementation.³

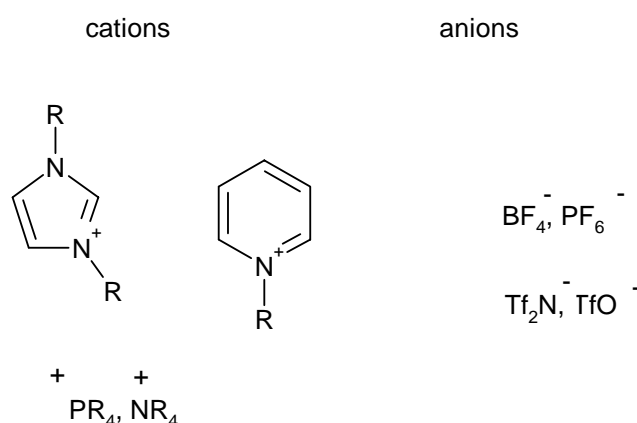


Figure 1. Cations and anions of room temperature ionic liquid (R = alkyl)

A number of room temperature ionic liquids based on large organic cations in combination with weakly coordinating anions such tetrafluoroborate, hexafluorophosphate and bis(trifluoromethanesulfonyl)imide (bis-triflimide) have been synthesized, characterized and applied in organic synthesis and catalyzed processes. All these compounds are reasonably air and moisture stable and are capable of dissolving a wide range of organic, organometallic and inorganic compounds⁴. Moreover, these salts are generally non-flammable, possess a negligible vapour pressure, a high thermal and chemical stability and offer the possibility of recycle. These characteristics render them promising replacements to volatile organic solvents (VOCs) which are a source of environmental problems. It is however noteworthy that ionic liquids represent an extremely large class of compounds (evaluated higher than 10^{18}) and not all ionic liquids necessarily possess all these properties. Recently, it has been shown that selected families of commonly used aprotic ionic

liquids can be distilled at 200-300 °C and low pressure,⁵ that a large group of ionic liquids are combustible,⁶ and that some commercially available ionic liquids may be toxic for fish⁷ or for other aquatic species.⁸ Finally, it is noteworthy that commonly used ionic liquids, as many molecular solvents, are generally synthetic chemicals arising from petroleum. As this resource continues to be consumed at prodigious pace and given the rather turbulent conditions present in some of the major oil-producing parts of the world alternative non-toxic and biodegradable materials, possible based on biorenewable resources, are of considerable interest⁹ and great practical benefit. Biorenewable natural compounds are ideal materials from the viewpoints of environmental and economic concerns.

Ionic liquids have been extensively reviewed in the last five years, with particular focus on synthesis and applications.³ Our common interest in the area of green solvents from renewable resources prompted us to focus our attention in this microreview on the more recent advances in this area. It is needless to say that a vast number of publications deal with this topic have been recently published (including reviews and minireviews),¹⁰ and probably many are in press— being comprehensive is therefore far beyond the scope of this review. This microreview presents recent advances in this area, accompanied by selected older work when necessary to better illustrate the direction the field is moving in.

Natural products as sources of the cationic part of room temperature ionic liquids

Both anions and cations can be obtained from natural sources, however, whereas little has been reported regarding natural or bio-renewable anions, the case is different for cations. Natural nitrogen containing compounds (amines, aminoalcohols and amino acids) have been preferentially used to obtain asymmetric cations, although recently also other classes of compounds have been employed. Two different strategies have been pursued in the derivatization approaches: 1) simple exhaustive alkylation on nitrogen, eventually followed by anion exchange; 2) transformation of the natural compounds (amino alcohol or amino acid) in heterocyclic systems through a more complex sequence of synthetic steps. Generally, the first approach presents the advantage to contain the costs of the derivatization process, the second one to give materials with improved properties.

One of the simplest approaches, to prepare room temperature ionic liquids, is clearly that recently reported by Davis and coworker.¹¹ Choline chloride, a natural ammonium salt having a high melting point (302°C) has been transformed in ionic liquids by 1:2 stoichiometric combination with tin (II) chloride or zinc chloride. Although both these salts are liquid at room temperature and not-

moisture-sensitive, they have the disadvantage to be highly viscous.. Improved results have been therefore obtained through the combination of the choline salts with urea; the simpler 1:2 mixture urea and choline chloride affords a material having a freezing point of 12 °C (figure 2). This mixture exhibits moreover rather unusual solubility and miscibility proprieties; highly ionic (metal salts) or strongly hydrogen bonding compounds (unprotected sugars and cellulose¹²) are significant soluble in this in this eutectic liquids whereas acetone, acetonitrile, ethylacetate, toluene are completely immiscible with it. Besides urea, other hydrogen-bond donors (ethylene glycol, carboxylic acids, etc.) form eutectic solvents with quaternary ammonium cations.¹³ The ability of these media to dissolve metal cations provides a promising perspective for application in selected electrochemical process (electroplating and electropolishing).¹³

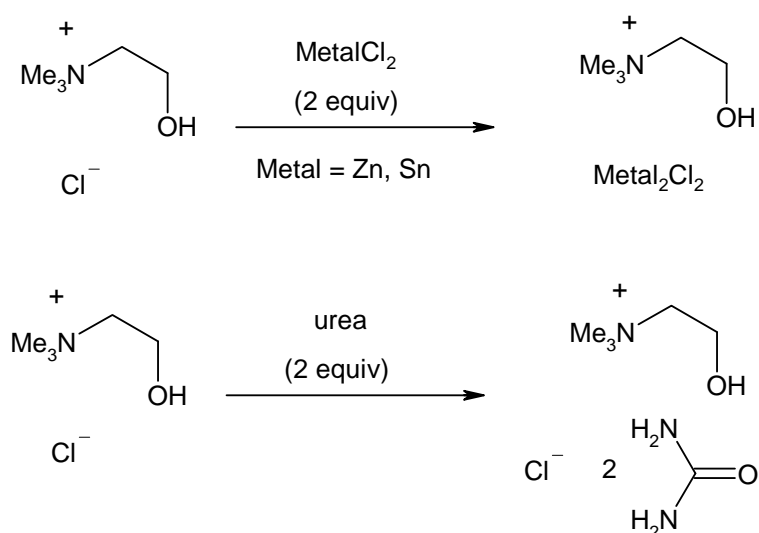
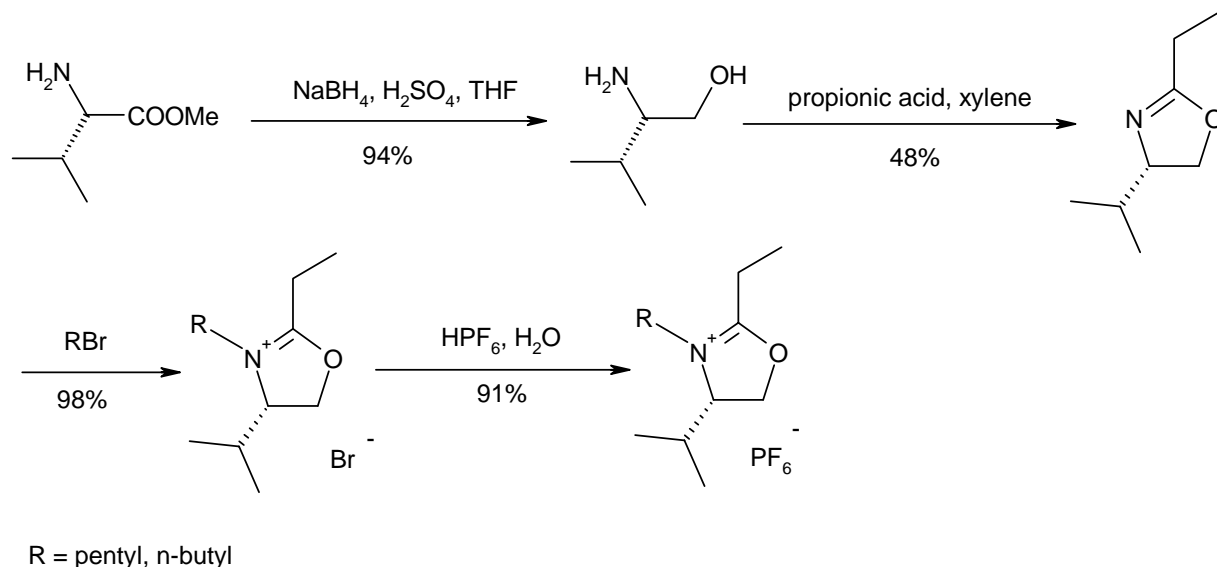


Figure 2. Choline chloride derived room temperature ionic liquids

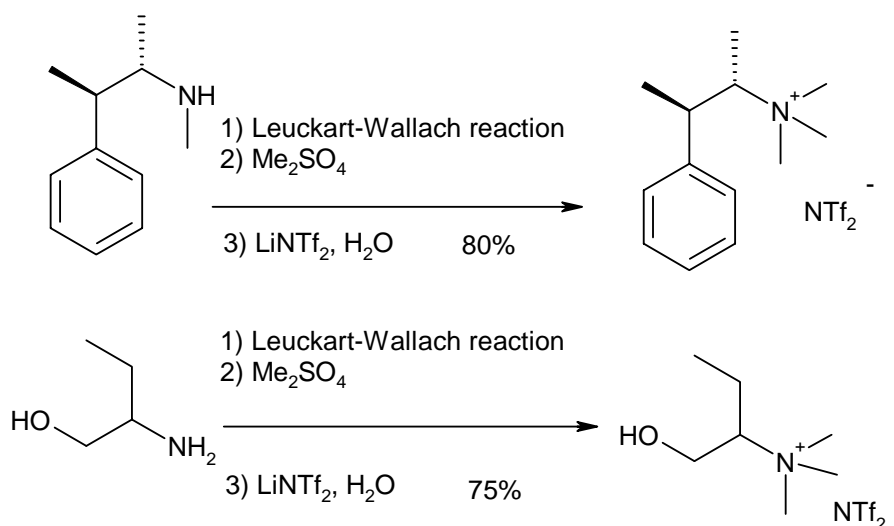
Natural compounds, easily available and containing one or more chiral carbons, have been used by Wasserscheid and coworkers to synthesize chiral ILs.¹⁴ Although the inherited chirality of these ionic liquids has been only marginally explored related to the application as solvents in asymmetric organic reactions, positive results have been obtained when these salts have been used as chiral shift reagents or chiral phases for gas chromatography. Three different groups of chiral salts were reported in this communication: based on oxazolium cation, based on hydroxy ammonium salts and based on ephedrinium salts. The oxazolium cations were prepared in four steps (overall yield 40%) starting from (*S*) valine (scheme 1). Reduction of the (*S*) valine methyl ester, following Masamune's protocol and using NaBH₄-H₂SO₄ in THF, afforded the corresponding amino alcohols. Cyclisation into oxazoline using bromopentane or bromoethane gave the corresponding salts, which after anion metathesis with aqueous HPF₆ afforded the expected ionic liquids. The melting points of the synthesized salts are comprised between 63 and 79°C. Although the oxazolium ionic liquids can be

prepared in multi gram scale, the relatively low overall yield and the low stability under acidic conditions preclude their use as solvents.



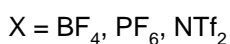
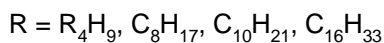
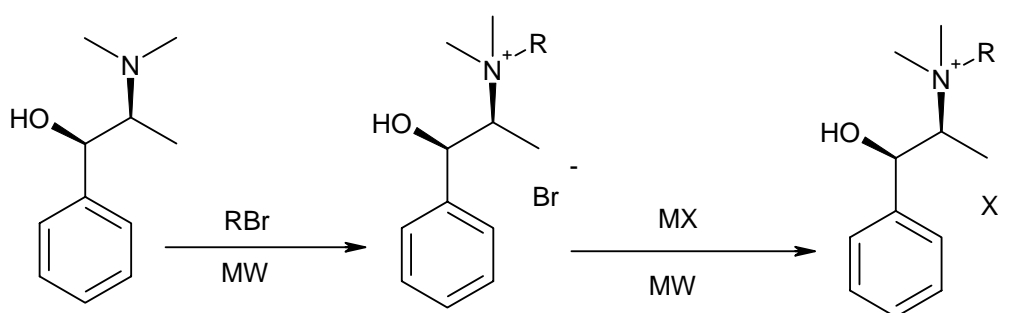
Scheme 1. Oxazolinium ionic liquids from (*S*)-valine

Ionic liquids based on hydroxylammonium and ephedrinium salts were prepared on a kilogram scale in a similar manner. The enantiopure aminoalcohol, (*R*)-2-aminobutan-1-ol and (-) ephedrine were methylated by dimethyl sulfate in dichloromethane, the solvent removed under reduced pressure and the residues were dissolved in water. The corresponding bis(triflimide) salts have been obtained by anion metathesis, using an aqueous solution of *N*-lithio trifluoromethanesulfonimide (scheme 2). The ephedrinium salt has a melting point of 54°C and is insoluble in water; the salt obtained from (*R*)-2-aminobutan-1-ol is liquid down to -18°C. Although no data have been reported about the use of these ILs as solvents for organic reactions, NMR investigations (¹⁹F NMR spectroscopy) evidenced the presence of diastereomeric interactions between the enantiopure chiral ionic liquid derived from ephedrine and the racemic mixture of the sodium salt of the Mosher acid. The ability to discriminate between enantiomers have been evidenced also using the same class of chiral ionic liquids as a stationary phase in gas chromatography.¹⁵ Several chiral ionic liquids have been used with success to separate the enantiomers of a range of chiral compounds, including alcohols and sulfoxides, showing that ionic liquids are actually more effective stationary phases than biological molecules.¹⁵



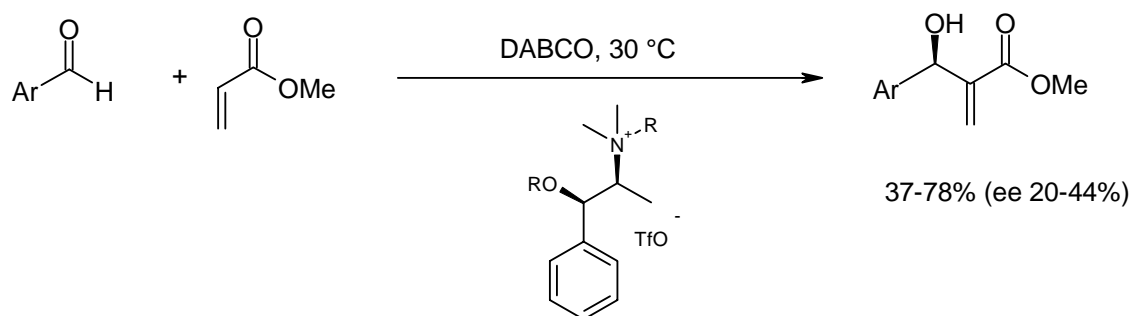
Scheme 2. Ammonium ionic liquid from (-)-ephedrine and (*R*)-2-amino-butanol-1-ol.

More recently, other ephedrinium salts were prepared by Vo-Thanh and coworkers¹⁶ using solvent-free conditions and microwave activation. The synthesis of these ionic liquids involves two steps (scheme 3). First, (*1R,2S*)-*N*-alkylmethylephedrinium bromide salts were produced by direct alkylation of (*1R,2S*)-*N*-methylephedrine (previously prepared by reductive amination of ephedrine using the Eschweiler-Clarck procedure). Four different alkyl chain lengths were tested. Subsequently, to lower the melting points, the anion exchange of the (*1R,2S*)-*N*-alkylmethylephedrinium bromide salts with alkaline or ammonium salts of large anions (BF₄⁻, PF₆⁻, NTf₂⁻) was performed, obtaining ten ionic liquids characterized by melting points lower than room temperature.



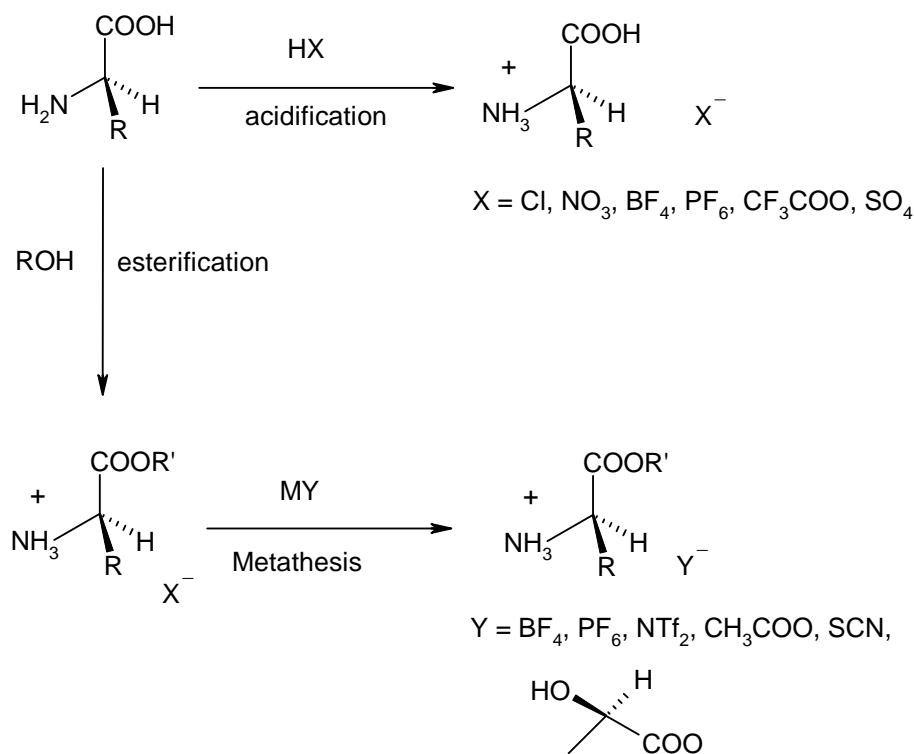
Scheme 3. Solvent free microwave assisted preparation of (*1R,2S*)-*N*-alkylmethylephedrinium.

It is noteworthy, that these latter ionic liquids have been used as solvents and sole source of chirality in the Baylis-Hillman reaction of benzaldehyde and methyl acrylate, in the presence of an equivalent of DABCO, obtaining one of the first examples of significant asymmetric induction using chiral ILs.¹⁶



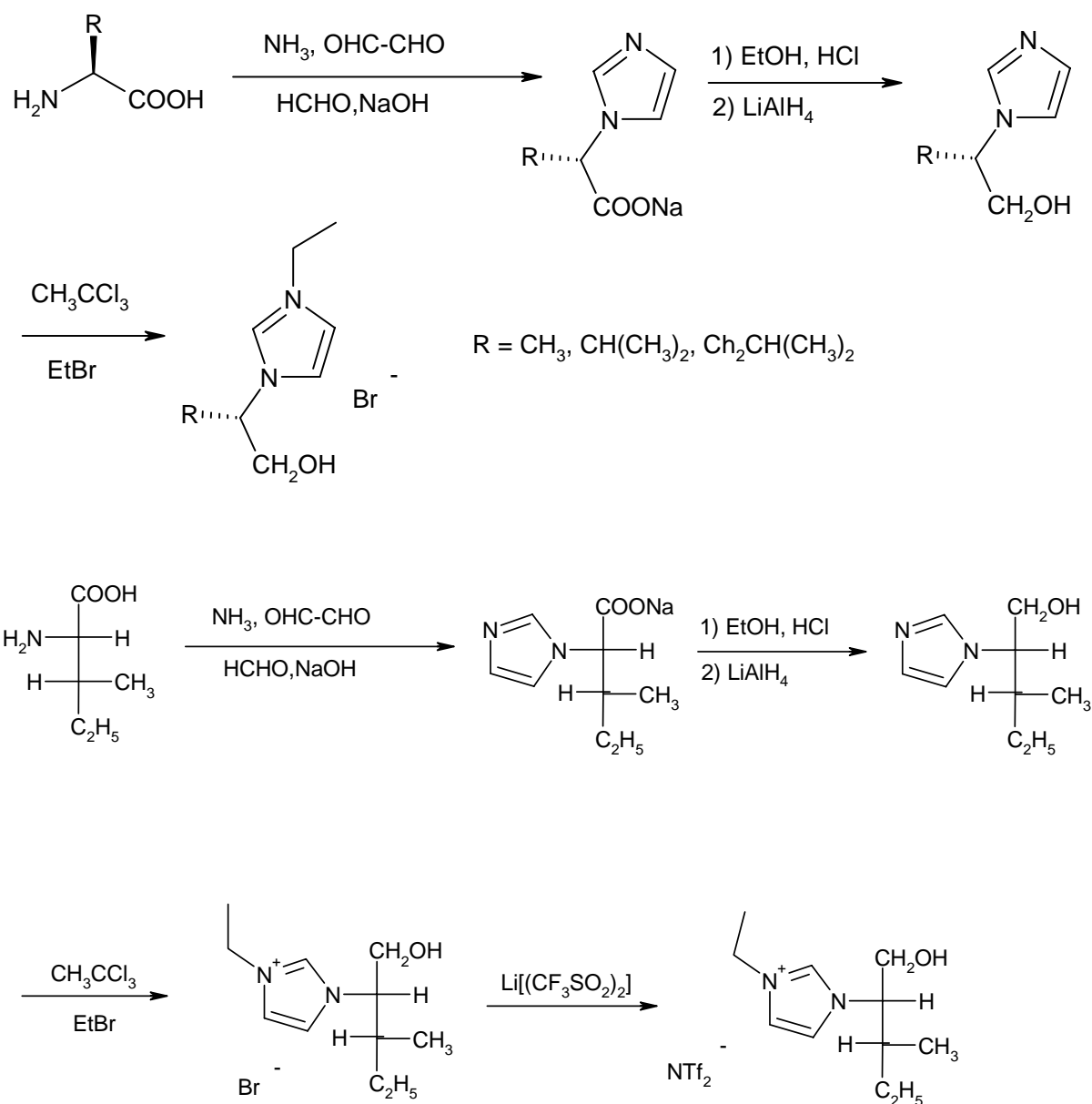
Scheme 4. A Baylis-Hilman reaction in a chiral ionic liquid.

Although amino acids and their derivatives are the most abundant natural source of quaternary nitrogen cations, they have been rarely directly used to prepare cations in ionic liquids. A simple procedure to prepare two other families of ionic liquids, starting from natural α -amino acids and α -amino acid esters, has been however recently reported.¹⁷ More than one hundred ionic liquids have been obtained *via* one step acidification of amino acids in water, followed by evaporation of the water in air and finally under vacuum (scheme 5). Due to strong hydrogen bonds involving the carboxylic acid function, most of the salts derived from α -aminoacids have high melting points, whereas the corresponding ester derived salts are viscous oils at room temperature. In all cases, the chiral centers present in the original α - amino acids have been successfully retained in the final ionic liquids and all ionic liquids show a good thermal stability up to 200°C. Within this class of ionic liquids, a family of novel salts with amino acids as cations and environmentally benign materials as anions (nitrate and saccharide) have been synthesized and characterized.¹⁸ The ionic liquids obtained have the same characteristics (thermal stabilities, phase behaviour, viscosities) as conventional imidazolium ionic liquids and the same chiralities as natural amino acids. Application in the cycloaddition of cyclopentadiene to methyl acrylate has given stereoselectivities similar to those obtained in [bmim][BF₄]. Unfortunately, despite the chiral nature of the solvent the enantiomeric excesses of the *endo* and *exo* products are found to be less than 3%.¹⁸



Scheme 5. Schematic strategy for the synthesis of amino acid based ionic liquids.

Natural amino acids have also been used to obtain imidazolium based ionic liquids. In 2003, Bao and coworkers¹⁹ described the synthesis of chiral imidazolium ionic liquids using as starting materials, *L*-alanine, *L*-leucine and *L*-valine. The synthetic procedure (four steps) gave the expected products with 30-33% overall yield. The imidazolium ring was formed by condensation of the amino acid with the proper aldehyde under basic conditions (scheme 6) and the subsequent esterification of the acid function gave the expected imidazolalkanoic ester. Reduction of the ester function, followed by alkylation, gave the expected chiral imidazolium based ionic liquids bearing a hydroxyl group on the alkyl chain. All these new ILs are miscible with water and polar solvents (MeOH, acetone) and immiscible with weakly polar solvents; their melting points range from 5 to 16 °C.

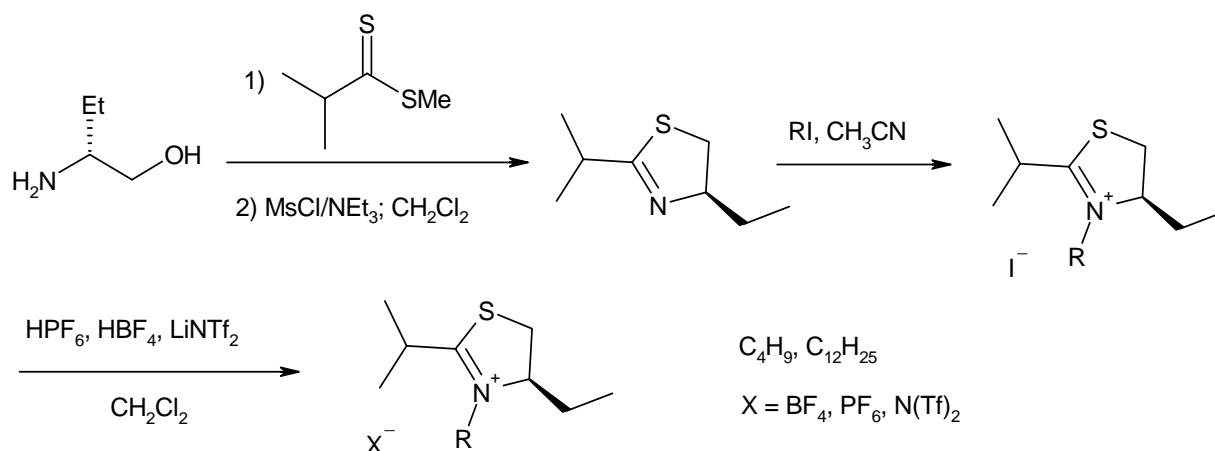


Scheme 6. Imidazolium ionic liquid from amino acids

The same approach has been used for *L*-isoleucine by Armstrong and coworkers²⁰ to synthesize imidazolium ionic liquids bearing two chiral centers (scheme 6), whereas chiral imidazolium salts were prepared in five steps by Guilleim and coworker starting from *N*-Boc-(*S*)-valine.²¹

On the other hand, thiazolinium based chiral ionic liquids have been prepared using amino alcohols as chiral material. Gaumont and coworkers have synthesized²² these new ionic liquids in four steps starting from (*R*)-2-aminobutan-1-ol or (*L*)-phenylalaninol, with fairly good overall yield (60-68 %). The synthesis, summarized in scheme 7, starts with the initial reaction of the aminoalcohol with a dithioester followed by cyclisation of the formed thioamide, nitrogen alkylation and metathesis of the anion. Melting points of these ionic liquids depend on the length of the *N*-alkyl chain and on the nature of counter anions, ranging from 137°C to below 0°C.

Within contrast to the chiral oxazolinium-based ILs, the thiazolium ILs are stable under basic and even acidic conditions.



Scheme 7. Thiazolium ionic liquid from an aminoalcohol.

Finally, chiral amino alcohols have been recently used to design a series of imidazolium based ILs bearing a chiral substituent at C-2.²³ These ionic liquids were assembled by incorporating chiral side chains on the C-2 positions of the imidazolium cation rings through condensation reactions involving 1-methyl-2-imidazolecarboxaldehyde and amino alcohol followed by reduction. These new ionic liquids overcome the shortcomings of their traditional counterparts that show participate in deprotonation side reactions on their C-2 positions.

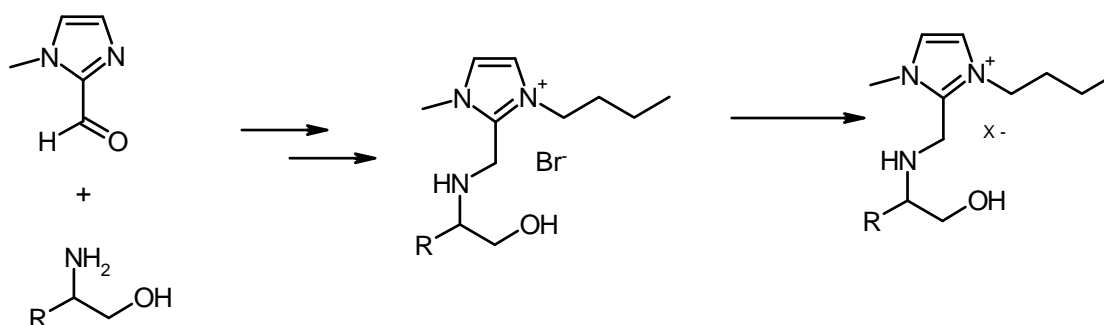
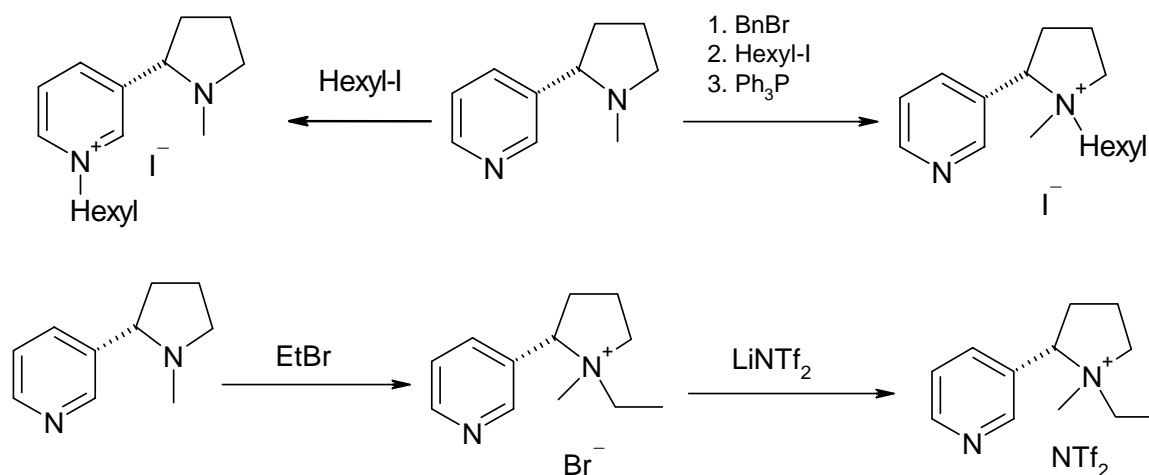


Figure 3. Imidazolium ionic liquids from chiral aminoalcohols.

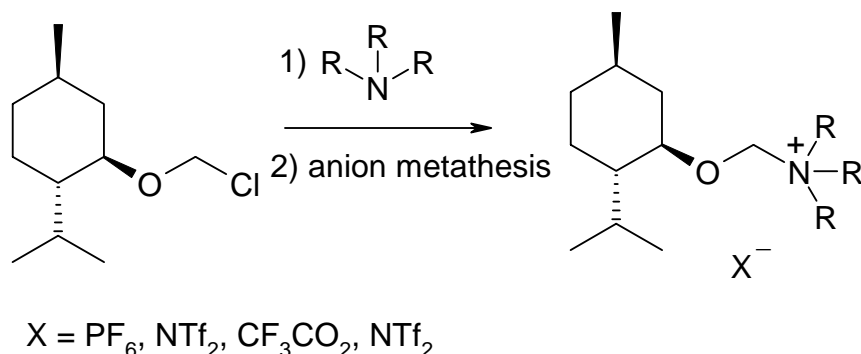
Another natural product, which potentially could give three different types of ionic liquids, is nicotine. Nicotine can be alkylated on pyridine, on imidazole or on both rings. Initial efforts have focused on the two monocations, as showed in scheme 8. The preparation of the pyridinium salt simply requires the use of a better leaving group, such as an alkyl iodide, whereas the synthesis of the pyrrolidinium salts takes advantage of the ability to selectively

alkylate the pyridine moiety as reported by Shibagaki.²⁴ On the other hand, (-)-*N*-ethylnicotinum bis-(trifluoromethan-sulfonyl)amide was prepared simply by alkylation of nicotine with ethyl bromide, followed by anion metathesis with LiNTf₂. Viscosity of all these salts, also bearing the bistriflimide anion, is higher than that of simple imidazolium salts.



Scheme 8. Nicotine based ionic liquids.

Although all the above discussed examples are related to the use of natural products bearing at least nitrogen atom, more recently also other classes of natural compounds have been used to obtain solvents. Feder-Kubis and coworkers²⁵ have proposed the synthesis of an ionic liquid based on (*1R,2S,5R*)-(-)-menthol by Menshutkin quaternization of the corresponding chloro methyl derivative, as shown in Scheme 9. Since chloride salts generally exhibit rather high melting points (the sole exception being the trimethyl derivative, mp = 31-33 °C), the initially formed salts were converted in the corresponding bis(triflimide) derivatives by anion metathesis, obtaining viscous liquids.



Scheme 9. Synthesis of menthol salts

The same (-)-chloromethylmenthylether and its enantiomer were used by Armstrong²⁶ for the synthesis of chiral imidazolium salts. These salts have been used as solvents, in the presence of a base, in the enantioselective photooxidation of dibenzobicyclo[2.2.2]octatriene diacid.

Analogously, imidazolium salts bearing a chiral group at N1 position (Figure 4) have been obtained by reaction of methylimidazole with triflates of (S)-ethyl lactate, ditosyltartrate and (1*S*,2*S*,5*S*) myrtanol tosylate,²⁷ whereas imidazolium and pyridinium salts with a chiral side chain derived from (3*R*)-citronellol were prepared from the corresponding citronellyl bromide and alkylimidazole or pyridine.²⁸

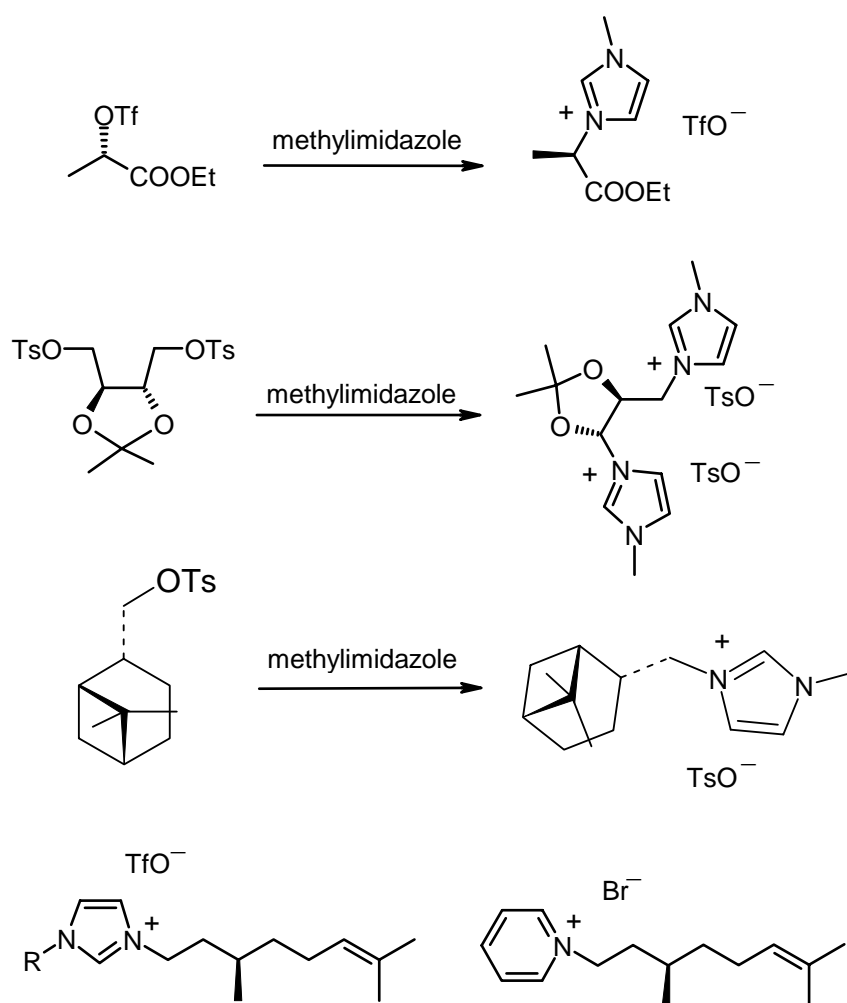
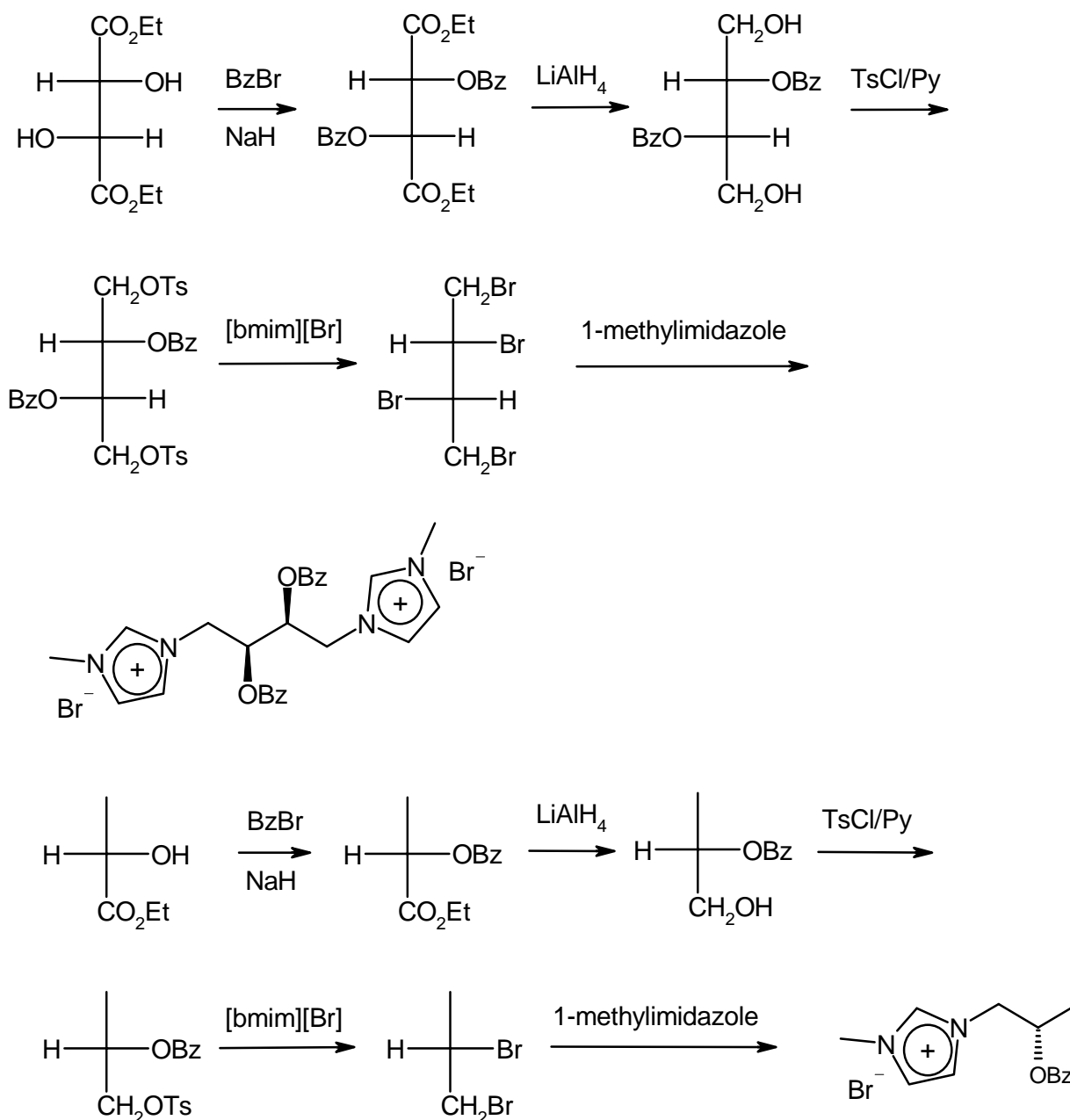


Figure 4. Chiral imidazolium salts.

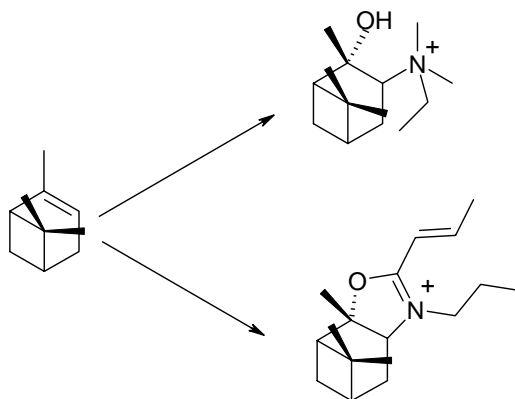
A similar approach has been followed²⁹ by Bao and coworkers to synthesize two kinds of novel chiral ionic liquids based on imidazolium using as starting material commercially available and inexpensive L-(+)-diethyltartrate and L-(-)-ethyl lactate (scheme 10). Briefly, the enantiopure esters have been O-benzylated with sodium hydride and benzyl bromide. Reduction with LiAlH₄ gave the corresponding alcohols from which tosyl derivatives were prepared under standard

conditions. The transformation into the corresponding bromides was performed using 1-methyl-3-butylimidazolium bromides; under these conditions the reaction went to completion in only one hour with rather high yields and the reagent-solvent could be recycled and reused. Finally, the target molecules were obtained by the quaternarization reaction using 1-methylimidazole in acetone. These ILs, obtained in good overall yields (44-60%), were used as reaction media and chiral reagent for the enantioselective Michael additions. However the observed enantiomeric excesses are moderate.



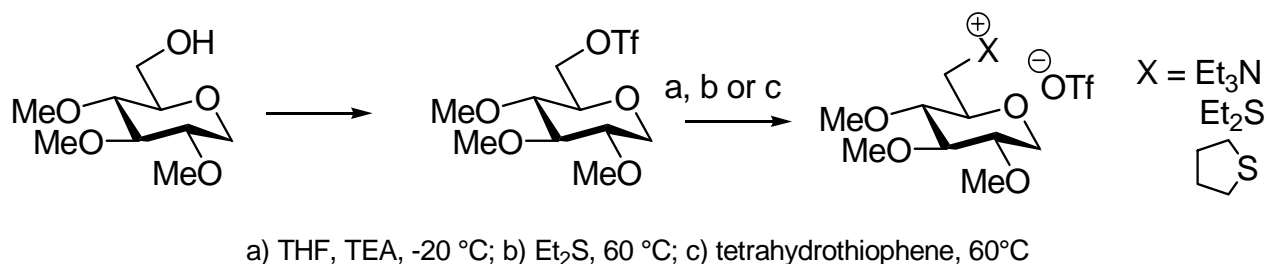
Scheme 10. Synthesis of chiral imidazolium salts from hydroxyl esters.

A series of chiral pinene-based ionic liquids bearing different anions (Scheme 11) has been recently designed³⁰ by Malhotra and coworkers, and they tested their potential in asymmetric synthesis. In particular, as a model reaction the copper-catalyzed addition of diethylzinc to enones was investigated, showing that the chiral reaction medium has a significant influence on chiral induction.³¹ Contemporaneously, the group of Armstrong has synthesized new ionic liquids derived from (-)-*N*-benzyl-*N*-methylephedrine, *D*(+) carnitinenitrile chloride and (-) scopolamine *N*-butyl bromide.^[20]



Scheme 11. Ionic liquids from α -pinene.

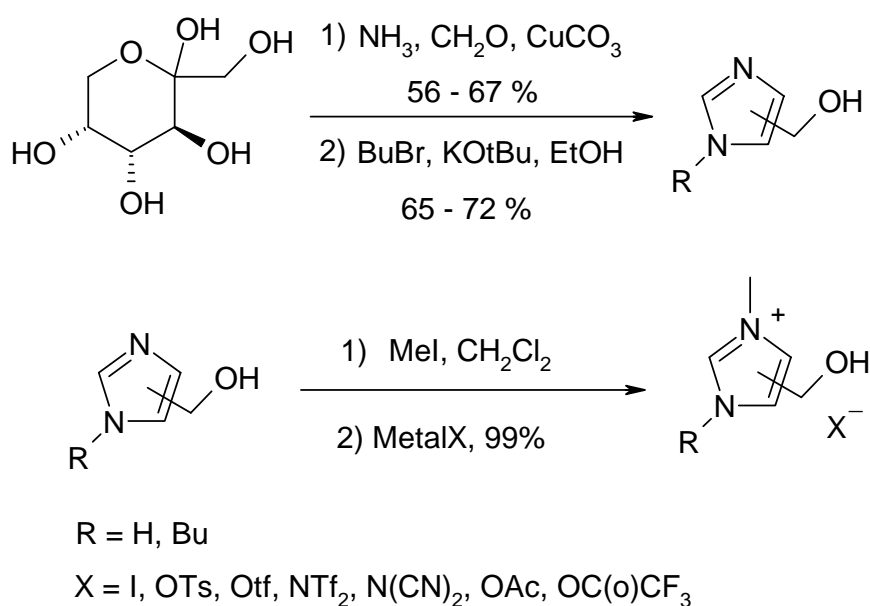
Finally, scheme 12 illustrates several new chiral ionic liquids derived from carbohydrates. Ammonium and sulfonium triflates have been synthesized starting from selectively protected 1-deoxy sugars, after transformation of the primary hydroxyl group into the corresponding triflate.³²



Scheme 12. Ionic liquids from sugars

All these examples show how simple natural compounds can be included in the structure of ionic liquids. However, it is worth to note that also natural compounds which do not appear to be capable of being transformed into cations can be used as source of new room temperature ionic liquids. Imidazolium ionic liquids have been synthesized by Handy³³ and coworkers starting from fructose.

Although fructose has no quaternizable elements, it can be readily converted into hydroxymethylimidazole using a modification of the method reported by Trotter and Darby (Scheme 13).



Scheme 13. Synthesis of ionic liquids based on fructose as starting material

After two sequential alkylations and an anion metathesis step, hydroxymethylene imidazole is obtained. The new ionic liquid can also be prepared on multi-gram scale with 65 – 72% overall yield. The properties of these new protic ionic liquids were investigated. All the examined salts are completely miscible with acetonitrile, acetone, methylene chloride and ethyl acetate and immiscible with hydrocarbon solvents. Furthermore, these new protic ionic liquids have been utilized in two different applications: as solvents in the Heck reaction and as supports for homogeneous supported-phase synthesis.

The possibility to use carbohydrate-urea-salt mixtures (Figure 5) as new organic media for organic reactions has been reported by König and coworkers.³⁴ The examined mixtures show melting points between 65°C and 85°C and their polarities, evaluated using solvatochromic dyes, are comparable to DMF and DMSO. These new solvents were investigated in some typical organic reactions: Diels-Alder cycloadditions, Stille reaction, Suzuki coupling, Wilkinson hydrogenation and aldol reaction. The results show that they are suitable media for different organic reactions and their water solubility facilitates work up procedures. The use of Lewis acids, e.g. to enhance the *endo/exo* selectivity of Diels-Alder reactions, is possible in these melts with good results. Control of the reactions stereochemistry by the chiral melt unfortunately has not been observed.



Figure 5: Sorbitol/Urea/NH₄Cl (70:20:10) melt at 80°C

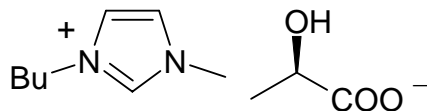
Finally, the possibility to use natural polyalcohols to increase the liquid range of ILs has been investigated by Chiappe and coworkers.³⁵ The eutectic mixtures of butylpyridium bromide [bupy][Br]/ sorbitol (3:1; 2:1) are viscous liquids at room temperature, which show improved properties in L-proline catalyzed aldol condensations; they are able to reduce the formation of elimination by-products.

Natural products as sources of the anion side of room temperature ionic liquids

Very little has been reported so far exploring the possibility to use anions prepared from natural or renewable materials.. In part this is doubtless due to the fact that the most ubiquitous naturally occurring anion, chloride, typically forms high melting salts. Other simple anions, such as sulfate and phosphate, have likewise been largely avoided, although a report by Engel and coworkers shows that phosphate based room temperature ionic liquids are readily achievable with a wide variety of quaternary ammonium salts.³⁶ In examining the more traditionally organic anions found in nature, the most common ones are carboxylate salts; acetate, lactate and tartrate. The latter is moreover particularly interesting since both antipodes are available in nature. As result, these anions would provide a simple entry into the area of chiral solvents with potential applications in resolution chemistry and even synthesis. Unfortunately, salts of these anions typically exhibit higher melting points than the corresponding tetrafluoroborate, hexafluorophosphates or triflimide salts. In 1998 R.K. Seddon and coworker reported³⁷ the use of [bmim][lactate] (Figure 6) as solvent in the Diels-Alder reaction between cyclopentadiene and acrylonitrile or ethyl acrylate. The lactate salt provided a slightly lower *endo/exo* selectivity than the corresponding triflate or tetrafluoroborate salts whereas the reaction rate, determined in [bmim][lactate], was between those characterizing

the other two salts. Unfortunately, no enantioselectivity was observed for this cycloaddition process when performed in the chiral lactate salt. This latter result has probably discouraged the use of lactate ILs in other applications.

Figure 6. Composition of [bmim][lactate]



While there are situations in which ionic liquids with fluoride anions will remain indispensable, there is much to be desired in identifying other (preferably innocuous) ions in formulating ionic liquids, especially for large volume applications.³⁸ Recently, Chiappe and coworkers have synthesized³⁹ some cholinium based ionic liquids having as counteranions simple naturally occurring species; like acetate, phosphate and citrate.

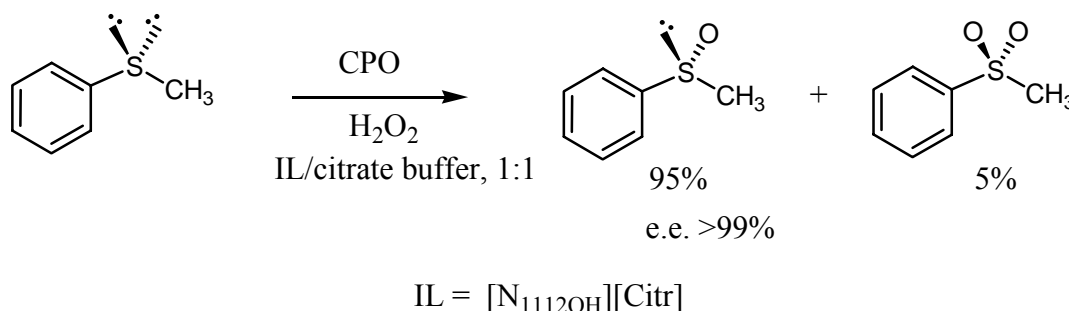


Figure 7. Use of cholinium based ILs as cosolvent in chloroperoxidase (CPO) catalyzed reactions.

These ILs have been used as co-solvents for chloroperoxidase catalyzed reactions. As compared to the behaviour observed in conventional organic solvents, CPO in cholinium citrate ([N₁₁₁₂OH][Citr]) presents enhanced activity, stability and selectivity.^[39]

J. H. Jr Davis and coworkers in 2004 reported⁴⁰ the use of saccharin and acesulfame as anions of new ionic liquids. As alkali-metal salts, the anions arising from both compounds are in widespread use in foodstuff as non-nutritive sweeteners; when incorporated into ionic liquids these anions exhibit properties that partly resemble those of certain fluorosulfonate containing anions with a melting point below 100 °C. Both these sweetener anions are *N*-acyl-*N*-sulfonyl imides (Figure 8) showing a similarity to the TSAC anion, introduced by Matsumoto as a substitute for bis(trifluoromethyl)sulfonyl imide (Tf₂N⁻) in ionic liquids chemistry. It is however to note, that the

saccharinate (Sac) and acesulfamate (Ace) are - unlike TSAC and Tf_2N^- - non fluorinated anions and both are characterized by a well established toxicological profile.⁴¹

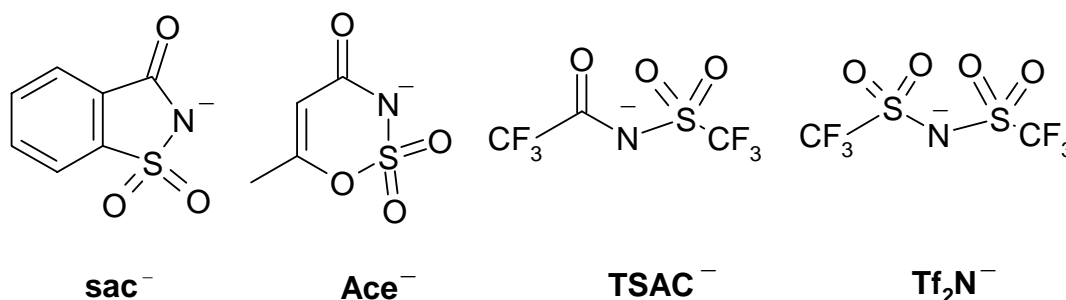


Figure 8. Structure of saccharinate (Sac), acesulfamate (Ace), and TSAC anions. The structure of widely used bis(triflyl)imide (Tf_2N^-) anion is shown for comparison.

Camphor based ionic liquids (Figure 10) have been described in 2005 by Y. Ishikawa⁴² and coworkers. Despite the anion bulkiness and high molecular weight, the camphor salt ($[\text{bmim}][\text{CS}]$) is a viscous liquid even on a salted ice bath, while $[\text{bmim}][\text{CH}_3\text{SO}_3]$ is solid at room temperature. By means of a specially designed ESI-mass spectrometer, the authors have evaluated the cation-anion association in several sulfonates ILs demonstrating that the bulky [CS] anion binds more loosely with the imidazolium cation than the small $[\text{CH}_3\text{SO}_3]^-$ and $[\text{CF}_3\text{SO}_3]^-$. The significant enhancement in the *endo/exo* stereoselectivity found for Diels-Alder reactions between cyclopentadiene and ethyl acrylate in this new ionic liquids was attributed To the increased number of free (naked) imidazolium cations, caused by the use of a camphorsulfonate as anion. The value of 10:3 determined in the presence of $[\text{bmim}][\text{MS}]$ represents indeed an excellent result for a reaction carried out without using a catalyst.

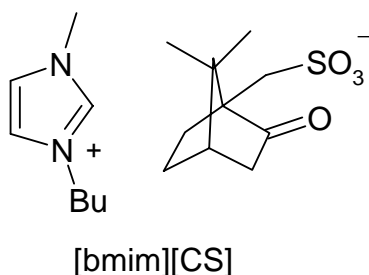
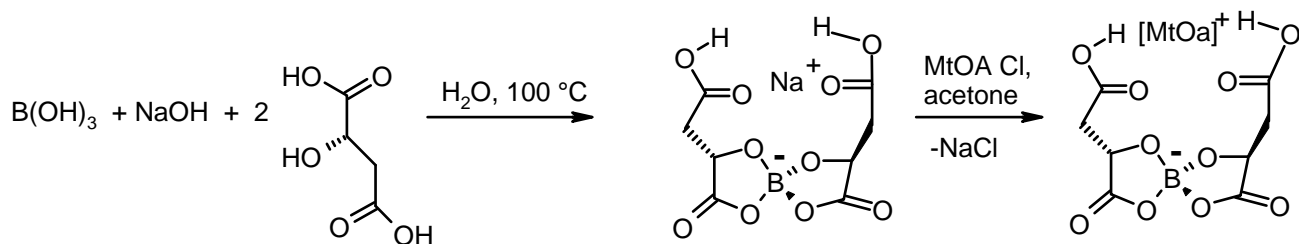


Figure 9. Composition of $[\text{bmim}][\text{CS}]$

Natural amino acids have been used also to develop room temperature ionic liquids in which the anion is a natural compound. In the first paper, published in 2005 by Ohno and coworkers,⁴³ ionic liquids were prepared starting from 1-ethyl-3-methylimidazolium hydroxide and 20 different natural amino acids; the use of an imidazolium hydroxide has allowed the direct synthesis of

various ionic liquids by neutralization of the carboxylic acid function of the selected amino acids, without the need of a metal salt. All of the resulting amino acid ionic liquids are transparent and nearly colorless liquids, showing a glass transition temperature ranging from $-57\text{ }^{\circ}\text{C}$ to $6\text{ }^{\circ}\text{C}$: however viscosity and thermal stability required improvement. Although ammonium and pyrrolidinium based amino-acid ionic liquids, subsequently prepared, do not show improved properties compared to the corresponding the imidazolium based salts, positive results have been obtained introducing the tetrabutylphosphonium cation. The coupling of *n*-tetrabutylphosphonium cation with amino acid anions has given 15 liquid salts having lower viscosities (generally, higher than 300 cP at $25\text{ }^{\circ}\text{C}$) and higher decomposition temperatures.⁴⁴ More recently, it has been shown⁴⁵ that tetrabutylphosphonium amino acid ionic liquids supported on porous silica gel are able to absorb CO_2 . The process is fast and reversible; the CO_2 absorption capacity at equilibrium was 50 mol\% of the ionic liquids, but in the presence of water (1 wt \%), the ionic liquids can absorb equimolar amounts of CO_2 . At variance, imidazolium ionic liquids carrying anions of chiral- or ω -amino acids have been used as media for the enzymatic resolution of phenylalanine.⁴⁶ These ionic liquids were capable of stabilizing the protease activity and increasing enantioselectivity at low concentrations. Higher enantiomeric excesses and yields were generally obtained in ionic liquids based on D-amino acids; results were rationalized considering the kosmotropic effect of the anion.

Finally, liquids bearing chiral anions have been synthesized⁴⁷ starting from boric acid, sodium hydroxide and chiral hydroxyl acids (L-malic acid, mandelic acid and diethyl tartrate) by the exchange of the sodium ions with methyltrioctylammonium, using aliquat 336 in acetone (Scheme 14).



Scheme 14. Two step synthesis of methyltrioctylammonium dimalonatoborate.

The obtained ionic liquid, methyltrioctylammonium dimaloborate, has been used as the only source of chirality in the aza-Baylis-Hillman reaction between methyl vinyl ketone and N-(4-bromobenzylidene)-4-toluenesulfonamide using PPh_3 as catalyst, obtaining enantioselectivities up to $84\% ee$. This is the highest enantioselectivity induced to date by a solvent; the ee are comparable to those obtained using the best catalysts. Moreover, these data show that also ionic liquids bearing chiral anions can be used to induce asymmetry. If the key to effective chirality transfer lies in a

strong interaction between the solvent molecules and the intermediates or transition states, as recently suggested,^[47] functional ionic liquids offer unique possibilities to create such arrangements for a wide range of transformations.

Conclusions

In summary, nature provides a vast new vista of opportunities for the preparation of new recyclable, biodegradable, chiral and/or functionalized solvents, having improved biocompatibility. These solvents, which can be obtained often through simple derivatization procedures, have the potential to find applications as (chiral) media in organic synthesis and catalyzed processes, in the separation sciences (GC, HPLC) and probably as materials in more specific applications.

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Low-melting sugar–urea–salt mixtures as solvents for Diels–Alder Reactions*

Abstract:

Sweet solutions are obtained upon heating mixtures of simple carbohydrates, urea and inorganic salts to moderate temperatures, to give new chiral media for organic reactions.

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The reduction of the use of organic solvents is one goal in current efforts towards more environmentally benign chemical processes. Organic solvents are typically used in large excess compared to the reactants and have the tendency to escape into the environment by evaporation or leakage. Therefore the scope of reaction media for chemical transformations in solution has been extended in the past years to ionic liquids¹, water² and scCO₂.³ In principle, water is the ideal solvent being non-toxic, cheap and available, but its use is limited because most organic compounds do not dissolve in pure water and many reactive substrates or reagents decompose in water⁴. scCO₂ is an interesting environmentally friendly, non-toxic alternative to organic solvents with additional benefits as a reaction medium, such as its ready availability, ease of removal, disposal or recycling. However, its use requires more sophisticated equipment than standard lab apparatus. Ionic liquids have received a lot of attention as green solvents for their properties: no measurable vapour pressure, stability in a wide temperature range and recyclability. However, in most cases their preparation uses non-renewable resources⁵ and toxicity issues remain to be addressed. We report here the use of low-melting mixtures of sugars or sugar alcohols, urea and inorganic salts as solvents for Diels–Alder reactions. The reaction medium consists only of non-toxic compounds from readily available resources and has, like ionic liquids, small vapour pressure. An initial screening identified stable and low-melting mixtures of bulk carbohydrates, urea and inorganic salts. Table 1 summarizes the most suitable melts in terms of stability and melting temperature (see ESI for additional data).

Table 1. Stable melts of carbohydrates, urea and inorganic salts:

Melting points^a	Carbohydrate^b	Urea	Salt
65 °C	Fructose (60%)	Urea (40%)	—
67 °C	Sorbitol (70%)	Urea (20%)	NH ₄ Cl (10%)
73 °C	Maltose (50%)	DMU _c (40%)	NH ₄ Cl (10%)
75 °C	Glucose (50%)	Urea (40%)	CaCl ₂ (10%)
75 °C	Mannose (30%)	DMU _c (70%)	—
77 °C	Sorbitol (40%)	DMU _c (60%)	—
77 °C	α-Cyclodextrin (30%)	DMU _c (70%)	—
65 °C	Citric acid (40%)	DMU _c (60%)	—

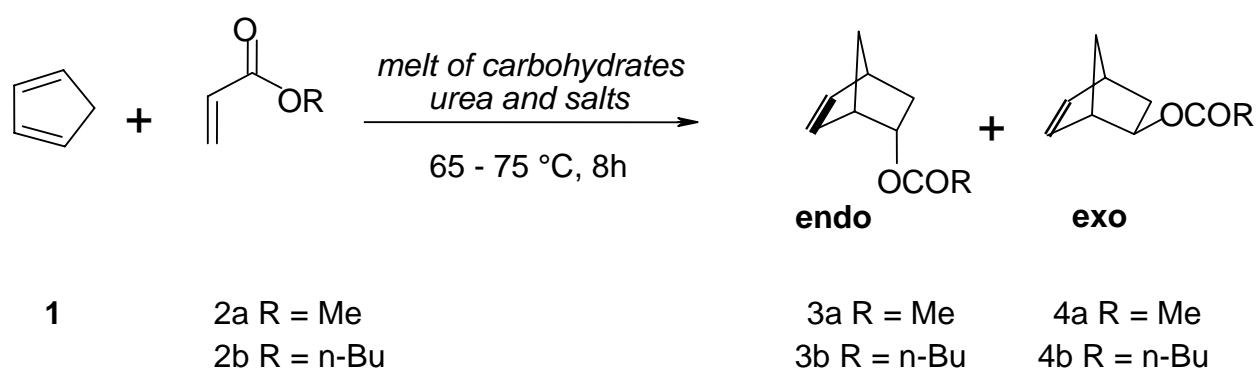
^a Melting points are at normal pressure in air. ^b w/w percent of the compounds in the mixture. ^c DMU 5 N,N-dimethylurea

To evaluate the thermal stability of the melts all mixtures were analysed by differential scanning calorimetry (DSC), through three heating–cooling cycles, which showed no thermal decay. In

addition, the mixtures were heated for 4 h to 95 °C without any evident decomposition. The fructose–urea mixture gives a clear viscose melt at 65 °C, while for sorbitol the addition of NH_4Cl was necessary to achieve such low melting temperature (see Figure 1). Other carbohydrate, urea and salt mixtures with melting temperatures around 75 °C were identified and surprisingly even a citric acid–urea mixture gave a stable melt at 65 °C. Our survey is not comprehensive and we presently cannot derive simple indicators to predict stability and melting temperature of such mixtures, but the examples show that the concept is rather general. The water content of a solvent is an important parameter, which was determined to be exemplary for the mixture of sorbitol (70), urea (20) and NH_4Cl (10) by Karl Fischer titration. Using vacuum-dried raw materials for preparation of the mixture, a typical water content of 0.07% was found; using raw materials as received, the water content is approx. 1.3% (see ESI). A vapour pressure of 1.2610 mbar at 70 °C was determined for a melt of this composition. The thermal stability of some mixtures was investigated by differential scanning calorimetry (see ESI for data). The melts are stable in subsequent heating–cooling cycles to 120 °C. For the mixture sorbitol (70), urea (20), NH_4Cl (10) a decomposition temperature of 220 °C was determined. The thermal behaviour is identical for mixtures prepared from dried or as-received raw material.



Fig. 1: Sorbitol (left) and a mixture of sorbitol/urea/ NH_4Cl (70:20:10) (right) at 80 °C.



Scheme 1. Diels–Alder reactions performed in carbohydrate melts.

The most suitable mixtures were then used as solvent for a Diels–Alder reaction. The reaction of cyclopentadiene with methyl (2a) and n-butyl acrylate (2b) (Scheme 1) proceeded cleanly and with high conversions in 8 h. Table 2 summarizes the results (for more data see ESI). Work up and product isolation requires simply addition of water to the reaction mixture while still hot. The reaction medium dissolves, leaving an aqueous phase and the organic product for isolation.⁶ Alternatively, products with a low boiling point can be removed from the reaction mixture by applying high vacuum, which allows a simple reuse of the melt for several reaction runs.

The observed endo–exo selectivity of the Diels–Alder reactions of **2a** and **2b** with cyclopentadiene in the melted mixtures range from 2.5:1 to 5:1, with the highest selectivity in the sorbitol melt. These ratios are comparable to selectivities reported for other green solvents, such as scCO₂ (**2a** at 50 °C, 3:1), ⁷ water (85 °C; **2a**, 3:1; **2b**, 2.5:1), ⁸ 1-butyl-3-methylimidazolium trifluoromethanesulfonate (20 °C, ethyl acrylate, 6:1), ⁹ 1-butyl-3-methylimidazolium tetrafluoroborate (-15 °C, ethyl acrylate, 5:1) or 1-butyl-3-methylimidazolium hexafluorophosphate (20 °C, ethyl acrylate, 8:1). As well known for reactions in organic solvents, Lewis acids catalyze Diels–Alder reactions and can improve rate and selectivity in alternative reaction media too.^{7,10} Therefore the reactions in carbohydrate–urea melts were repeated with the addition of 1 equiv. of LiClO₄ or 10 mol% of Ce(OTf)₃, but selectivity ratios did not change significantly (see ESI for data). Interestingly the addition of 10 mol% of Sc(OTf)₃ to the sorbitol/DMU/NH₄Cl (70:20:10) melt improved the endo–exo selectivity to 6:1 for **2a** and 10:1 for **2b**.

Table 2. Diels–Alder reactions in carbohydrate–urea–salt melts

<i>Compositions of melts</i>	Reaction temp. °C	Dienophile	Yield %^a	Endo/Exo ratio^b
Fructose/DMU ^c (70:30)	71	2a	quantitative ^d	2.9 : 1
Fructose/DMU ^c (70:30)	71	2b	95	3.0 : 1
Maltose/DMU ^c /NH ₄ Cl (50:40:10)	83	2a	79	3.3 : 1
Maltose/DMU ^c /NH ₄ Cl (50:40:10)	83	2b	80	3.9 : 1
Lactose/DMU ^c /NH ₄ Cl (60:30:10)	88	2a	83	3.6 : 1
Lactose/DMU ^c /NH ₄ Cl (60:30:10)	88	2b	72	2.1 : 1
Mannitol/DMU ^c /NH ₄ Cl (50:40:10)	89	2a	74	2.7 : 1
Mannitol/DMU ^c /NH ₄ Cl (50:40:10)	89	2b	92	3.5 : 1
Glucose/urea/CaCl ₂ (50:40:10)	75	2a	76	3.2 : 1
Glucose/urea/CaCl ₂ (50:40:10)	75	2b	93	2.6 : 1
Sorbitol/DMU ^c /NH ₄ Cl (70:20:10)	67	2a	quantitative ^d	5.0 : 1 (6.0 : 1) ^e
Sorbitol/DMU ^c /NH ₄ Cl (70:20:10)	67	2b	83	3.7 : 1 (10 : 1) ^e
Citric acid/DMU ^c (40:60)	65	2a	quantitative ^d	3.6 : 1
Citric acid/DMU ^c (40:60)	65	2b	quantitative ^d	2.6 : 1
α -Cyclodextrin/DMU ^c (30:70)	77	2a	quantitative ^d	3.5 : 1
α -Cyclodextrin/DMU ^c (30:70)	77	2b	quantitative ^d	3.6 : 1

a Isolated yields after extraction. b Determined by gas chromatography (GC). c DMU: N,N dimethylurea. d Quantitative conversion as monitored by GC. e Selectivity ratio with addition of 10 mol% of Sc(OTf)₃.

The effect of this Lewis acid is comparable to selectivity improvements observed for Diels–Alder reactions in toluene [50 °C, 10 mol% Sc(OTf)₃: 2a, 4:1; 2b, 10:1], but smaller than in scCO₂ [50 °C,

10 mol% Sc(OTf)₃: **2a**, 10:1; **2b**, 24:1]. All of the reaction media used in this study are chiral solvents and therefore the possibility of a stereinduction was investigated. However, the analysis of the products by chiral GC did not reveal any significant stereinduction, as for many other attempts using chiral solvents.^{11,12}

In summary, we have reported the use of low-melting mixtures of bulk natural products, such as simple carbohydrates, sugar alcohols or citric acid, with urea and inorganic salts as reaction media for Diels–Alder reactions. In comparison to conventional organic solvents a fast conversion¹³ with good endo–exo selectivities was observed. The addition of Sc(OTf)₃ improved the endo–exo selectivity ratios similarly as observed for the reaction in toluene, but less than in scCO₂. Although chiral, no significant stereinduction of the medium on the course of the reaction was detected. The non-toxic reaction media, made only from bulk, readily available compounds, qualify as green solvents. Their application as reaction media for other organic transformations and as a substitute to ionic liquids may be envisaged.

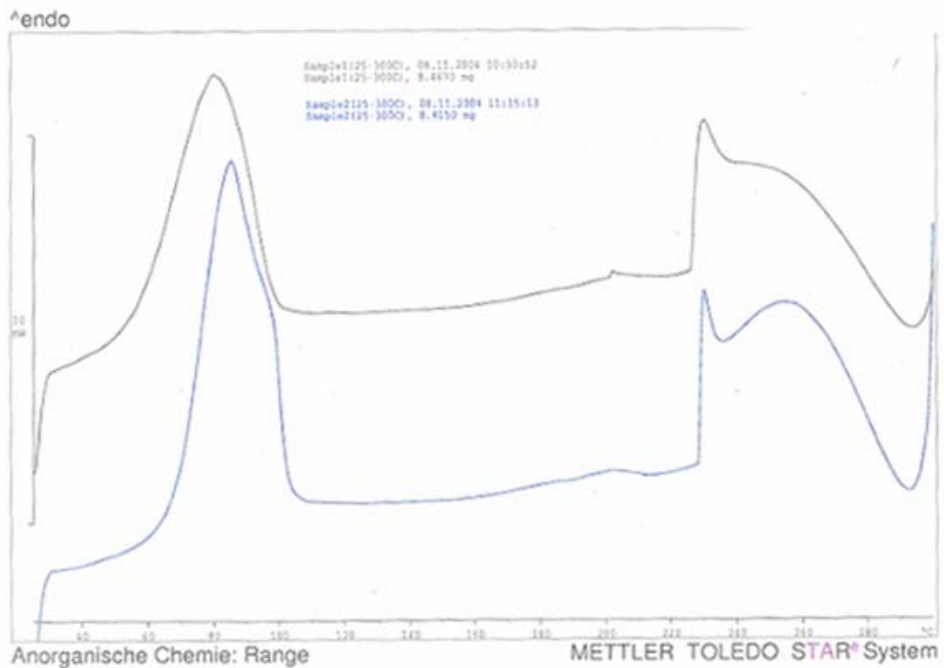
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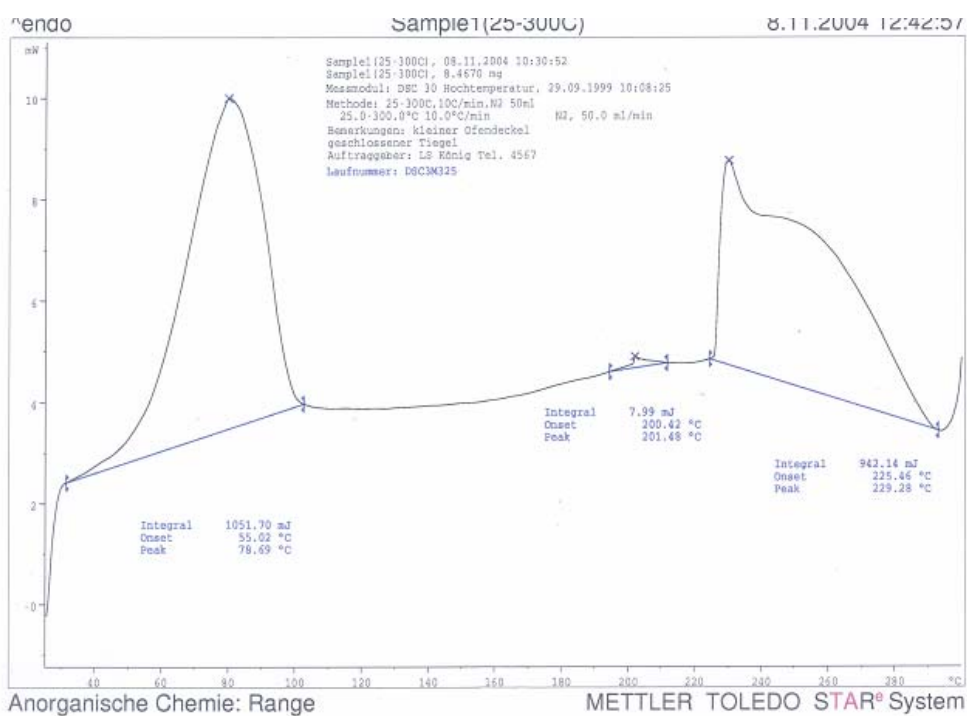
Supporting information:

DSC spectrum of several melting sugar mixture, the spectra was collecting using Toledo instrument.

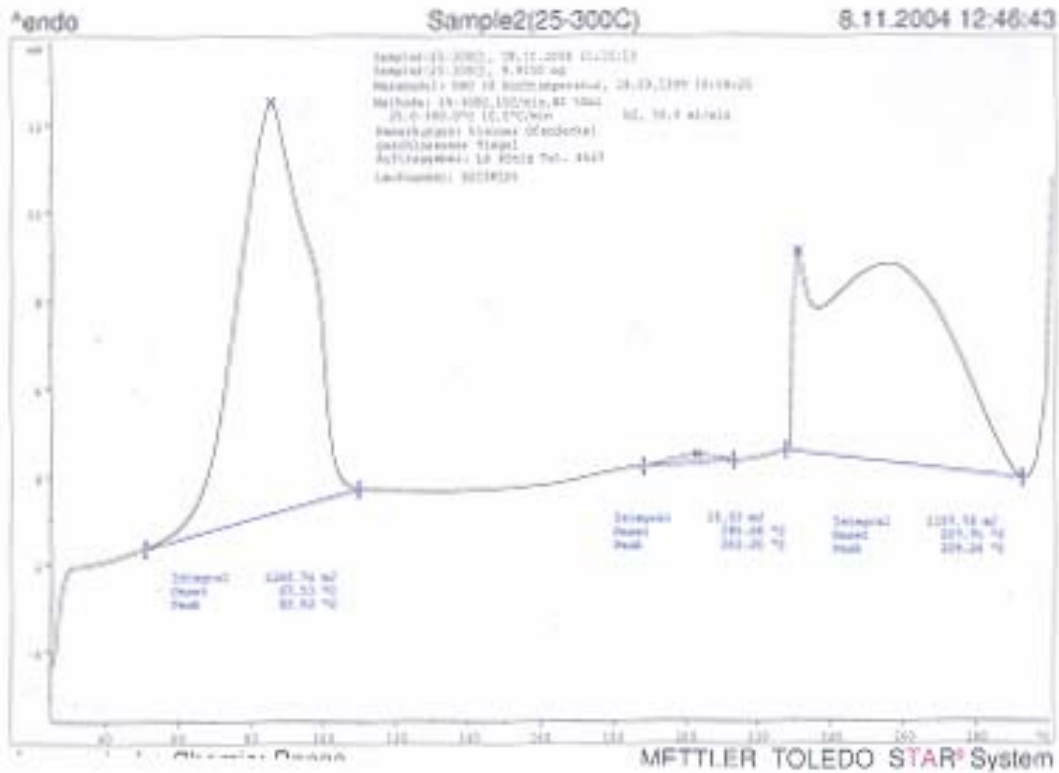
Sorbit/Dimethylurea/ NH_4Cl 70:20:10 w % ; sample 1 (blue) not dry mixture; sample 2 (black) mixture dry over P_2O



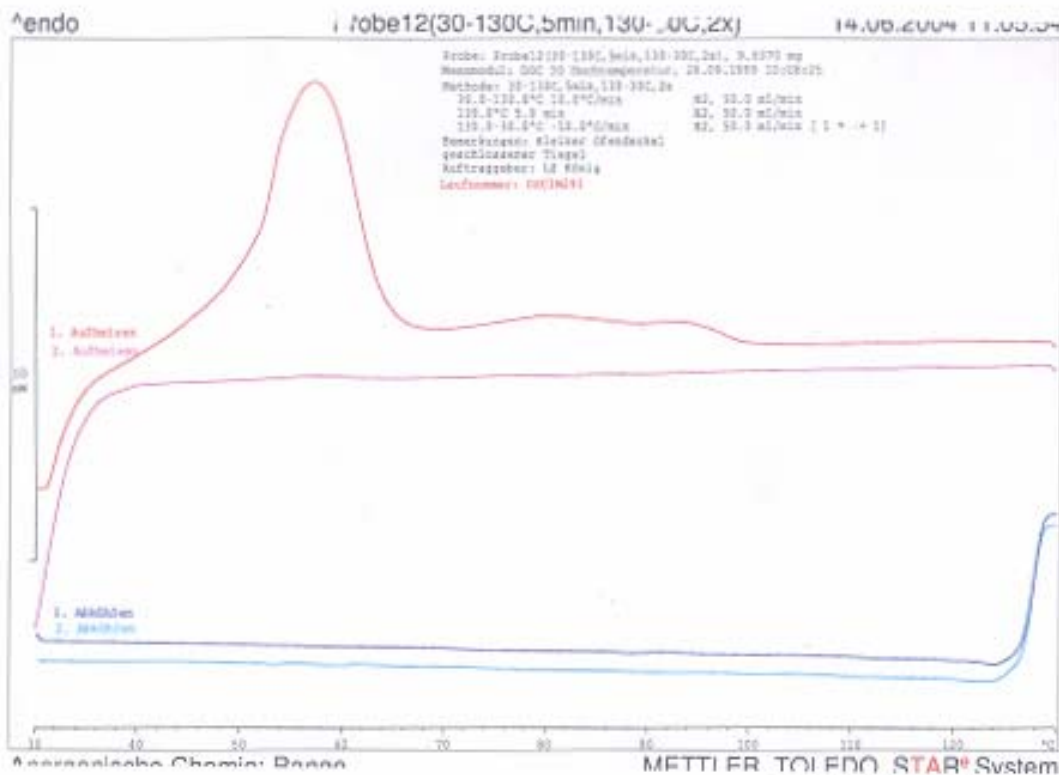
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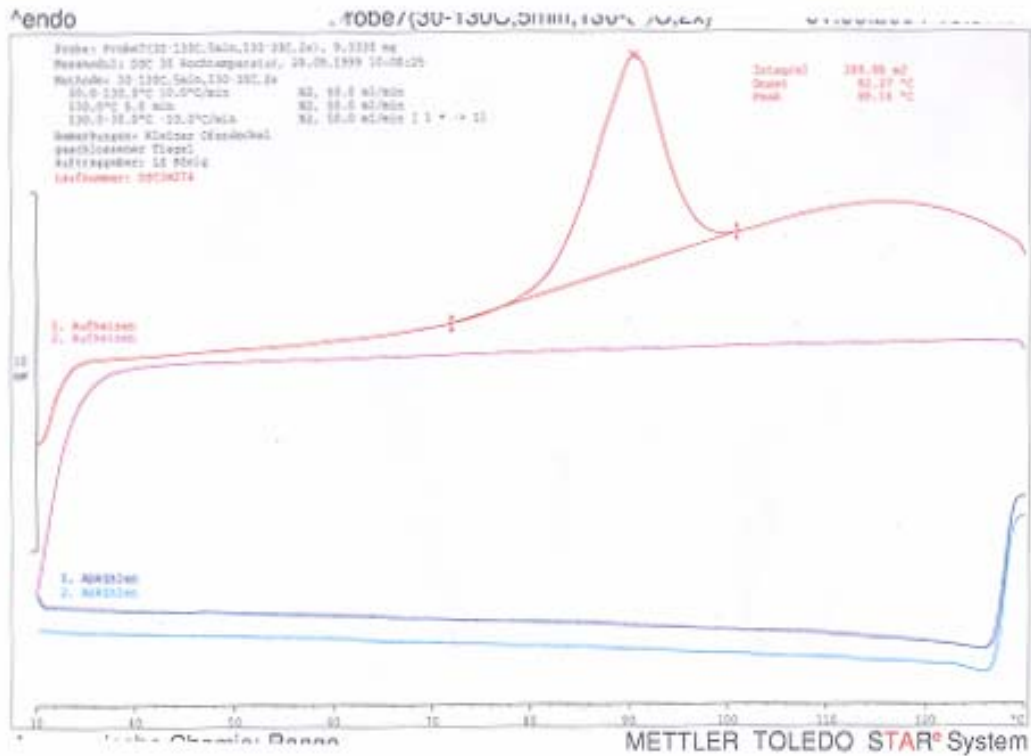
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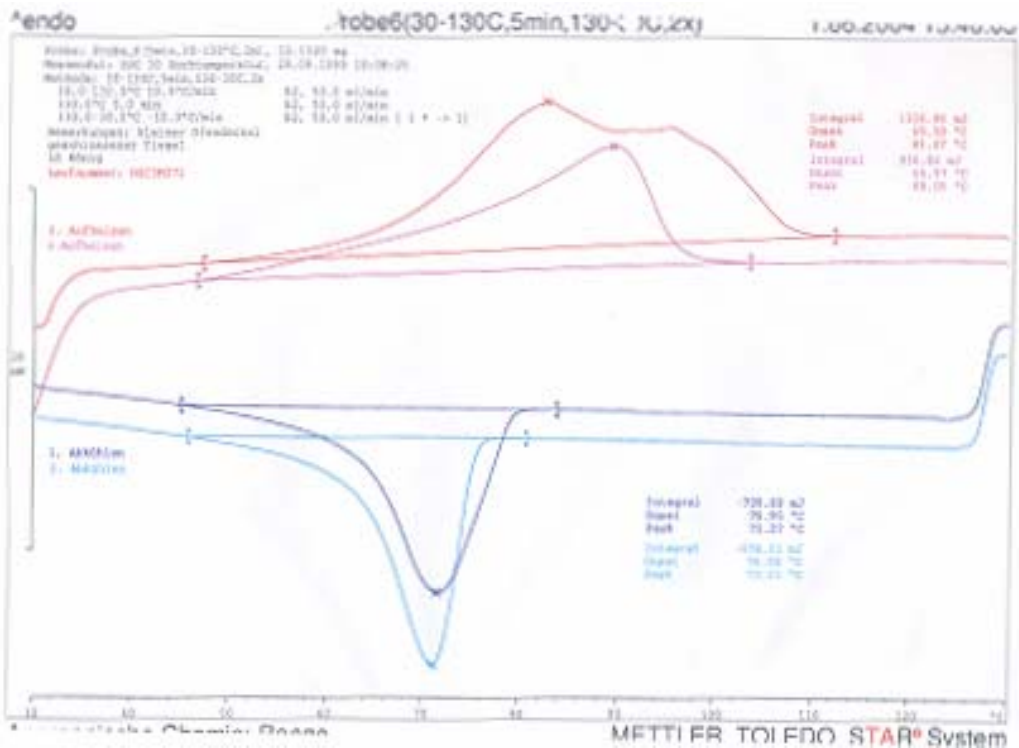
Citric acid/ Dimethylurea 40:60 w%



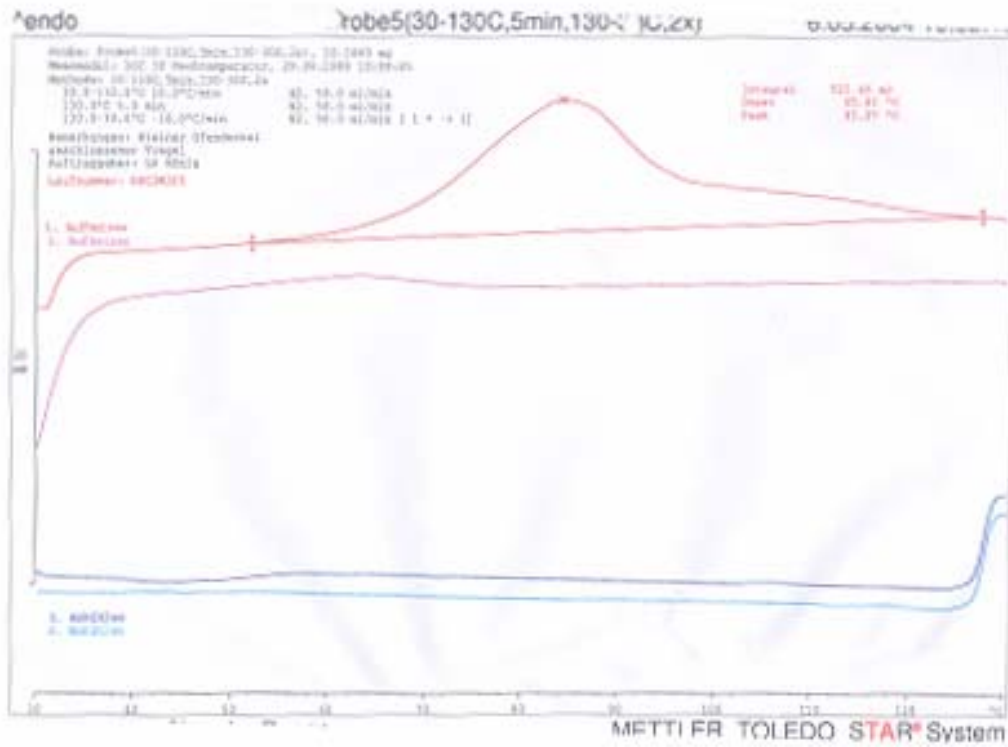
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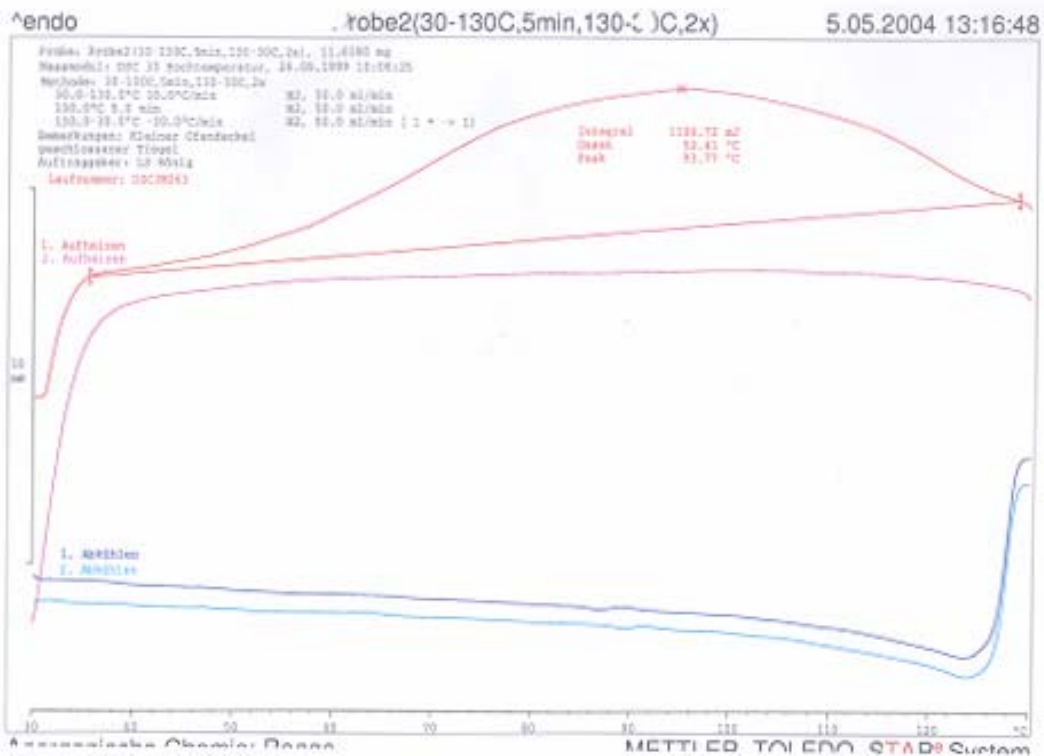
Mannose/Dimethylurea 30:70 w %



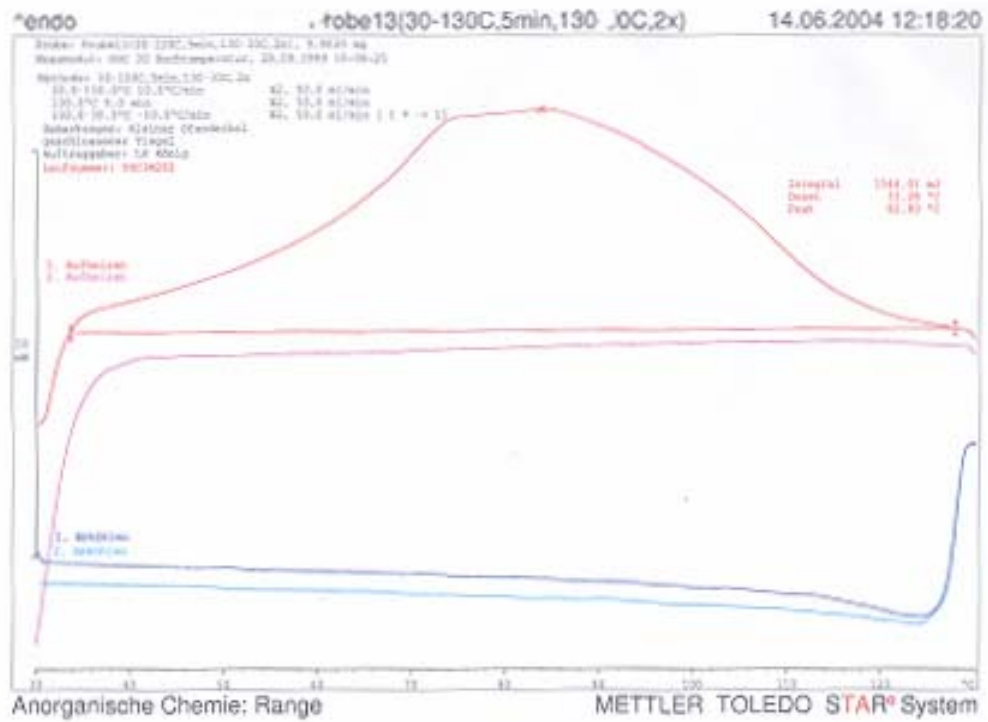
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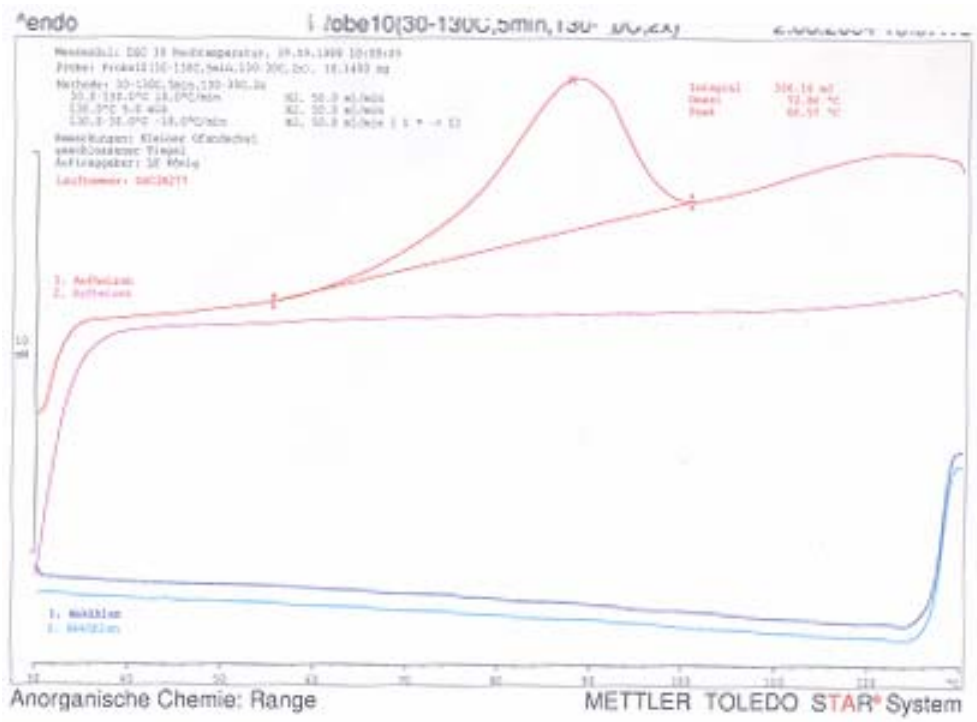
Fructose/Urea/NaCl 70:20:10 w%



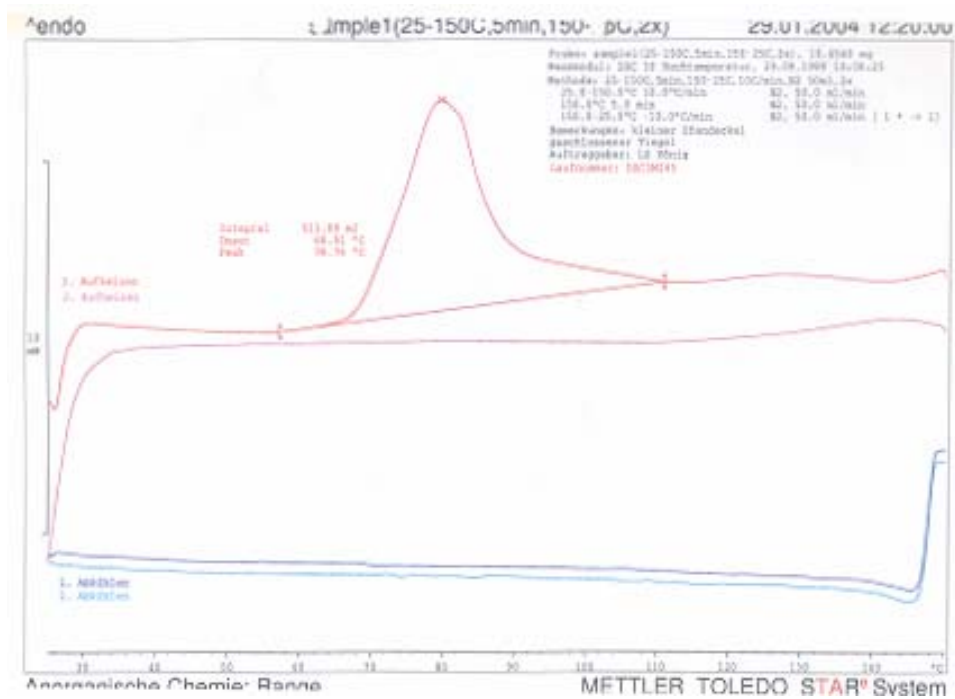
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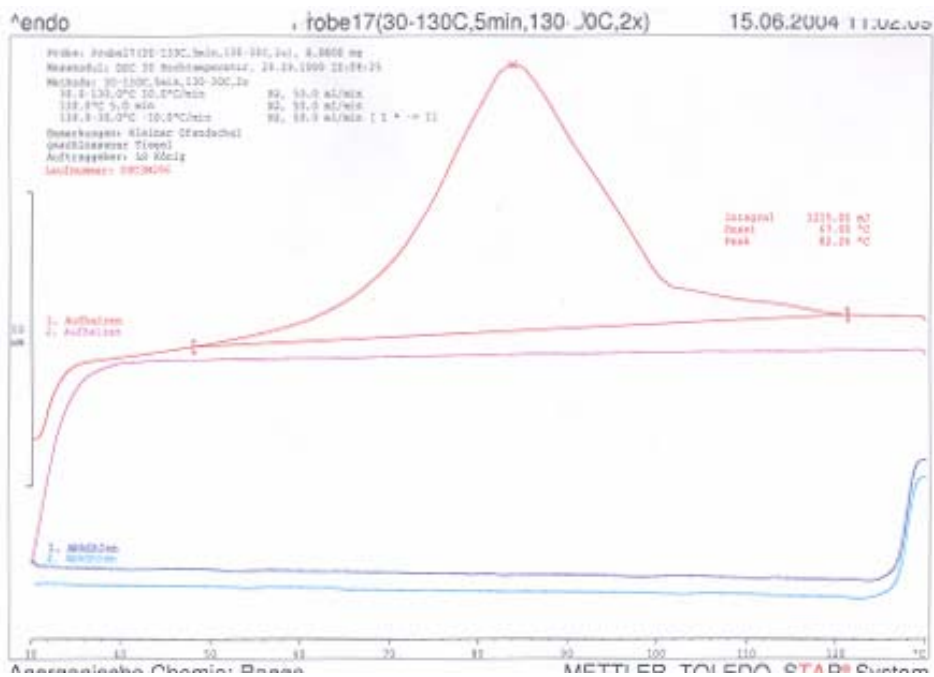
Glucose/Dimethylurea/NH₄Cl 50:40:10 w %



Saccarose/Urea/CaCl₂ 70:20:10



Sorbit/Urea/NH₄Cl 70:20:10 w %



Melting points of several carbohydrates, inorganic salts and urea or dimethylurea

Melting point	Fructose	Urea	Dimethylurea	NH ₄ Cl	NaCl
65 °C	60	40			
67 °C	50	50			
73 °C	70	20			10
71 °C	60	20			20
78 °C	60	30			10
78 °C	50	25			25
71 °C	50	40			10
73 °C	50	30			20
73 °C	50	20			30
75 °C	70		30		
71 °C	60		40		
72 °C	50		50		
75 °C	40		60		
77 °C	30		70		
73 °C	60		30	10	
71 °C	50		40	10	
72 °C	50		30	20	

Melting point	Maltose	Dimethylurea	NaCl	NH ₄ Cl
83 °C	30	70		
82 °C	60	30	10	
84 °C	50	40	10	
83 °C	50	30	20	
84 °C	50	40	10	
73 °C	50	40		10

Melting point	Sorbit	Dimethylurea	Urea	NH ₄ Cl
77 °C	40	60		
76 °C	30	70		
67 °C	70		20	10

Melting point	Mannitol	Dimethylurea	NH ₄ Cl
89 °C	50	40	10

Melting point	α Cyclodex.	Dimethylurea
77°	30	70

Melting point	Glucose	Dimethylurea	Urea	NH ₄ Cl	CaCl ₂
92 °C	60	40			
89 °C	50	50			
88 °C	40	60			
87 °C	30	70			
81 °C	60	30		10	
75 °C	50	40		10	
89 °C	50	40		10	
78 °C	60		30	10	
84 °C	50		25	25	
76 °C	50		40	10	
77 °C	50		30	20	
75 °C	50		40		10

Melting point	Mannose	Dimethylurea
92 °C	60	40
75 °C	30	70

Melting point	Lactose	Dimethylurea	NH ₄ Cl
88 °C	60	30	10
86 °C	50	40	10

Melting point	Citric acid	Dimethylurea
65 °C	40	60
64 °C	30	70

Reaction of cyclopentadiene with methyl and *n*-butyl acrylate in 20 melting sugar solvents with additional Lewis acid.

	Reaction temperature	Dienophile	Yield [%] ¹	Endo/Exo Ratio	Endo/Exo ratio ² 1eq LiClO ₄	Endo/Exo ratio ² 10% mol Ce(OTf) ₃	Endo/Exo ratio ² 10% mol Sc(OTf) ₃
Fruct. / DMU 70:30	71°C	2a	quant. ³	2.9 : 1	3.0 : 1	3.6 : 1	---
		2b	95	3.0 : 1	3.4 : 1	3.3 : 1	---
Malt / Dimeth.Urea / NH ₄ Cl 50:40:10	73°C	2a	79	3.1 : 1	3.2 : 1	3.8 : 1	---
		2b	80	2.6 : 1	3.3 : 1	3.1 : 1	---
Lactose / DMU / NH ₄ Cl 60:30:10	88°C	2a	83	3.6 : 1	3.1 : 1	3.6 : 1	---
		2b	72	2.1 : 1	4.5 : 1	2.4 : 1	---
Mannitol/DMU NH ₄ Cl 50:40:10	89°C	2a	74	2.7 : 1	3.8 : 1	3.4 : 1	---
		2b	92	3.5 : 1	3.8 : 1	4.0 : 1	---
Citric Acid / DMU 40:60	65°C	2a	quant. ³	3.6 : 1	4.5 : 1	3.8 : 1	---
		2b	quant. ³	2.6 : 1	3.4 : 4	4.0 : 1	---
Glucose / Urea / CaCl ₂ 50:40:10	75°C	2a	76	3.2 : 1	2.3 : 1	3.3 : 1	---
		2b	93	2.6 : 1	2.7 : 1	2.6 : 1	---
Sorbit / DMU / NH ₄ Cl 70:20:10	67°C	2a	quant. ³	5.0 : 1	4.0 : 1	3.7 : 1	6.0 : 1
		2b	83	3.7 : 1	4.0 : 1	3.1 : 1	10.0 : 1
α-Cyclodext./DMU 30 : 70	77°C	2a	quant. ³	3.5 : 1	2.3 : 1	2.3 : 1	---
		2b	quant. ³	3.6 : 1	---	2.7 : 1	---
Fruct. / Urea 60 : 40	65°C	2a	---	2.7 : 1	2.3 : 1	2.3 : 1	---
		2b	---	2.3 : 1	dec.	2.7 : 1	---
Fruct./Urea/NaCl 70:20: 10	73°C	2a	---	2.6 : 1	3.2 : 1	3.8 : 1	---
		2b	---	2.8 : 1	3.3 : 1	3.9 : 1	---
Malt / DMU 30 : 70	83°C	2a	---	3.3 : 1	3.9 : 1	3.4 : 1	---
		2b	---	3.9 : 1	3.6 : 1	3.6 : 1	---
Malt / DMU / NaCl 50:40:10	84°C	2a	---	2.2 : 1	3.5 : 1	3.2 : 1	---
		2b	---	3.5 : 1	3.7 : 1	3.2 : 1	---
Glucose / DMU 60 : 40	92°C	2a	---	3.1 : 1	3.0 : 1	3.3 : 1	---
		2b	---	2.4 : 1	2.4 : 1	3.0 : 1	---
Glucose / DMU 30 : 70	87°C	2a	---	3.5 : 1	4.1 : 1	3.5 : 1	---
		2b	---	4.1 : 1	5.2 : 1	3.3 : 1	---
Glucose / DMU / NH ₄ Cl 50 : 40 : 10	75°C	2a	---	2.5 : 1	4.1 : 1	3.4 : 1	---
		2b	---	3.0 : 1	3.3 : 1	2.8 : 1	---
Glucose / Urea / NH ₄ Cl 60:30:10	78°C	2a	---	2.5 : 1	2.6 : 1	2.5 : 1	---
		2b	---	3.1 : 1	2.9 : 1	2.5 : 1	---
Mannose / DMU 30 : 70	75°C	2a	---	3.4 : 1	3.8 : 1	3.2 : 1	---
		2b	---	3.1 : 1	3.8 : 1	3.8 : 1	---
Sorbit / DMU 40 : 60	77°C	2a	---	3.7 : 1	4.0 : 1	3.7 : 1	---
		2b	---	4.4 : 1	4.0 : 1	3.1 : 1	---
Fruct. /DMU/NH ₄ Cl 60:30: 10	73°C	2a	---	3.7 : 1	3.4 : 1	3.7 : 1	---
		2b	---	2.7 : 1	2.3 : 1	3.0 : 1	---

¹ isolated yields after extraction, ² determined by gas chromatography, ³ quantitative conversion as monitored by gas chromatography

Yield using n-pentane or benzene in the work up

	Methyl/Cy Extraction ⁽¹⁻³⁻⁴⁾ with n-pentane	Methyl/Cy Extraction ⁽¹⁻³⁻⁴⁾ with benzol	Methyl/Cy no extraction ⁽³⁻⁴⁾	n-But/Cy Extraction ⁽¹⁻³⁻⁵⁾ with n-pentane	n-But/Cy Extraction ⁽¹⁻³⁻⁵⁾ with benzol	n-But/Cy no extraction ⁽³⁻⁵⁾
Fruct./Dimethyl urea 70:30	80% (0.912gr)	100% (1.127gr)	54% (0.621gr)	73% (1.073gr)	94.9% (1.396gr)	51% (0.745gr)
Malt./Dimethyl urea NH ₄ Cl 50:40:10	68.5% (0.789gr)	78.5% (0.904gr)	55.3% (0.636gr)	74.8% (1.100gr)	79.9% (1.176gr)	51.2% (0.753gr)
Lactose/Dimethylurea NH ₄ Cl 60:30:10	83.2% (0.957gr)	74.3% (0.855gr)	31.2% (0.359gr)	72.1% (1.060gr)	77% (1.143gr)	27% (0.397gr)
Mannitol/Dimethylurea NH ₄ Cl 50:40:10	73% (0.839gr)	74% (0.849gr)	37% ⁽²⁾ (0.426gr)	83.1% (1.222gr)	92.4% (1.359gr)	45.7% ⁽²⁾ (0.672gr)
Glucose/Urea/CaCl ₂ 50:40:10	73% (0.840gr)	76% (0.873gr)	42.4% (0.488gr)	94.3% (1.386gr)	92.6% (1.362gr)	51.6% (0.759gr)
Sorbit/Dimethylurea NH ₄ Cl 70:20:10	100% (1.108gr)	100% (1.097gr)	62.7% (0.721gr)	79% (1.161gr)	83.3% (1.225gr)	57.4% (0.844gr)
Water 85°C	76.4% (0.879gr)			68.7% (1.010gr)		

- (1) five times with 4ml of organic solvents
- (2) after centrifugation
- (3) reaction time 24h
- (4) theoretical grams 1.151
- (5) theoretical grams 1.471

Reaction rate in hours

	Butyl/Cy ⁽¹⁻³⁾ 1h	Butyl/Cy ⁽¹⁻³⁾ 4h	Butyl/Cy ⁽¹⁻³⁾ 8h
Sorbit/DimethylUrea/NH ₄ Cl 70:20:10	49.5% 998.7mg	75.7% 1011.9 mg	89.5% 907.1mg
Glucose/urea/CaCl ₂ 50:40:10	80% 1030.3mg	87% 949.4mg	91.5% 996.3mg
Lactose/DimethylUrea/NH ₄ Cl 60:30:10	83% 928.1 mg	88% 1017.2g	99% 999.1mg
Maltose/DimethylUrea/NH ₄ Cl 50:40:10	81% 985.3 mg	90% 923.8 mg	96.7% 941.2mg
Fructose/DimethylUrea 70.30	80.7% 986.9 mg	96.1% 767.0 mg	91.7% 1012.3mg

- (1) Extraction five times with 4ml of n-pentane.
- (2) Theoretical grams 1.151
- (3) Conversion GC

Low Melting Sugar-Urea-Salt Mixtures as Solvents for Organic Reactions - Estimation of Polarity and Use in Catalysis *

Abstract:

Mixtures of sugars, sugar alcohols or citric acid with urea and inorganic salts form stable melts if heated to 70°C. The polarity of the melts was estimated using solvatochromic dyes and found to be in the range of DMF or water depending on the sensitivity of the dye for hydrogen bonds. To explore the use of the melts as solvents in catalysis, Rh-catalyzed hydrogenations and Pd-catalyzed Suzuki reactions were performed. The hydrogenation is sensitive to the composition of the melt and no effect of the chiral melts on the stereochemical outcome of the reaction was observed. The Suzuki coupling proceeds rapidly, clean and quantitatively in all examined melts. The results recommend the non-toxic sugar-urea-salt melts as more sustainable reaction media for many chemical transformations.

* Giovanni Imperato, Silke Höger, Dieter Lenoir and Burkhard König: *Green Chemistry* accepted

Introduction

The majority of chemical transformations are done in solution to control more efficiently the heat flow of exothermic and endothermic reactions. In addition, polar reactions which proceed via polar or ionic intermediates or transition states are promoted by polar solvents due to a strong stabilization by solvation of the polar intermediates. A small number of organic reactions can be performed in the solid state¹ and solventless reactions have been developed for organic synthesis,² but both approaches are limited. Several solvents used for reactions in the laboratory and in industry belong to the group of volatile organic compounds (VOC). Solvents like chlorinated hydrocarbons derived from methane, ethane, and propane are volatile and chemically relatively stable, they are harmful to the environment. Because of their stability they accumulate in the atmosphere and contribute to ozone depletion and to smog in urban areas.³ To overcome this concern of synthetic organic chemistry, new “green solvents” have been developed, which slowly find their way into laboratories and chemical production. The new “green” solvents include supercritical carbon dioxide, ionic liquids, water, and fluorous biphasic mixtures.⁴ We have contributed to this field by using low melting mixtures consisting of sugars, urea, and inorganic salts as solvent for organic transformations.⁵ The stable melts of the mixtures are environmentally benign, because they are easily biodegradable, non-toxic and they are available from bulk renewable resources without modification steps. Melting points are in the range of 65° to 85°C and Diels-Alder reactions, which were performed in the solvent system illustrate the use in organic synthesis.⁶

To characterize the solvent properties of the sugar-urea-salt melts more closely, we have investigated their polarities using two solvatochromic aromatic dyes, Reichardt's dye⁷ and Nile red.⁸ In addition, the use of the melts for catalytic transformations was explored exemplarily by Rh-catalyzed hydrogenation reactions and Pd-catalyzed biaryl formation (Suzuki reaction).

Results and discussion

Determination of solvent polarities of sugar melts by solvatochromic dyes

Solvents can be classified into different types according to their behaviour as medium for chemical reactions⁹ and they are typically divided into three main categories: non polar

solvents (hydrocarbons), polar protic solvents (e.g. water, alcohols) and polar aprotic solvents (e.g. DMSO, acetone). The dielectric constant of a solvent, a macroscopic property, describes polarity. The use of solvatochromic dyes allows a direct probe of polarity of a solvent affecting the absorption properties of the dissolved dye molecule. Melted sugar-urea-salt mixtures were investigated by this method and the results are compared to the polarity of typical conventional solvents used in synthesis.

Solvatochromic behavior of Reichardt's dye

Reichardt's betaine dye 2,6-diphenyl-4-(2,4,6-triphenyl-*N*-pyridino)phenolate (Figure 1, right) is the most solvatochromic compound reported to date, showing a range of transition energies for the $\pi \rightarrow \pi^*$ adsorption band from 37.7 kcal mol⁻¹ (810 nm) in diphenyl ether to 67.7 kcal mol⁻¹ (453 nm) in water. This exceptional behaviour makes this dye a useful indicator for solvent polarity. It can be observed, that the absorption range is almost entirely within the visible region, and more quantitatively, by use of UV/Vis spectroscopy, as shows the Figure 2: the dye is red in sorbitol/dimethylurea/NH₄Cl (**2**), orange in mannitol/dimethylurea/NH₄Cl (**5**) and yellow in citric acid/dimethylurea (**1**) melts.

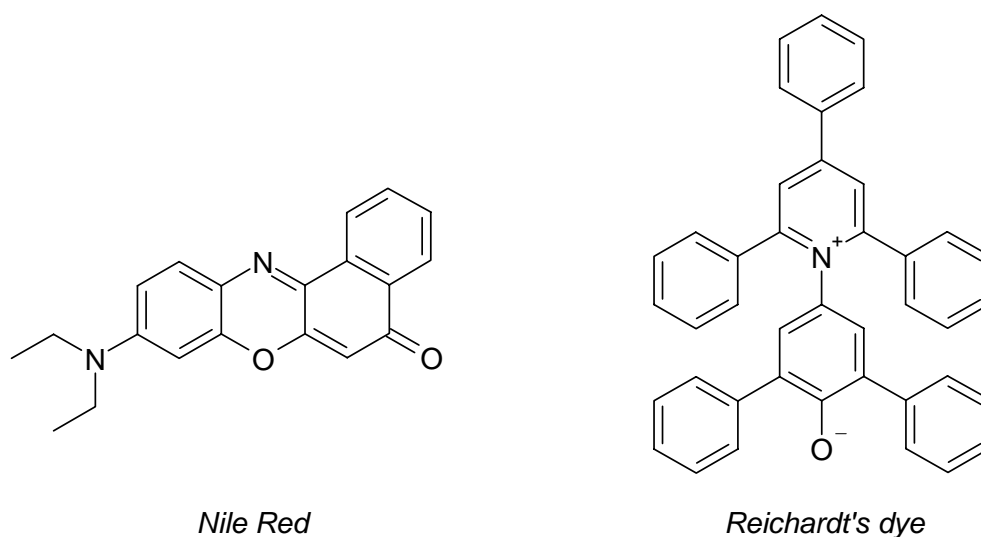


Fig. 1. Solvatochromic dyes used to estimate the polarity of sugar-urea-salt melts.

The original solvent polarity scale, known as the $E_T(30)$ scale, is defined as the molar transition energy of the dye measured in solvents of different polarity at 30°C and atmospheric pressure according to the following equation:

$$E_T(30) \text{ kcal mol}^{-1} = hc\nu_{\max}N_A = 28591/\lambda_{\max}$$

h = Planck's constant; c speed of the light ; ν_{\max} = wavenumber; N_A = Avogadro's constant



Fig. 2. From left to right: mannose/DMU (30:70) (**8**), sorbitol/DMU/NH₄Cl (70:20:10) (**2**), mannitol/DMU/NH₄Cl (50:40:10) (**5**), citric acid/DMU (40:60) (**1**).

The $E_T(30)$ values are defined for a temperature of 30°C, but sugar-urea-salt melts are liquid above 70°C only. To show that an estimation of polarity from solvatochromic measurements is still possible at higher temperatures, the absorption maxima of Reichardt's dye in several solvents (water, ethylene glycol, 2-propanol, dimethylsulfoxide, dimethylformamide) were determined at 90°C and compared to the value at 30°C. The changes in maximum absorption wavelength are small, and we conclude that an estimation of the relative order of polarity is possible from absorption values at 90°C.

Table 1 shows the longest wavelength adsorption band from intramolecular charge-transfer $\pi \rightarrow \pi^*$ excitation of Reichardt's dye in several sugar-urea-salt melts, water and selected solvents at 90°C. An examination of the results in Table 1 reveals that the $E_T(30)$ polarity values obtained for most sugar-urea-salt melts are much larger compared to water.

$E_T(30)$ polarity values exceeding the water value are known for aqueous salt solutions¹⁰ and some ionic liquids.¹¹ The $E_T(30)$ values of the lactose/DMU/ NH_4Cl (7) and the mannose/DMU (8) melt are smaller and in the range of ethylene glycol and 2-propanol.

Table 1. Intramolecular charge-transfer absorption bands (λ_{max}) and corresponding $E_T(30)$ solvent polarity values for melting sugar mixtures and other solvents at 90°C (Reichardt's dye)

Solvent	Melting point	λ_{max}/nm 25°C	λ_{max}/nm 90°C	$E_t(30)$ kcal mol ⁻¹
<i>Citric acid/DMU</i> ^a (1) 40 : 60	65°C	---	404	70,8
<i>Sorbit/DMU</i> ^a / <i>NH</i> ₄ <i>Cl</i> (2) 70 : 20 : 10	67°C	---	420	68,1
<i>Maltose/DMU</i> ^a / <i>NH</i> ₄ <i>Cl</i> (3) 50 : 40 : 10	84°C	---	422	67,8
<i>Fructose/Urea/NaCl</i> (4) 70 : 20 : 10	73°C	---	430	66,5
<i>Mannitol/DMU</i> ^a / <i>NH</i> ₄ <i>Cl</i> (5) 50 : 40 : 10	89°C	---	436	65,8
<i>Glucose/Urea/NaCl</i> (6) 60 : 30 : 10	78°C	---	444	64,4
<i>Water</i>	---	453	453	63,1
<i>Ethylene glycol</i>	---	507	510	56,1
<i>Lactose/DMU</i> ^a / <i>NH</i> ₄ <i>Cl</i> (7) 50 : 40 : 10	88°C	---	530	53,9
<i>Mannose/DMU</i> ^a (8) 30 : 70	75°C	---	530	53,9
<i>2-propanol</i>	---	588	589 ^b	48,5
<i>Dimethyl sulfoxide</i>	---	635	635	45,0
<i>Dimethylformamide</i>	---	652	655	43,6

^a DMU = *sym* dimethyl urea; ^b determined at 83°C.

Solvatochromic behavior of Nile Red

Although the exact molecular structure of the sugar-urea-salt melts remains speculative, a tight hydrogen bond network might be expected. It was reported that $E_T(30)$ values are very sensitive to solvents with acidic hydrogen bonds, which may adulterate the relative polarity ranking with organic solvents. Nile Red (Figure 1, left) is another dye, which shows a solvatochromic effect, but the absorbance maximum shift is less sensitive to acidic solvents due to its low basicity ($pK_a = 1$).¹² The dye dissolves in very polar liquids and is used to measure the polarity of acids and other very polar solvents. Its colour remains unchanged for several months even in neat, strong acids, such as trifluoroacetic acid.



Fig. 3. From left to right: mannose/DMU (8); sorbitol/DMU/NH₄Cl (2); mannitol/DMU/NH₄Cl (5); citric acid/DMU (1).

Depending on the solvents polarity, Nile red shows a bathochromic wavelength shift¹³ consistent with stabilization of the excited state in $p \rightarrow \pi^*$ or $\pi \rightarrow \pi^*$ electronic transition and comparable with the π^* scale of Kamlet and Taft.¹⁴ An empirical value, $E_T(\text{NR})$, can be defined for the polarity of solvents and provides an alternative useful scale to estimate the relative polarity of organic solvents and ionic liquids. Large shifts in the wavelength of maximum absorbance are observed with the dye in sugar-urea-salt melts. A pink solution is obtained in sorbitol/dimethylurea/NH₄Cl (2), fuchsia in mannitol/dimethylurea/NH₄Cl (5), dark violet in mannose/DMU (8), and a violet-blue color in citric acid/dimethylurea (1) (Fig. 3).

In Table 2 the λ_{max} values for Nile Red at 90°C dissolved in sugar-ure-salt melts and five solvents are summarized. The Nile Red λ_{max} data reclassify the melts to be less polar than water. From the

$E_T(\text{NR})$ values a relative polarity of maltose/dimethylurea/ NH_4Cl (**3**), sorbitol/DMU/ NH_4Cl (**2**) and citric acid/DMU (**5**) similar to ethylene glycol is estimated, whereas mannose/dimethylurea (**8**) is similar to dimethyl sulfoxide and mannitol/dimethylurea/ NH_4Cl (**5**) close to dimethylformamide.

Table 2 Intramolecular charge-transfer absorption band (λ_{max}) and corresponding $E_{\text{T}(\text{NR})}$ solvent polarity value for Nile Red dye in sugar-urea-salt melts and other solvents for comparison at 90°C

Solvent	Melting point	$\lambda_{\text{max}}/\text{nm}$ 25°C	$\lambda_{\text{max}}/\text{nm}$ 90°C	$E_{\text{T}(\text{NR})}$ kcal mol ⁻¹
<i>Water</i>	---	593	593	48,21
<i>Citric acid/DMU^a (1)</i> 40 : 60	65°C	---	575	49,72
<i>Sorbit/DMU^a/NH_4Cl (2)</i> 70 : 20 : 10	67°C	---	570	50,16
<i>Ethylene glycol</i>	----	565	565	50,60
<i>Maltose/DMU^a/NH_4Cl (3)</i> 50 : 40 : 10	84°C	---	565	50,60
<i>Glucose/Urea/NaCl (6)</i> 60 : 30 : 10	78°C	---	562	50,78
<i>Mannose/DMU^a (8)</i> 30 : 70	75°C	---	551	51,79
<i>Dimethyl sulfoxide</i>	---	549	549	52,07
<i>Fructose/Urea/NaCl (4)</i> 70 : 20 : 10	73°C	---	544	52,55
<i>Lactose/ DMU^a/NH_4Cl (7)</i> 50 : 40 :	88°C	---	544	52,55
<i>Dimethylformamide</i>	---	541	541	52,84
<i>Mannitol/DMU^a/NH_4Cl (8)</i> 50 : 40 : 10	89°C	---	540	52,94
<i>2-propanol</i>	---	540	540¹	52,94

^a DMU = *sym* dimethyl urea; ^b determined at 83°C.

In Fig. 4 the measured $E_{\text{T}(\text{NR})}$ values are plotted against Reichardt's, $E_{\text{T}(30)}$ values. The relative order is consistent, but absolute values differ. Nile Red response is less sensitive to hydrogen bonding solvents and proton donor/acceptor solvents than ET values of Reichardt's dye, which leaves all values in a much more narrow range.

It should be mentioned, that E_T values for both series have been developed mostly for pure solvents. The sugar-urea-salt melts are binary or tertiary mixtures, for which no additive behavior of its components can be expected. Synergistic (non-additive) behavior of physical properties of solvent mixtures have been found in special cases: e.g. some Rh(III) complexes are neither soluble in pure water nor in neat pyridine but in a 1:1 mixture of the two solvents.¹⁵

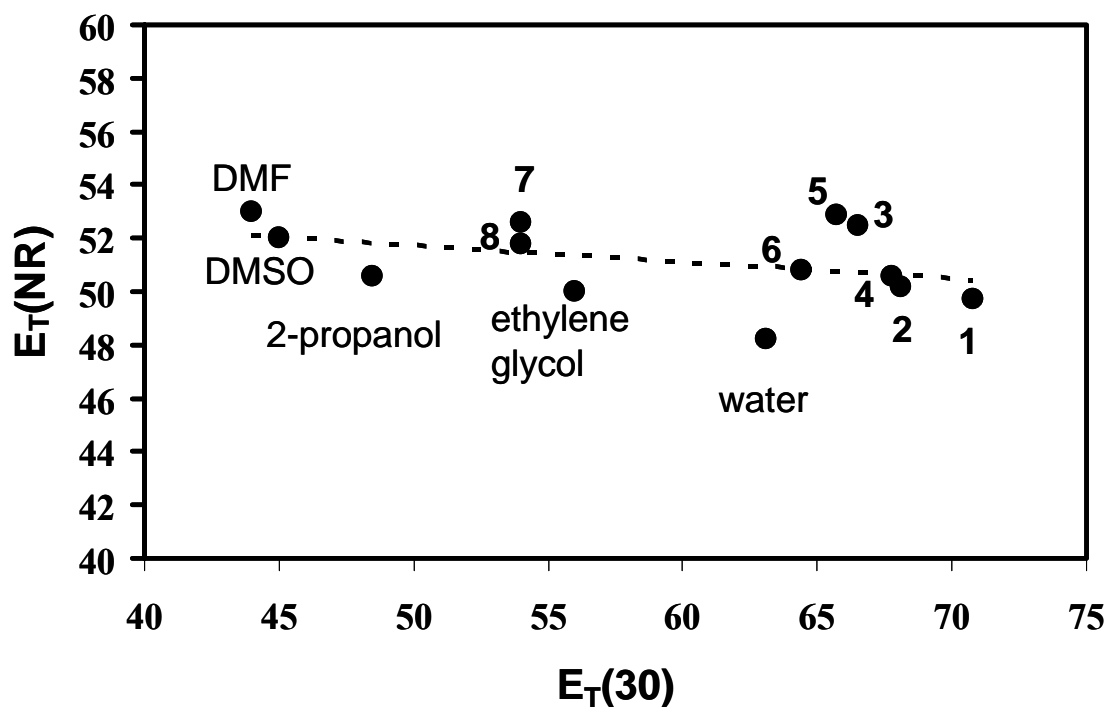


Fig. 4. Comparison of transition energies calculated from the absorption wavelength of Nile Red, E_T (NR) and Reichardt' dye, E_T in sugar-urea-salt melts and some polar solvents.

Addition of inorganic salts like sodium chloride to various solvents can lead to a strong increase of the polarity of the mixture.¹⁶

Nile Red is uniquely stable in extremely acidic media and is not susceptible to loss of molar absorptivity in presence of acids like Richardt's dye. Nile Red, because is more stable in acidic media, is somewhat more useful than $E_t(30)$ in measuring the solvents strength of acid and other very polar solvents (in neat, strong acids, such as trifluoroacetic acid, maintained nearly constant colour for months). As reported by J.F.Deye, T.A Berger and A.G. Anderson $E_t(30)$ is extremely

sensitive to hydrogen bonding solvents. The absorbance maximum of Nile red does not appear to shift significantly when subject to hydrogen bonding. Thus we judge the estimates based on the Nile Red absorption shifts as the more realistic ones for the sugar-urea-salt melts. The values place their polarity in a range comparable to DMSO from ethylene glycol and show significant polarity differences depending on the composition of the melt. The citric acid/DMU (**1**) melt is most polar, while mannose and lactose based melts (**7**) and (**8**) are least polar.

Reactions in Sugar Melts

Hydrogenation in melting sugar mixtures

Low melting mixtures of sugars, urea and salt have been successfully used as solvent for typical organic reactions, e.g. Diels-Alder⁶ or aldol reactions.⁵ To extend the scope of application, hydrogenation reactions were performed in the melts. Catalytic hydrogenation is a key synthetic method for the reductions of organic compounds. The reaction can be performed in various organic solvents,¹⁷ water¹⁸ or ionic liquids.¹⁹ and supercritical carbon dioxide²⁰ The methyl ester of α -cinammic acid (**9**) was used as the substrate for catalytic hydrogenation with Wilkinson's catalyst at 90°C and 1 atm of hydrogen.

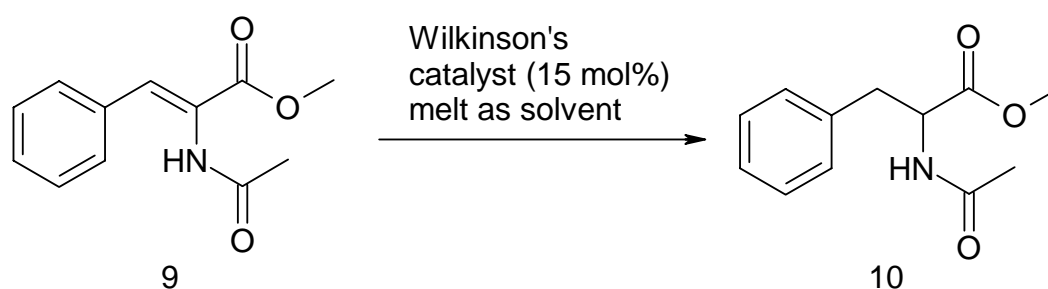


Fig. 5 Catalytic hydrogenation of methyl α -cinammate (**9**) in a melt using Wilkinson's catalyst.

The reaction proceeds fast, clean and quantitative in the citric acid/dimethylurea melt (**1**) and less efficient (50 % conversion) in melts (**2**) and (**5**). In the other sugar-urea-salt melts the catalytic systems shows only low reactivity. Product (**10**) contains a chiral center and its configuration was investigated by chiral HPLC. Melts (**2**) and (**5**) are chiral and may affect the orientation of the hydrogenation reaction. However, the analysis revealed racemate formation, which shows that the chiral melts are not able to bias the stereochemical outcome of the reaction.

Entry	Solvent	Yield in %
4	<i>Fruct/Urea/NaCl</i> <i>70:20:10</i>	20
1	<i>Citric acid/DMU</i> <i>40 : 60</i>	100
7	<i>Lactose/DMU/NH₄Cl</i> <i>60:30:10</i>	0
5	<i>Mannitolo/DMU/NH₄Cl</i> <i>50:40:10</i>	50
2	<i>Sorbit/DMU/NH₄Cl</i> <i>70:20:10</i>	51
6	<i>Glucose/Urea/NH₄Cl</i> <i>60:30:10</i>	10

Table 3. Rh(PPh₃)Cl catalyzed transfer hydrogenation of **9** in various sugar melting mixture at 1 atm hydrogen and 90°C

Suzuki reaction

The palladium-catalyzed cross coupling of aryl halides with boronic acids (Suzuki reaction) is one of the most versatile and widely utilized reactions for the selective construction of carbon-carbon bonds, in particular for the formation of biaryls. The biaryl motif is found in pharmaceuticals, herbicides, natural products, conducting polymer and liquid crystalline materials.²¹ Suzuki reactions have been described in organic solvents,²² in water²³ and in supercritical carbon dioxide²⁴ and in ionic liquids.²⁵ We extend the scope by using sugar-urea-salt melts as solvent. Phenyl boronic acid (**11**) was coupled with three aryl bromides (**12**) in the melts **2** - **8** at 90°C using 10mol% of Pd(OAc)₂ as catalyst and 1.2 equiv. of Na₂CO₃ as base. All reactions show quantitative conversion

of the starting materials after 6 h. Hydrodeboronation as a competing process was not observed under these conditions.

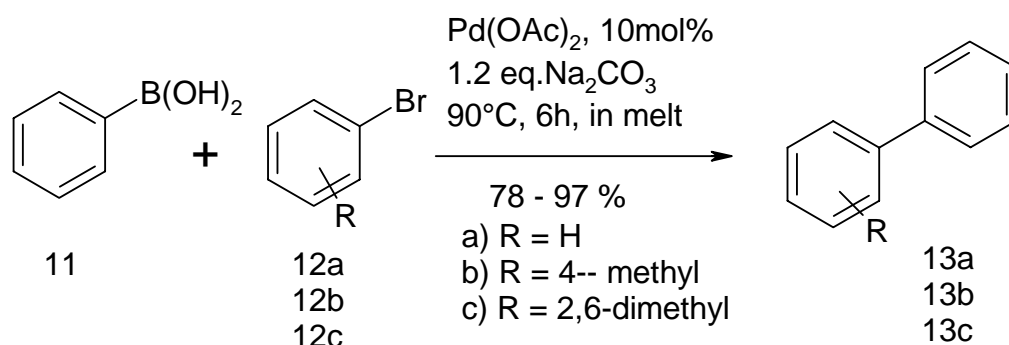


Fig. 6 Suzuki coupling in sugar-urea-salt melts

Work up of the reaction mixture is very easy. After cooling to room temperature water was added and the aqueous phase was extracted with pentane. Product analysis by NMR and GC shows clean formation of the expected product. The isolated yields range from 78 to 97 %, which is mainly caused by different efficacy of product extraction in work up.

Table 4 Suzuki coupling in sugar – urea – salt melts

Composition of melt	Isolated yield [%]		
	13a	13b	13c
fructose/urea/NaCl (4) 70:20:10	82	81	78
maltose/DMU ^a /NH ₄ Cl (3) 50:40:10	84	83	81
mannose/DMU ^a (8) 30:70	98	93	88
lactose/DMU ^a /NH ₄ Cl (7) 60:30:10	89	86	91
mannitol/DMU ^a /NH ₄ Cl (5) 50:40:10	97	96	97
sorbitol/DMU ^a /NH ₄ Cl (2) 70:20:10	98	95	94
glucose/urea/NH ₄ Cl (6) 60:30:10	86	80	83

^a sym *N,N*-dimethylurea

Conclusions

Stable melts are obtained at around 75°C from several mixtures of sugars, sugar alcohols or citric acid with urea and inorganic salts. As an important solvent parameter, the polarity of the melts was estimated using solvatochromic dyes. While Reichardt's dye rates all melts more polar than water, the more suitable estimation using Nile Red places their polarity in the range of DMSO and ethylene glycol. While previous experiments demonstrated the use of sugar-urea-salt melts as solvents for typical organic transformations, we have now extended the application to catalyzed reactions. Hydrogenation with Wilkinson's catalyst proceeds very well in a citric acid/dimethylurea melt. The reaction is sensitive to the composition of the melt and results vary with the sugar or sugar alcohol used. No stereochemical induction of the hydrogenation in chiral melts was observed. The palladium-catalyzed Suzuki reaction proceeds equally well in all investigated melts as solvents and variations in isolate yield are caused by different product extraction efficacy.

In summary, the reported sugar-urea-salt melts represent a suitable replacement for polar organic solvents, like DMF, DMSO or ethylene glycol in organic synthesis. The non-toxic melts are available from bulk renewable resources and simple inorganic salts without prior steps by simple mixing of the components. With these properties they may contribute to the development of more sustainable chemical transformations and processes.

Experimental

Solvatochromic Measurements of Solvents and Melts

Reichardt's dye and Nile red were obtained from Aldrich Chemical Co. and were used as received. Samples for spectroscopic studies were prepared as follows: An appropriate aliquot of the solvatochromic dye was added at 90°C to the analyzed solvent and allowed to equilibrate for a sufficient time. Then 1ml of the appropriate solvent were added to the cuvette before evacuated with Argon.

Hydrogenation reaction:

All reactions were carried out in dihydrogen atmosphere and all chemicals were used as purchased. In a typical experiment 0.1 mmol of methyl α -cinammate and Wilkinson's catalyst (15 mol%) were added under argon to 10 ml of a sugar-urea-salt melt at 90°C. The mixture was degased and flushed with dihydrogen three times. The reaction was stopped when no more dihydrogen was consumed. After cooling to room temp. the product was extracted with ethyl acetate, dried over MgSO₄ and chromatographed on silica gel using hexane:ethyl acetate, 2: 1, as eluent. The product was analyzed by ¹H and ¹²C NMR.

Suzuki Reaction:

All reaction were carried out in air and all chemicals were used as purchased. In a typical experiment 2.2 mmol of boronic acid, 2 mmol of the aryl bromide, 2.5 mmol of Na₂CO₃ and 0.4 mmol of Pd(OAc)₂ were added to 5 ml of a sugar-urea-salt melt at 90°C. The reaction tube (10 ml) was sealed (Caution: All necessary precaution should be taken when such experiments are performed. Pressure may develop inside). The reaction was stirred for 6 h and then cooled to room temp. The product was extracted with pentane (6 x 2 ml), the solvent was evaporated and analyzed by ¹H and ¹²C NMR. Spectroscopic data match the values reported in the literature.²⁶

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Stille Reactions with Tetraalkylstannanes and Phenyltrialkylstannanes in Low Melting Sugar – Urea - Salt Mixtures[§]

Abstract. The transfer of simple alkyl groups in Stille reactions usually requires special solvents (HMPA) or certain organotin reagents (stannatranes, monoorganotin halides) to be efficient. Using low melting mixtures of sugar, urea and inorganic salt as solvent, a fast and efficient palladium-catalyzed alkyl transfer with tetraalkyltin reagents was observed. The high polarity and nucleophilic character of the solvent melt promotes the reaction.

Stille biaryl synthesis using electron-poor and electron-rich aryl bromides proceeds with quantitative yields in the sugar-urea-salt melt. Catalyst loading may be reduced to 0.001 mol% and the catalyst melt mixture remains active in several reaction cycles. Showing the same or improved performance for Stille reactions than organic solvents and allowing a very simple work up, sugar-urea-salt melts are a non-toxic, cheap and available in bulk quantities alternative reaction medium for the catalytic process.

[§] Giovanni Imperato, Rudolf Vasold and Burkhard König *Adv.Synth.Catal.* accepted.

1. Introduction

The Stille cross-coupling protocol is a powerful and widely used method for the construction of new carbon-carbon bonds.^{1,2,3,4} It is defined as the Pd-catalyzed coupling of organic electrophiles, usually halides or triflates, with organotin reagents. The reaction tolerates a variety of functional groups and most organotin reagents are sensitive to neither oxygen nor moisture, which makes the process very versatile. Aryl and alkenyl moieties are rapidly transferred, but the scope of the reaction is somewhat limited by the low efficiency of alkyl transfer from tetraalkyltin reagents; for this reason, they are used as non-transferable ligands in mixed organotin compounds. Several reports have addressed the problem. Stille reported the reaction to proceed well in HMPA, DMF and dioxane as solvent.^{5,6} The addition of diethylamine to Stille alkylation reaction improves yields by reducing competing β -hydride elimination and reduction.⁷ Monoorganotin reagents, such as secondary alkyl halides⁸ and stannatranes⁹ cross couple efficiently. The effect of alkyl imidazolium salt ionic liquids on the transfer of alkyl groups from simple tetraorganotin reagents to iodobenzene was recently investigated,^{10,11} but found to be difficult and accompanied by formation of biphenyl.

Likewise the synthesis of biaryls becomes an attractive process which have a diverse spectrum of application, ranging from pharmaceuticals to material science¹².

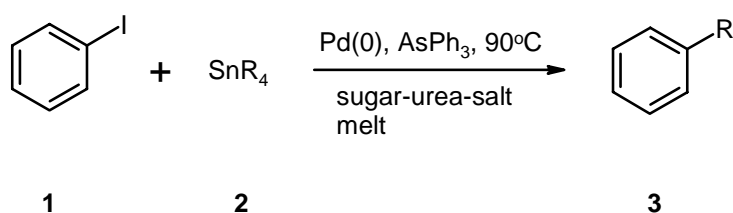
Low melting sugar-urea-salt mixture for reactions represents new solvents with interesting properties and several benefits including low cost¹³ and improved safety in comparison to classical organic solvents. The toxicity of the melt ingredients is generally very low; e.g. NaCl LD₅₀ orally in rats 3.8 gr/kg; no LD₅₀ reported for sorbitol, lactose, urea or dimethylurea.¹⁴ In addition, all components of the carbohydrate-based solvents are biodegradable. Furthermore, a simplified work up without the use of organic solvents becomes possible. The use reported here of low melting sugar-urea-salt mixtures as solvents for efficient Stille alkylation and biaryl synthesis may therefore contribute to a more sustainable chemistry.

2. Results and Discussion

Mixtures of sugars, urea and inorganic salts, which melt around 70°C were recently introduced as solvent for Diels-Alder reactions.¹⁵ The polarity of the melts is very high,¹⁶ although they do not contain any water. The well-documented effect of the solvent polarity and nucleophilic assistance theory¹⁷ on the Stille alkylation with tetraalkyltin reagents, prompted us to investigate this reaction in

the unusual medium. Iodobenzene was coupled at 90°C with tetravinyltin (entry 1-8, table 1), tetramethyltin (entry 9-16) and tetrabutyltin (entry 18-24) in different sugar-urea-salt

melts using a Tris(dibenzylideneacetone)dipalladium(0) chloroform adduct as palladium(0) source and AsPh₃ as ligand. As expected, the transfer of the vinyl group to the arene is efficient and complete in all experiments. GC analysis of the crude product shows that no iodobenzene starting material remains. Alkyl group transfer from tetraalkylorganotin reagents typically requires special conditions (toxic solvents as HMPA, DMF or dioxane) or reagents to be effective as discussed above. Therefore, we were pleasantly surprised to observe product yields for the methyl group transfer from tetramethyltin between 45% and 90% (entries 11, 13, 15 and 16) if performed in the sugar-urea-salt melt. The butyl group is even more difficult to transfer from tetrabutyltin. Three solvent melts were identified, which allowed a butyl group transfer with yields from 37% to 44% (entries 19, 20 and 24).



Scheme 1. Stille alkylation in sugar-urea-salt melts

Table 1. Stille alkylations in sugar-urea-salt melts

Entry	Composition of melt ⁴	R	Reaction time	Conversion ² [%]	Ph-R [%] ³	Byproduct
1	<i>Citric acid/DMU¹</i> 40 : 60	- C ₂ H ₃	6 h	100	95	---
2	<i>Sorbit/DMU¹/NH₄Cl</i> 70 : 20 : 10	- C ₂ H ₃	6 h	100	95	---
3	<i>Maltose/DMU¹/NH₄Cl</i> 50 : 40 : 10	- C ₂ H ₃	6 h	100	100	---
4	<i>Fructose/Urea/NaCl</i> 70 : 20 : 10	- C ₂ H ₃	6 h	100	85	---

5	<i>Mannitol/DMU¹/NH₄Cl</i> 50 : 40 : 10	– C ₂ H ₃	6 h	100	71	---
6	<i>Glucose/Urea/NaCl</i> 60 : 30 : 10	– C ₂ H ₃	6 h	100	97	---
7	<i>Lactose/DMU¹/NH₄Cl</i> 60 : 30 : 10	– C ₂ H ₃	6 h	100	96	---
8	<i>Mannose/DMU¹</i> 30 : 70	– C ₂ H ₃	6 h	100	92	---
9	<i>Citric acid/DMU¹</i> 40 : 60	– CH ₃	6 h	25	20	---
10	<i>Sorbit/DMU¹/NH₄Cl</i> 70 : 20 : 10	– CH ₃	6 h	19	12	---
11	<i>Maltose/DMU¹/NH₄Cl</i> 50 : 40 : 10	– CH ₃	6 h	55	51	---
12	<i>Fructose/Urea/NaCl</i> 70 : 20 : 10	– CH ₃	6 h	18	10	---
13	<i>Mannitol/DMU¹/NH₄Cl</i> 50 : 40 : 10	– CH ₃	6 h	94	90	---
14	<i>Glucose/Urea/NaCl</i> 60 : 30 : 10	– CH ₃	6 h	23	18	---
15	<i>Lactose/DMU¹/NH₄Cl</i> 60 : 30 : 10	– CH ₃	6 h	49	45	---
16	<i>Mannose/DMU¹</i> 30 : 70	– CH ₃	6 h	85	81	---
17	<i>Citric acid/DMU¹</i> 40 : 60	– C ₄ H ₉	6 h	100	6	benzene
18	<i>Sorbit/DMU¹/NH₄Cl</i> 70 : 20 : 10	– C ₄ H ₉	6 h	90	14	benzene
19	<i>Maltose/DMU¹/NH₄Cl</i> 50 : 40 : 10	– C ₄ H ₉	6 h	100	42	benzene
20	<i>Fructose/Urea/NaCl</i> 70 : 20 : 10	– C ₄ H ₉	6 h	100	37	benzene
21	<i>Mannitol/DMU¹/NH₄Cl</i> 50 : 40 : 10	– C ₄ H ₉	6 h	100	25	benzene
22	<i>Glucose/Urea/NaCl</i> 60 : 30 : 10	– C ₄ H ₉	6 h	75	28	benzene
23	<i>Mannose/DMU¹</i> 30 : 70	– C ₄ H ₉	6 h	100	15	benzene

24	<i>Lactose/DMU¹/NH₄Cl</i>	– C ₄ H ₉	6 h	100	44	benzene
	<i>60 : 30 : 10</i>					

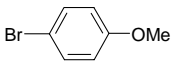
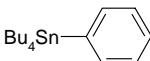
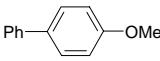
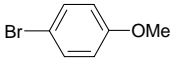
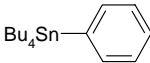
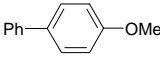
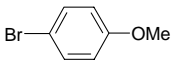
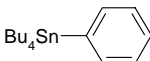
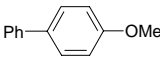
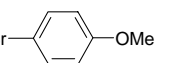
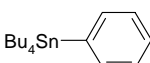
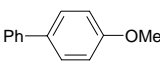
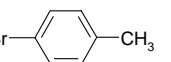
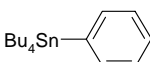
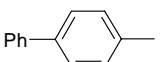
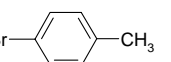
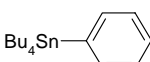
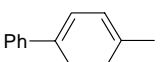
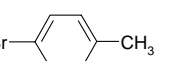
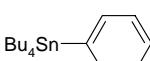
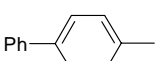
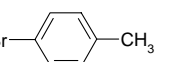
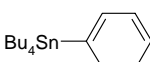
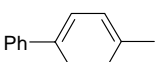
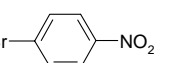
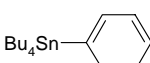
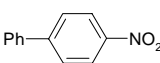
¹ Dimethylurea; ² determined using hexamethylbenzene as internal standard; ³ determined by GC-MS analysis; ⁴ The ratio is given in weight %

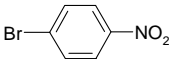
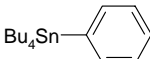
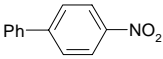
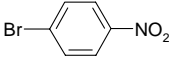
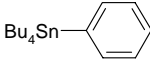
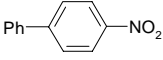
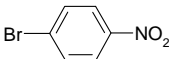
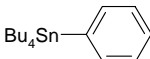
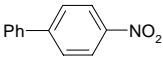
The work up of the reactions is very simple: at the end of the reaction water and 1 ml of a hydrocarbon is added. In our experiments pentane was used to simplify GC analysis; for larger scale applications hydrocarbons with a higher flash point, e.g. isooctane should be used. After filtration, the separated pentane phase was analyzed by GC-MS. No additional extraction of the aqueous phase is necessary for quantitative product isolation.

The composition of the melt significantly affects the outcome to the reaction. The mixture of mannitol – dimethylurea - ammonium chloride (50:40:10) gave best results for methyl group transfer, while maltose – dimethylurea - ammonium chloride was good for butyl group transfer. The presence of dimethylurea is not crucial; replacing it by urea does not affect the reaction, as shown in entry 6.¹⁸ The molecular structure of the melts is complex and currently we cannot describe the molecular origin of the differences of the reaction course in different compositions. Stille alkylations in *N*-butyl-*N*-methylimidazolium salt ionic liquids yield up to 30% biphenyl as a side product.¹⁰ In melted sugar-urea-salt mixtures no biphenyl, but benzene formation was observed, in the case of tetrabutyltin coupling. A reductive process competes with the slow butyl group transfer.

We started our investigation of Stille biaryl synthesis in sugars-urea-salt melts with the coupling of tributylphenylstannane with 4-bromoanisole and 1-bromo-4-methyl-benzene, as electron-rich arenes, and 1-bromo-4-nitrobenzene, as an electron-poor arene, using 1 mol% tris(dibenzylideneacetone) dipalladium(0) as catalyst and AsPh₃ as ligand. The melts consisting of lactose/dimethylurea/NH₄Cl, maltose/dimethylurea/NH₄Cl, mannitol/dimethylurea/NH₄Cl and sorbitol/dimethylurea/NH₄Cl showed the best results for Stille alkylations and were selected for the biaryl synthesis. Table 2 summarizes the results.

Table 2. Stille coupling of arylbromide and tributylphenylstannane in melting sugar at 90°C^a

Entry	Composition of melt ^d	Aryl halides	Arylstannanes	Product	Conv ^b /yield ^c (%)
1	Lactose/ DMU ¹ /NH ₄ Cl 60 : 30 : 10				100 / 100
2	Mannitol/DMU ¹ / NH ₄ Cl 50 : 40 : 10				100 / 100
3	Maltose/DMU ¹ / NH ₄ Cl 50 : 40 : 10				100 / 100
4	Sorbit/DMU ¹ / NH ₄ Cl 70 : 20 : 10				90 / 80
5	Lactose/ DMU ¹ /NH ₄ Cl 60 : 30 : 10				100 / 100
6	Mannitol/DMU ¹ / NH ₄ Cl 50 : 40 : 10				100 / 100
7	Maltose/DMU ¹ / NH ₄ Cl 50 : 40 : 10				100 / 100
8	Sorbit/DMU ¹ / NH ₄ Cl 70 : 20 : 10				100 / 85
9	Lactose/ DMU ¹ /NH ₄ Cl 60 : 30 : 10				95 / 90

10	<i>Mannitol/DMU¹/NH₄Cl</i> 50 : 40 : 10				95 / 90
11	<i>Maltose/DMU¹/NH₄Cl</i> 50 : 40 : 10				95 / 90
12	<i>Sorbit/DMU¹/NH₄Cl</i> 70 : 20 : 10				89 / 85

^a in 3 ml of melting sugar was added 1.5 mmol. Aryl bromide, 1.6 mmol of phenyltributylstannane, 1% Pd₂(dba)₃ and ArPh₃ as ligand. The reaction time was 6h.

^b Determinated by ¹H NMR of the crude product mixture.

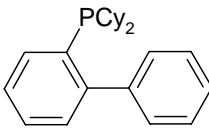
^c Isolated yield by chromatography (3 : 1 petrol ether ethyl acetate)

¹ Dimethylurea

^d The composition ratio of the melt is given as weight %

Best results were obtained using a melt consisting of lactose, maltose or mannitol. Reactions in the melt tolerate electronic variation of the arylbromide component and yield cleanly and in most cases quantitatively the biaryl coupling products. Next, the catalyst loading was reduced to 0.001% and the coupling of 4-bromoanisole and phenyltributylstannane was investigated using three different ligands. Table 3 summarises the results. Using Pd₂(dba)₃ and triphenylarsine as ligand 87% isolated product yield was obtained after 48 h, which corresponds to a catalyst turn over number of 87,000. Using (2-biphenyl)dicyclohexylphosphine as ligand or ligandless conditions gives lower conversion and yields. To benchmark the results obtained in sugar-urea-salt melts the identical reaction was performed in 1,4 dioxane (entry 4) yielding comparable conversion and yield as entry 1.

Table 3. Stille coupling of 4-bromoanisole and phenyltributylstannane at 90 °C in several ligand conditions; reaction time 48h^a

entry	Solvent ^d	Pd (mol%)	Ligand	Conv ^b / yield ^c
1	<i>Lactose/ DMU¹/NH₄Cl 60 : 30 : 10</i>	0.001%	ArPh ₃	92: 87
2	<i>Lactose/ DMU¹/NH₄Cl 60 : 30 : 10</i>	0.001%		65/61
3	<i>Lactose/ DMU¹/NH₄Cl 60 : 30 : 10</i>	0.001%	No ligand	30/27
4	Dioxane	0.001%	ArPh ₃	87/81

^a in 3 ml of melting sugar was added 1.5 mmol. Aryl bromide, 1.6 mmol of phenyltributylstannane, 0.001%mol Pd₂(dba)₃ and ArPh₃ as ligand.

^b Determined by ¹H NMR of the crude product mixture.

^c Isolated yield by chromatography (3 : 1 petrol ether ethyl acetate)

¹ Dimethylurea

^d The composition ratio of the melt is given as weight %

To test the robustness of the palladium catalyst under the sugar-urea-salt melt conditions the coupling of 4-bromoanisole with phenyltributylstannane was performed at 90°C in three subsequent batches using the same catalyst melt mixture with 0.01 mol% Pd₂(dba)₃ and 0.04 mol% ArPh₃ as ligand. The conversion of the reaction was determined by removing the organic phase under argon atmosphere after 12, 24 and 36 h and work up of this phase. New starting material was added to the remaining melt. The catalyst remained active over the three cycles, although a decrease in conversion from 83 % (first run) to 70 % (second run) and 66 % (third run) indicates some loss of activity.

Work up and product isolation determines significantly the overall efficiency of a chemical transformation. Here, the melt mixtures offer a very simple handling: after completion of the reaction simply water is added. The components of the melt dissolve in water and organic products precipitate

amorphously, the organic product was washed two times with water and analytically pure samples are obtained from the crude product after recrystallization. Solids with low melting points or liquids are isolated from the water phase with minimal amounts of organic solvents. In any case, the work up is simple and requires no or very small amounts of organic solvents for product isolation.

The results are summarized in table 4.

Table 4. Stille coupling of 4-bromoanisole and phenyltributylstannane^a

	Temp	Total time in hours	Conversion ^b
1 run	90°C	12h	83
2 run	90°C	24h	70
3 run	90°C	36h	66

^a in 3 ml of melting sugar was added 1.5 mmol. Aryl bromide, 1.6 mmol of phenyltributylstannane, 0.01%mol Pd₂(dba)₃ and ArPh₃ as ligand.

^b Determinated by ¹H NMR of the crude product mixture.

As summarized in table 4 the catalyst remains efficient and active after three runs. The conversion after 36h is 66%.

3. Conclusion

Conclusion

In summary, we have reported the use of sugar-urea-salt melts as solvent for Stille alkylations and biaryl synthesis. The transfer of simple alkyl groups, such as methyl or butyl, which usually requires special reagents or conditions, proceeds smoothly with tetraalkyltin in the unusual solvent. The high solvent polarity and the presence of nucleophilic groups may promote the alkyl transfer. Stille

alkylation reaction in sugar-urea-salt melts is therefore a suitable alternative to the use of HMPA as solvent or the preparation of stannatranes for efficient alkyl group transfer.

The synthesis of biaryls by Stille coupling proceeds in sugar-urea-salt melts with good yields for electron-poor and electron-rich aryl bromides. The catalyst loading may be reduced to 0.001 mol% still achieving a turn over number of 87,000. Repeated use of the catalyst melt mixture is possible and product isolation does not require the use of organic solvents.

Overall, the reported reaction conditions allow performing Stille coupling reactions of aryl iodides and aryl bromides as efficient as in organic solvents. The use of polar additives, such as HMPA, is avoided and the work up is simplified. In addition, the reaction medium is non-toxic,¹⁴ has a low vapour pressure¹⁵ and presumably high flash points,¹⁹ is rather cheap¹³ and readily available in bulk quantities. The recycled use of a carbohydrate reaction melt was demonstrated in three cycles of a Stille coupling. However, the economic or ecological benefit from melt recycling in batch reactions strongly depends on the individual application. Being biodegradable, the disposal of carbohydrate melts may use typical organic waste streams.

4. Experimental Section

General procedure for Stille alkylation in sugar-urea-salt melts

All reactions were carried out at 90°C (oil bath temperature) in 10 ml sealed tubes under argon. The use of sealed tubes avoids any loss of reagents or products under the reaction conditions and ensures a quantitative reaction monitoring. Chemicals were used as purchased. In a typical experiment 0.025 mmol of catalyst [tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct], 0.1 mmol of Ph₃As, 0.4 mmol of iodobenzene and 0.6 mmol of the organostannane were added to the sugar-urea-salt mixture (2.5 ml) under argon. The reaction mixture was stirred for 6 h at 90°C. After cooling to room temperature water was added and the product was extracted with pentane (1 x 1ml; the first extraction collects all organic products) and analyzed by GC-MS after the addition of hexamethyl benzene as an internal standard.

General procedure for Stille biaryl synthesis in sugar-urea-salt melts

All reactions were carried out at 90°C (oil bath temperature) in 10 ml sealed tubes under argon. The use of sealed tubes avoids any loss of reagents or products under the reaction conditions and ensures a quantitative reaction monitoring. Chemicals were used as purchased. In a typical experiment 1 mol% of catalyst [tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct], 4 mol% of Ph₃As, 1.5 mmol of aryl bromide and 1.6 mmol of the organostannane were added to the sugar-urea-salt mixture (3 ml) under argon. The reaction mixture was stirred for 6 h at 90°C. After cooling to room temperature, water was added to the mixture, which precipitates the organic product. The crude organic products were collected by filtration and washed with water (2 x 15 mL). The NMR analysis indicated that the crude product was > 95% pure. The slightly yellow crude product was further purified by recrystallization or filtration over silica gel (3 : 1 petrol ether : ethyl acetate) to give colorless pure products with analytical data matching all literature reported values.

Acknowledgments

G.I. thanks the Deutsche Bundesstiftung Umwelt for a graduate scholarship. We thank the Fonds der Chemischen Industrie for support of the work. We thank Dr. V. Farina and Dr. E. Napolitano for the helpful discussion.

Supplementary data

Gas chromatographic analyses of Stille alkylations with tetravinyltin, tetramethyltin and tetrabutyltin in different sugar-urea-salt melt.

References and notes

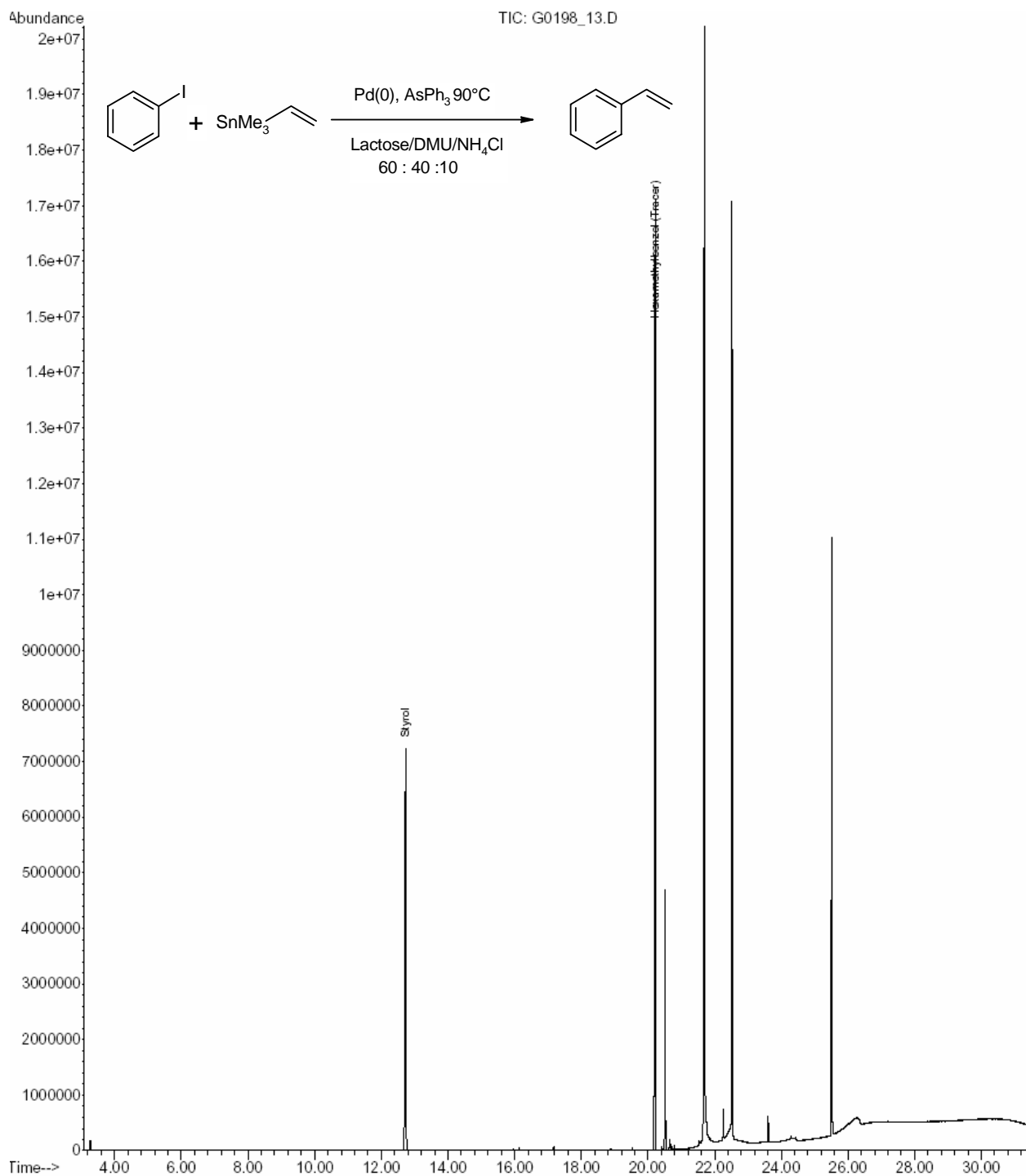
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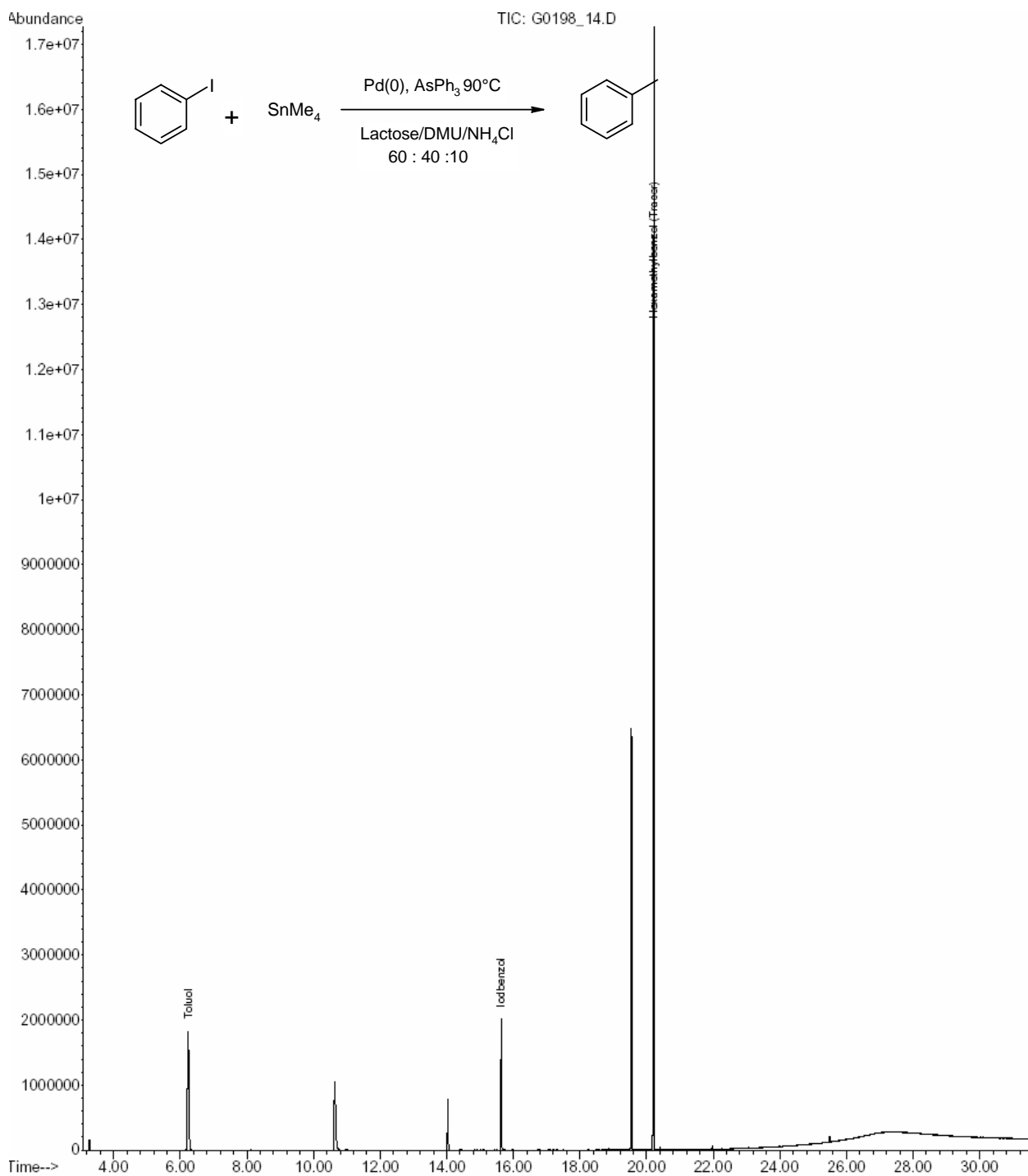
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- [13] Based on commercial prices for fine chemicals, which do not fully reflect bulk material cost, the cost of the sorbitol melt, entry 2 in table 1, is estimated to be approx. 18 EUR/Kg. Prices for DMSO, as a solvent with comparable properties strongly depend on solvent purity and are in the order of 60 EUR/Kg.
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- [19] No flash points are available for the components of the melt. Only urea and dimethylurea have a significant vapour pressure and sublime in vacuum.

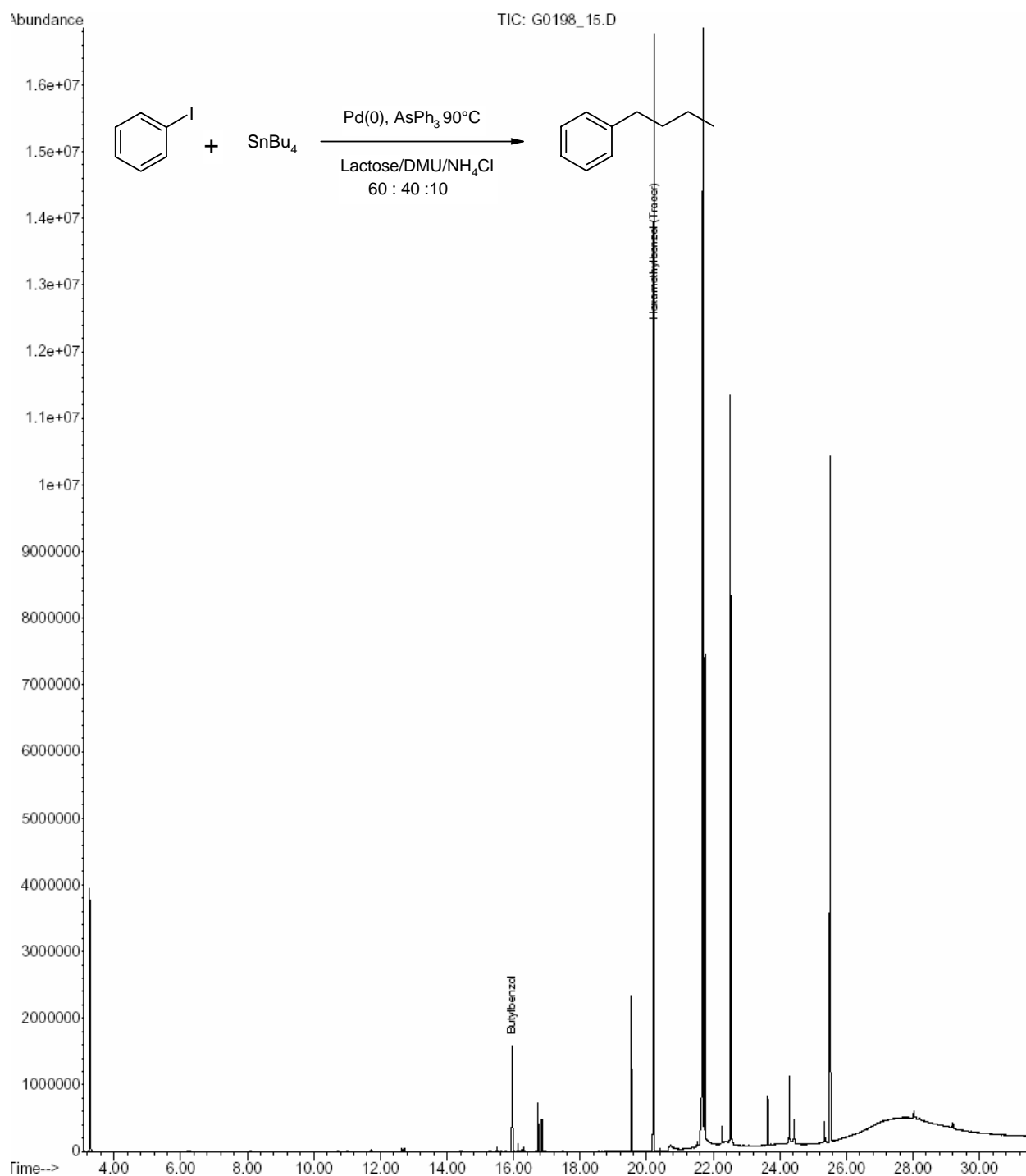
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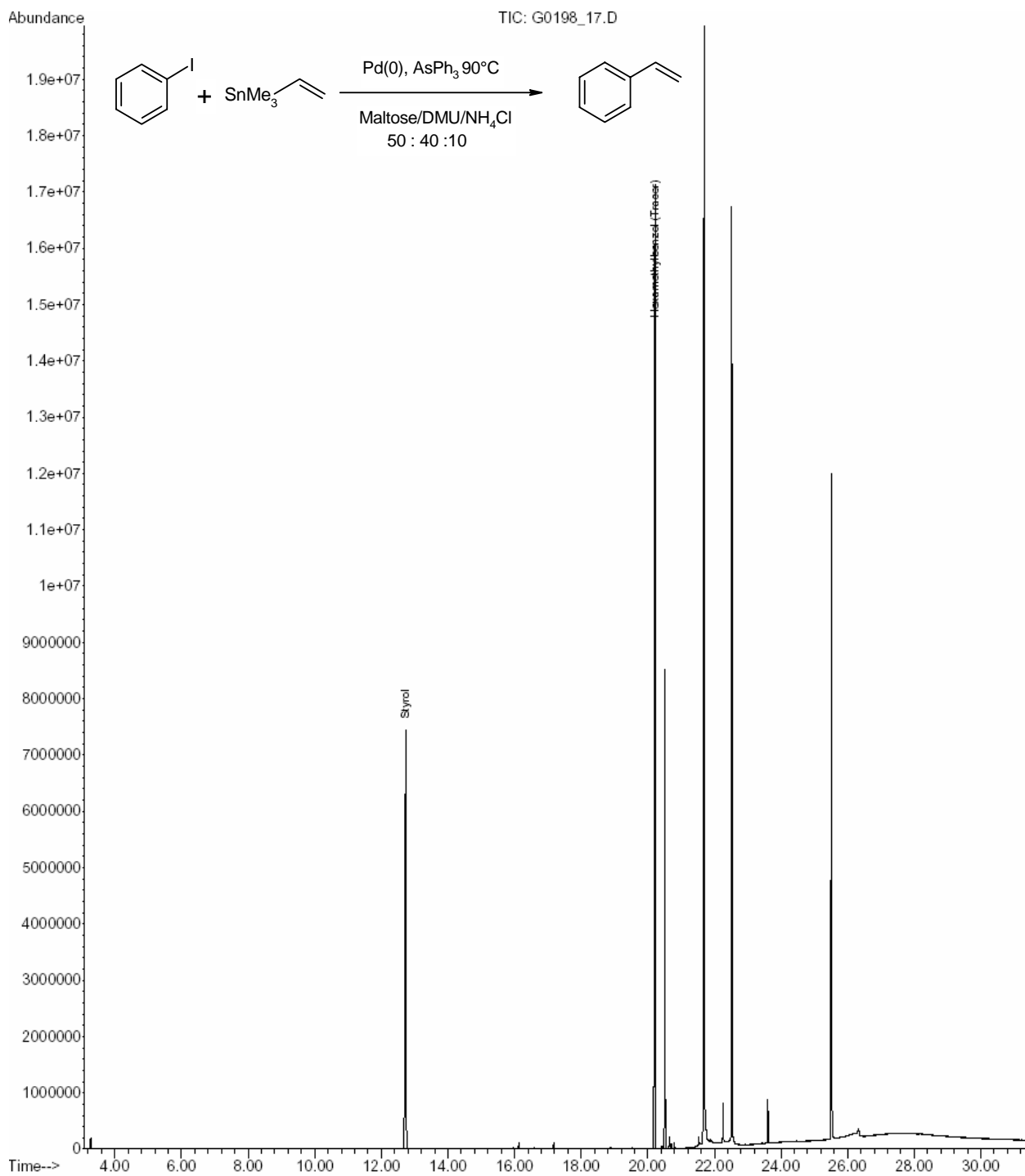
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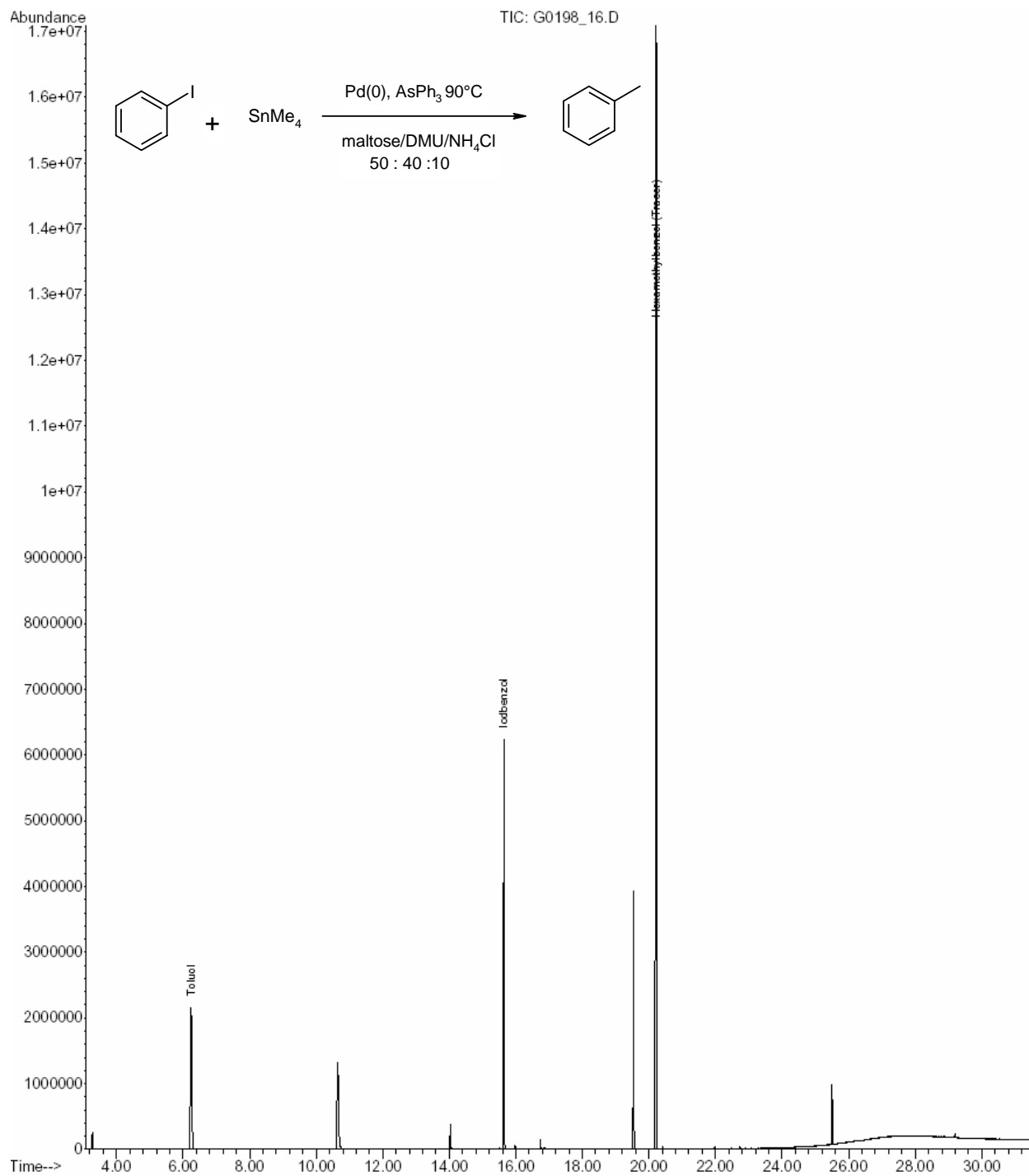
Column: Capillary model J+W 19091S-433 HP-5MS length 30m diameter 250.00 μm ; initial temperature 30 $^{\circ}\text{C}$, final temperature 280 $^{\circ}\text{C}$; flow 39.7 ml/min./ injection volume 0.2 microliters

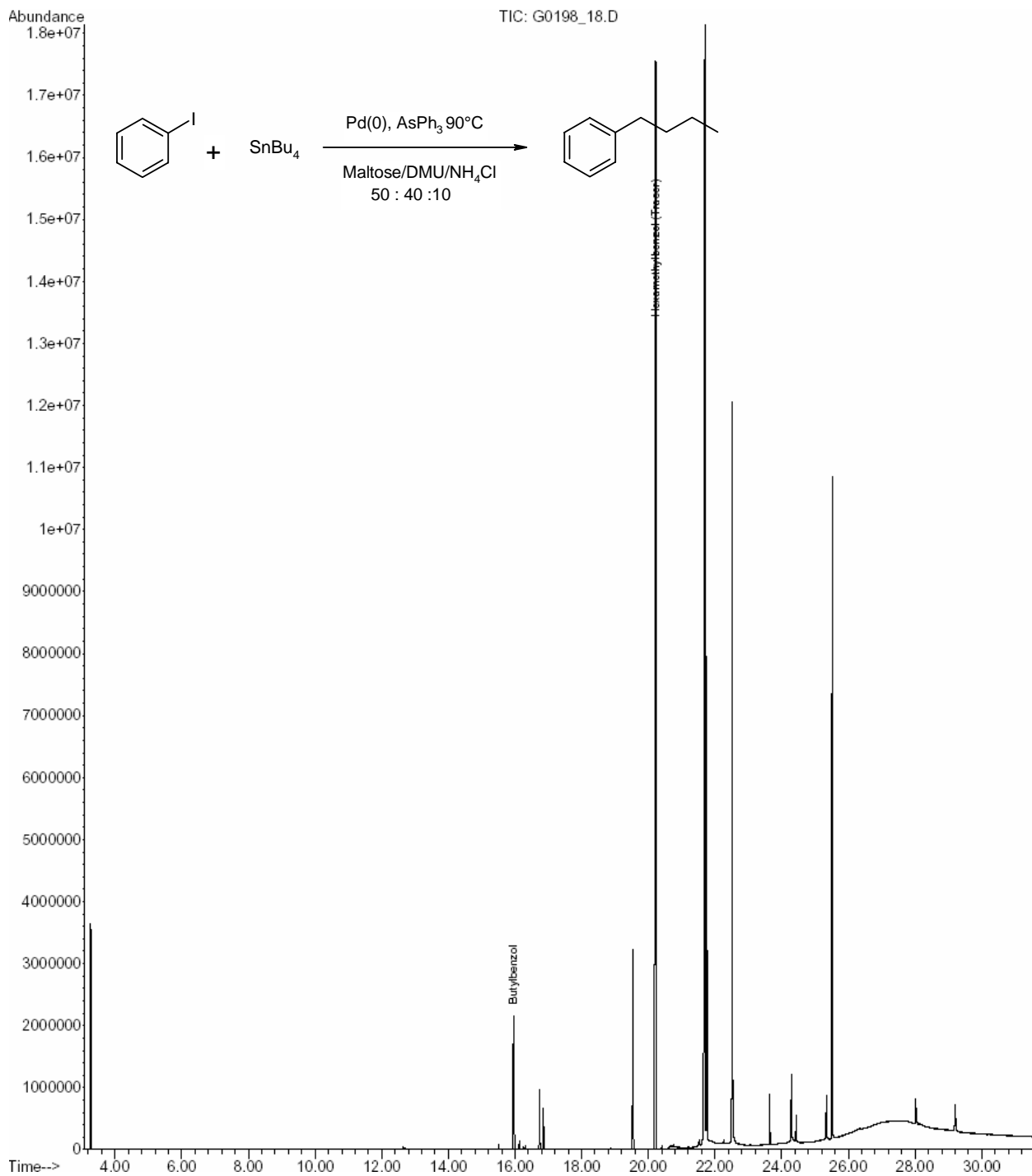


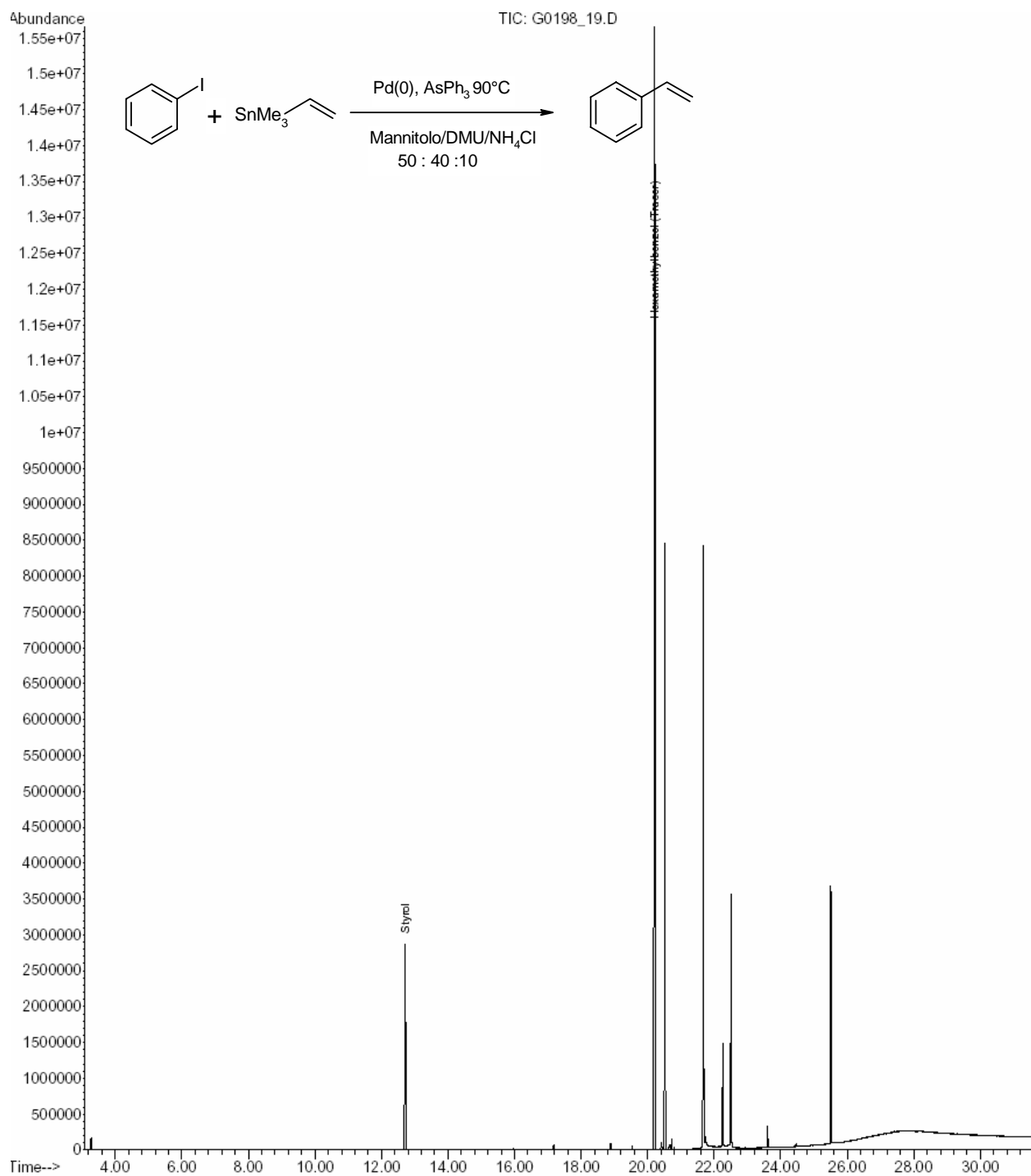


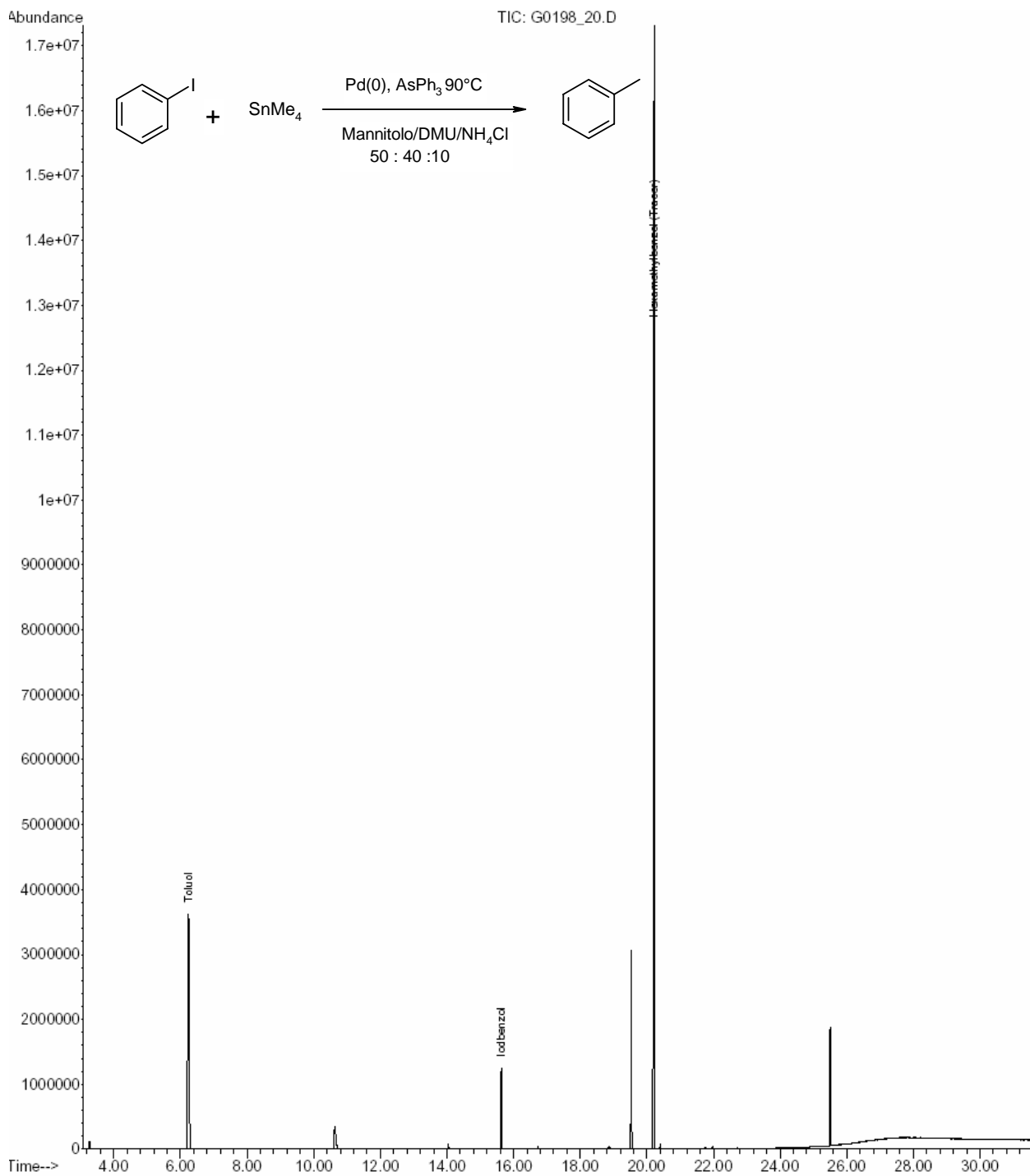


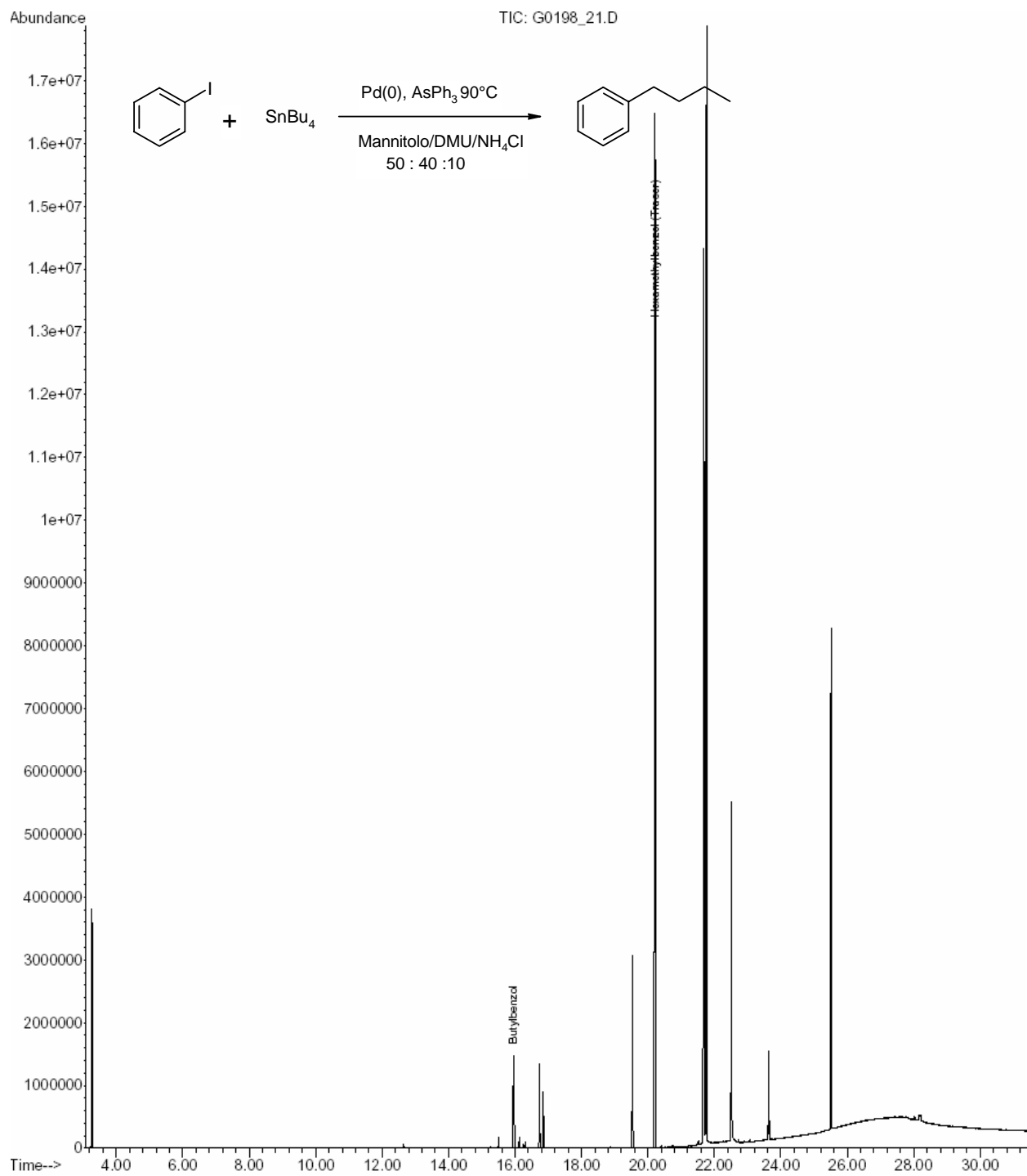


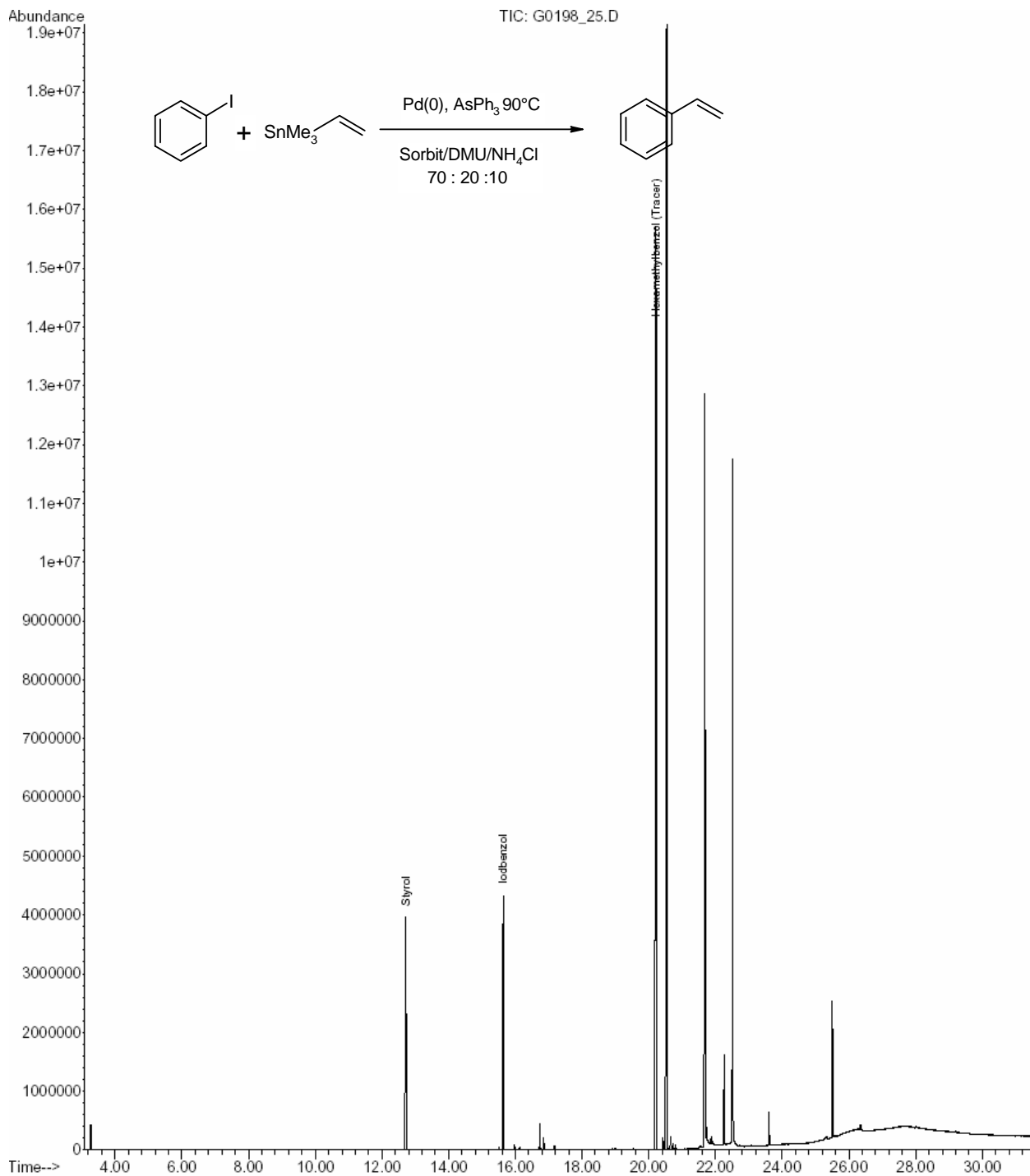


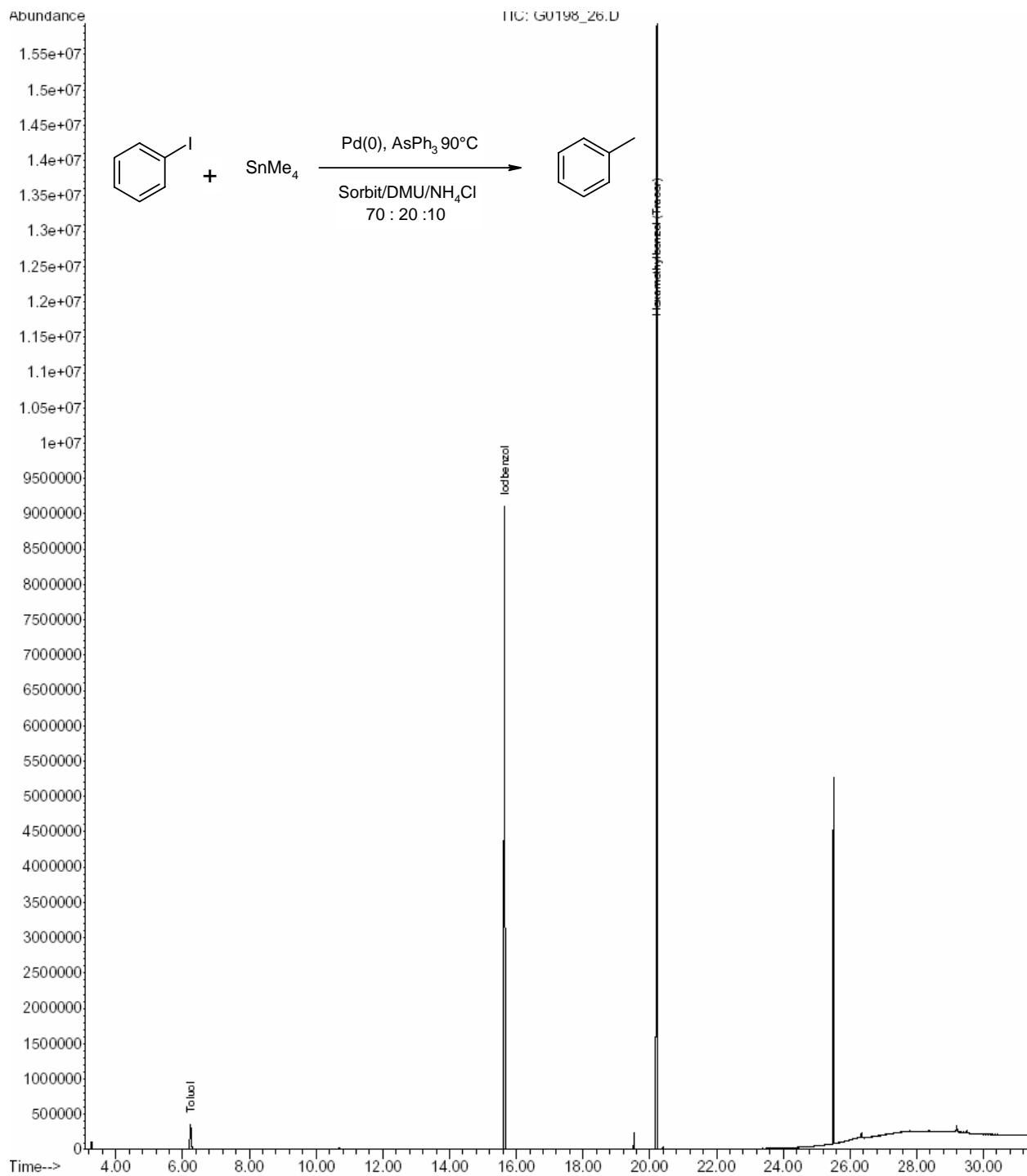


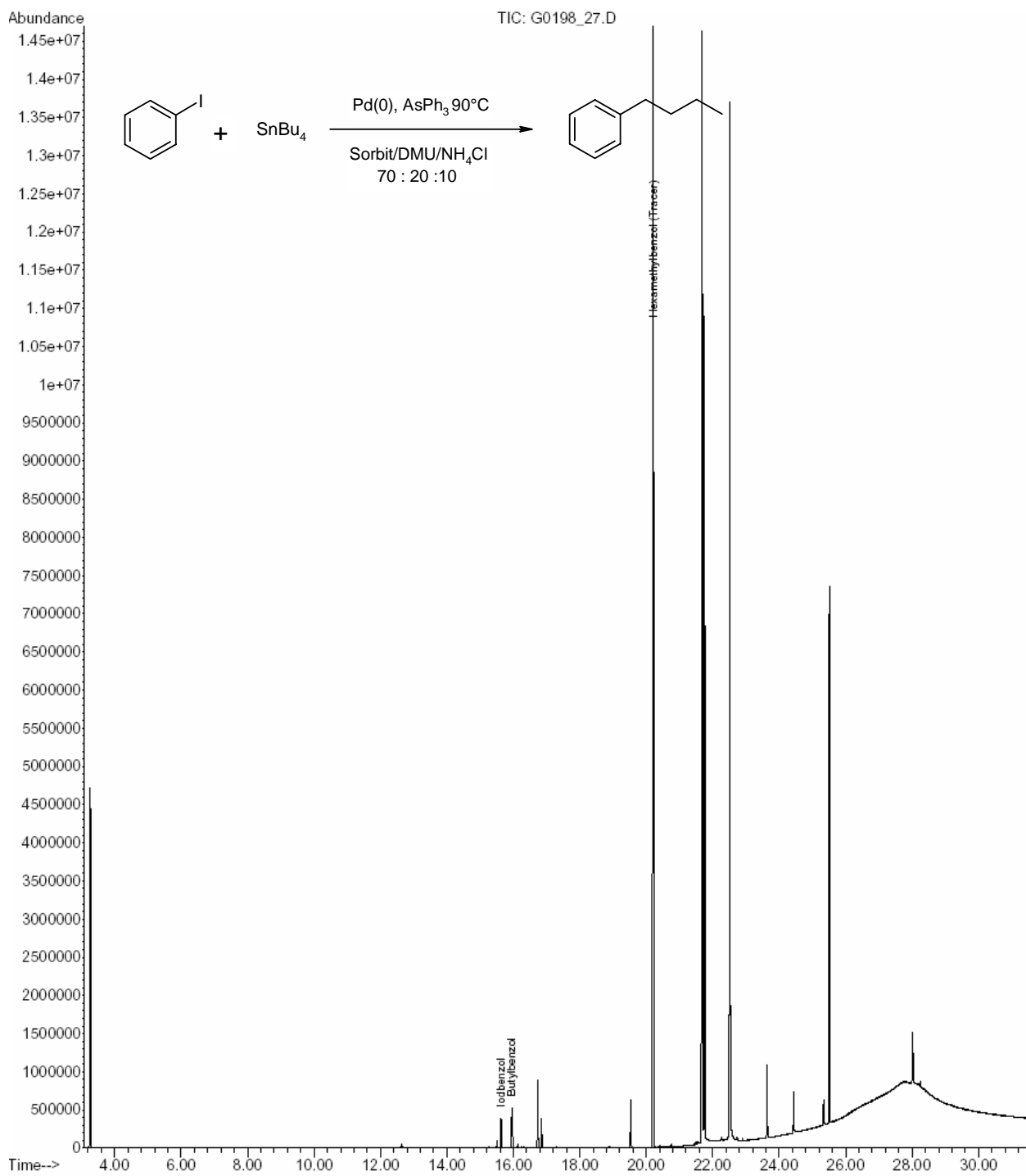












Synthesis of chiral amino acids with metal ion chelating side chains from L-serine using Negishi cross-coupling reaction**

Abstract:

The scope of the Negishi cross-coupling reaction of organozinc compounds derived from chiral amino acids was extended to electron rich iodoanilines and iodobenzylamines as coupling reagents. The protocol allows the direct modification of serine into phenylalanine derivatives bearing metal ion chelating ligands in their side chain, such as amino esters **6** and **7**. The preparation of metal complex labeled peptides, the construction of synthetic receptors and hybrid materials are potential applications of the modified chiral amino acids.

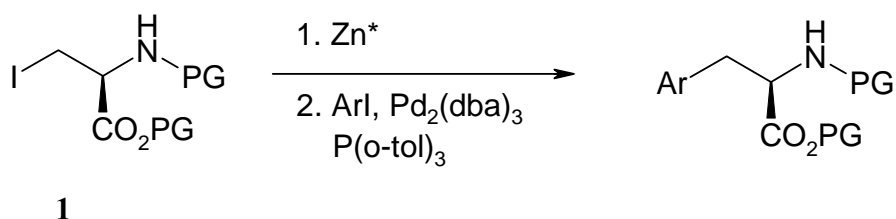
** Michael Kruppa, Giovanni Imperato and Burkhard König: *Tetrahedron* **2006**, 1360-1364

Introduction

The function of peptides and proteins is strongly correlated with their secondary and tertiary structure,¹ which is induced by side chain interactions and determined through the amino acid sequence. Non-proteinogenic amino acids²⁻⁴ and amino acid mimics are widely used to define,⁵ modulate⁶ or switch⁷ the structure of peptides, which may result in changes of their biological properties. One concept⁸ to control a peptide structure is the inter- or intramolecular formation of a metal complex, whereby parts of the peptide function as donor ligands. This requires modified amino acids bearing a strong metal ion chelating ligand for stable complex formation for incorporation into a peptide sequence.⁹ Different research groups used alkylation reactions of lysine or diaminopropionic acid to generate imino diacetic acid (IDA)¹⁰ or bis-(2-picoly)-amine (BPA)¹¹ chelates directly on protein surfaces.

As this modification of amino acid side chains is limited to a certain kind of chelates a more general solution to transform natural amino acids into metal ion chelating amino acids is desired.

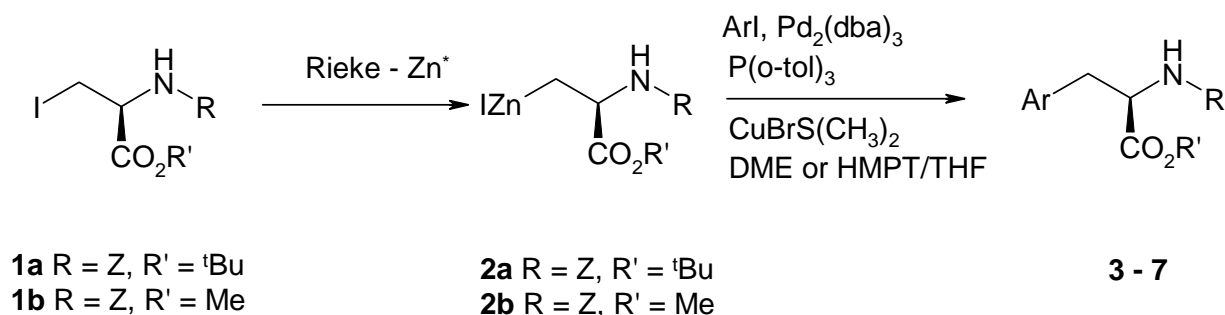
Jackson already showed that palladium-catalyzed coupling of the organozinc compound derived from **1**¹² with aryl iodides is a feasible route to derivatives of phenylalanine (Scheme 1).¹³ We extend the scope of this reaction to phenylalanine derivatives bearing p-NH₂ (**4**), p-NH-Boc (**5**), and p-Me (**3**) aryl substituents and report the efficient synthesis of the non-natural chiral amino acids **6** and **7** having protected IDA and cyclen metal ion chelating ligands in their side chain.



Scheme 1. Palladium-catalyzed coupling of aryl iodides with **1**.

Results and discussion

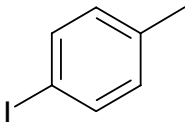
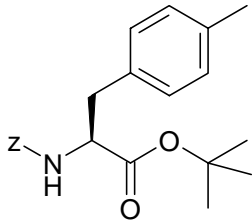
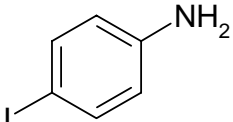
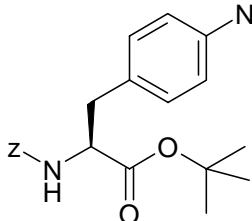
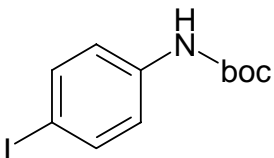
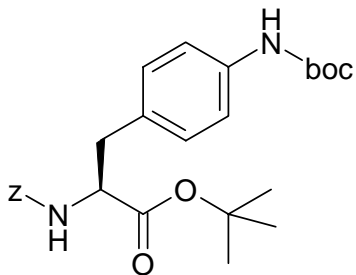
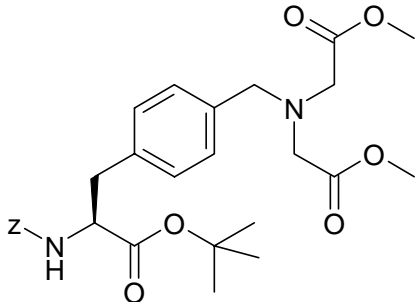
So far, no Negishi coupling¹⁴ reaction has been reported for alkylorganozinc compounds with p-iodoaniline derivatives as reactants.¹⁵ Previous preparations of the unnatural amino acid H-p-NH₂-Phe-OH and protected derivatives of it used either the reduction of p-nitrophenyl alanine¹⁶ or Staudinger reactions¹⁷ of p-azidophenyl alanine. The required iodo precursors **1a**^{18,19} and **1b**²⁰ were synthesized from serine. The corresponding organozinc reagents **2a** and **2b** were obtained by direct insertion of freshly prepared Rieke zinc.²¹ The alternative method of zinc dust activation by Me₃SiCl in DMF was in our hands not as efficient as the use of Rieke zinc.²² The disappearance of the black zinc indicates the complete conversion by insertion reaction (Scheme 2).²³



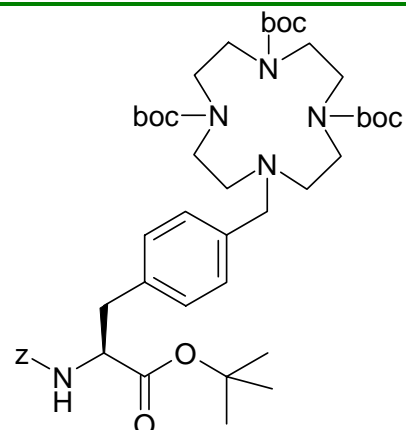
Scheme 2. Preparation of the organozinc reagents **2a** and **2b** and their coupling with aryl iodides.

The reaction conditions of the palladium-catalyzed coupling reaction were optimized using organozinc reagent **2a** and p-iodotoluene and p-iodoaniline as aryl iodides. While p-iodotoluene gave 66% yield of the coupling product (Table 1, entry 1) using DME as solvent with 0.1 equiv CuBr·SMe₂,¹⁸ the more electron rich p-iodoaniline requires a solvent mixture of HMPT and THF (1:1) to give 73% of Z-p-NH₂-Phe-OtBu **4** (Table 1, entry 2).

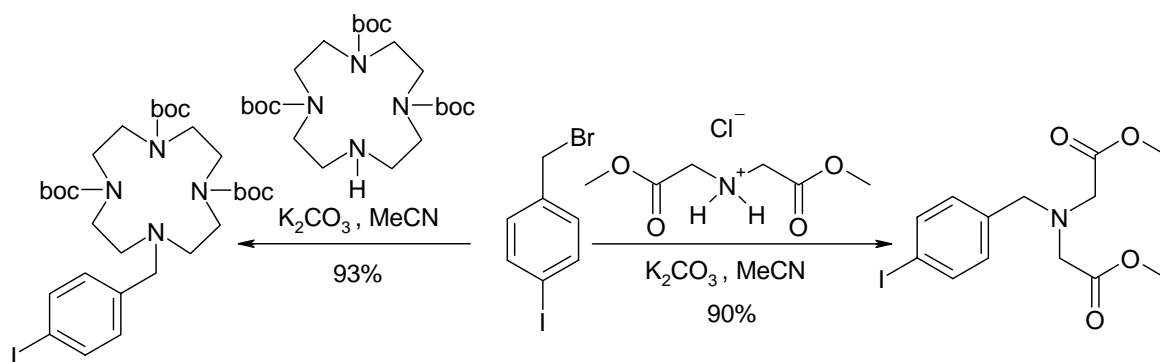
Table 1. Palladium-catalyzed synthesis of the Phe derivatives **3–7**

Entry	iodoaniline	Ar-I	Solvent	Yield %	Product
1	2a		DME	66	
2	2a		HMPT/THF 1 : 1	73	
3	2b		HMPT/THF 1 : 1	75	
4	2a	9	HMPT/THF 1 : 1	65	

5 2b 8 HMPT/THF 86
1 : 1



To apply the method to the synthesis of metal chelating chiral amino acids, aryl iodide substituted protected metal chelates were prepared starting from p-iodobenzyl bromide. Methyl imino diacetate and trifold Boc-protected cyclen²⁴ were alkylated in good yield giving aryl iodides **8** and **9** (Scheme 3). Applying the same conditions as used for the coupling of p-iodoaniline, ID derivative **6** was obtained in moderate 65% yield (Table 1, entry 4). Negishi coupling of aryl iodide **8** with iodoalanine **2a** gave cyclen-modified amino acid **7** in good yield of 86% (Table 1, entry 5).



Scheme 3. Synthesis of aryl iodides **8** and **9**.

Conclusion

We have extended the scope of the Negishi cross-coupling reaction of organozinc compounds derived from chiral amino acids to electron rich iodoanilines and iodobenzylamines as coupling reagents. This allows now the direct modification of serine into phenylalanine derivatives **4** and **5** and amino esters **6** and **7**, bearing metal ion chelating ligands in their side chain. Such and similar modified chiral amino acids are useful for the preparation of peptides labeled with metal complexes as binding sites or probes, for the construction of synthetic receptors and hybrid materials having a peptide backbone and metal complex functionality.

Experimental

General procedure for the generation of organozinc reagents **2a** and **2b**

Rieke zinc was prepared from ZnCl₂ using a catalytic amount of naphthalene: to a Schlenk tube charged with finely divided lithium (1% Na) (3.0 mmol), naphthalene (0.3 mmol) and 2 mL of anhydrous THF (distilled from benzophenone–sodium ketyl under N₂) or DME (in case of Z-p-Me-Phe-OtBu **3**) under argon a solution of anhydrous zinc chloride [1.5 mmol in 2 mL of THF or DME (in case of Z-p-Me-Phe-OtBu **3**)] was transferred via syringe. The mixture was stirred vigorously until all lithium was consumed (0.5 h). To the Rieke zinc suspension under argon a solution of iodoalanine (1.28 mmol) in 3 mL of DME (in case of Z-p-Me-Phe-OtBu **3**) or THF was added via syringe. The exothermic reaction was completed in 5 min (the end of reaction is indicated when the black zinc disappeared). The mixture was stirred for an additional 0.5 h.

Tri-tert-butyl-10-(p-iodo-benzyl)-1,4,7,10-tetraaza cyclododecane-1,4,7-tricarboxylate (**8**).

p-Iodobenzylbromide (0.5 g, 1.7 mmol) was dissolved in 35 mL of MeCN. Trifold-Boc protected cyclen (1 g, 2.2 mmol) and K₂CO₃ (1.21 g, 8.8 mmol) were added, and after completion of the reaction the reaction mixture was filtered and concentrated. The crude product was purified by chromatography on silica gel (hexanes/dichloromethane = 5:1 then AcOEt) giving **8** (1.09 g, 93%) as a colorless solid, mp = 75–77 °C. R_f (AcOEt) = 0.84; ¹H NMR (CDCl₃, 300 MHz): δ = 1.25–

1.56 (m, 27H), 2.39–2.78 (m, 4H), 3.11–3.73 (m, 14H), 7.00 (d, J=8.2 Hz, 2H), 7.61 (d, J=8.2 Hz, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ = 28.5, 28.7, 47.9, 50.0, 54.8, 55.5, 56.7, 79.5, 92.8, 132.2, 136.7, 137.2, 155.4, 155.7, 156.1; LR-MS (ESI/DCM/MeOH+10 mmol/L NH₄OAc): m/z=689 [(M+H)⁺].

Methyl [(4-iodo-benzyl)-methoxycarbonylmethylamino]-acetate (9).

Dimethyl iminodiacetate hydrochloride (0.87 g, 4.4 mmol) and NaH (60% suspension) (0.18 g, 4.4 mmol) were dissolved in 35 mL of MeCN and stirred for 5 min. K₂CO₃ (2.42 g, 17.5 mmol) and p-iodobenzylbromide (1 g, 3.4 mmol) were added to this suspension. After completion of the reaction, the mixture was filtered and concentrated. The crude product was purified by chromatography on silica gel (hexanes/dichloromethane = 5:1 then AcOEt) yielding **9** (1.49 g, 90%) as a colorless oil. R_f (hexanes/dichloromethane = 5:1) = 0.44; ¹H NMR (CDCl₃, 300 MHz): δ = 3.52 (s, 4H), 3.68 (s, 6H), 3.84 (s, 2H), 7.13 (d, J=8.2 Hz, 2H), 7.62 (d, J=8.2 Hz, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ = 51.6, 54.1, 57.3, 92.9, 130.7, 137.2, 137.8, 171.5; LR-MS (CI/NH₃): m/z=378 [(M+H)⁺].

Z-p-Me-Phe-OtBu 3.

A Schlenk flask was charged with p-iodotoluene (0.34 g, 1.5 mmol), Pd₂(dba)₃ (40 mg, 2.5 mol%), P(o-tol)₃ (47 mg, 10 mol%), CuBr·DMS (32 mg, 0.1 equiv) and 4 mL of DME. At -10 °C a solution of the organozinc derivate of Z-I-Ala-OtBu (1.2 mmol) in 4 mL of DME was added. The reaction mixture was slowly allowed to warm to room temperature over night. The reaction mixture was concentrated under argon and the solvent was removed in vacuum. AcOEt was added and the organic phase was washed twice with water and brine, the combined organic layers were dried over MgSO₄ and concentrated. The crude resulting oil was purified by chromatography on silica gel (hexanes/AcOEt=4:1) affording **3** (0.31 g, 66%) as a colorless solid, mp=51–52 °C. R_f (hexanes/AcOEt = 4:1) = 0.28; [α]²⁰ +17.0 in CHCl₃; ¹H NMR (CDCl₃, 300 MHz): δ=1.41 (s, 9H), 2.31 (s, 3H), 3.04 (d, J=5.5 Hz, 2H), 4.51 (dt, J=5.9, 8.1 Hz, 1H), 5.10 (s, 2H), 5.21 (d, J=8.2 Hz, 1H), 7.00–7.11 (m, 4H), 7.30–7.39 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz): δ=21.1, 28.0, 37.9, 52.2, 66.8, 82.3, 128.1, 128.5, 129.1, 129.4, 132.9, 136.4, 136.5, 143.4, 155.6, 170.7; LR-MS (ESI/DCM/MeOH+10 mmol/L NH₄OAc): m/z=756 [(2 M+NH₄)C], 387 [(M+NH₄)C], 370 [(M+H)⁺].

Anal. Calcd for C₂₂H₂₇NO₄ (369.46): C 71.52, H 7.37, N 3.79; found C 71.60, H 7.14, N 3.60.

Z-p-NH₂-Phe-OtBu 4.

A Schlenk flask was charged with p-iodoaniline (0.34 g, 1.5 mmol), Pd₂(dba)₃ (40 mg, 2.5 mol%), P(o-tol)₃ (47 mg, 10 mol%), CuBr·DMS (32 mg, 0.1 equiv), and 4 mL of DME. At -10 °C a solution of the organozinc derivate of Z-I-Ala-OtBu (1.2 mmol) in 4 mL of DME was added. The reaction mixture was slowly allowed to warm to room temperature over night. The reaction mixture was concentrated under argon and the solvent was removed under vacuum. AcOEt was added and the organic phase was washed twice with water and brine. The combined organic layers were dried over MgSO₄ and concentrated. The crude resulting oil was purified by chromatography on silica gel (3:2 hexanes/AcOEt=3:2) affording the pure product **4** (0.35 g, 73%) as a yellowish glass. R_f (hexanes/AcOEt=3:2)=0.2; [α]²⁰ +40.0 in CHCl₃; ¹H NMR (CDCl₃, 300 MHz): δ=1.37 (s, 9H), 2.92 (d, J=5.8 Hz, 2H), 3.56 (br s, 2H), 4.41 (dt, J=5.9, 8.1 Hz, 1H), 5.05 (s, 2H), 5.15 (d, J=8.0 Hz, 1H), 6.54 (d, J=8.2 Hz, 2H), 6.87 (d, J=8.2 Hz, 2H), 7.25–7.35 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz): δ=28.0, 37.5, 55.3, 66.8, 82.1, 115.2, 125.8, 128.1, 128.5, 128.6, 130.4, 136.5, 146.3, 155.7, 170.8; LR-MS (ESI/DCM/MeOH+10 mmol/L NH₄OAc): m/z=388 [(M+NH₄)⁺], 371 [(M+H)⁺]. Anal. Calcd for C₂₁H₂₆N₂O₄ (370.45): C 68.09, H 7.07, N 7.56; found C 68.23, H 7.20, N 7.38.

Z-p-Boc-NH-L-Phe-OMe 5.

A Schlenk flask was charged with (4-iodo-phenyl)-carbamic acid tert-butyl ester (0.38 g, 1.2 mmol), Pd₂(dba)₃ (40 mg, 2.5 mol%), P(o-tol)₃ (47 mg, 10 mol%), CuBr·DMS (32 mg, 0.1 equiv), 2 mL of HMPT, and 2 mL of THF. At K10 8C a solution of the organozinc derivate of Z-I-L-Ala-OMe (1.1 mmol) in 2 mL of THF was added. The reaction mixture was slowly allowed to warm to room temperature over night. The reaction mixture was concentrated under argon and the solvent was removed under vacuum. AcOEt was added and the organic phase was washed twice with water and brine. The collected organic layers were dried over MgSO₄ and concentrated. The crude resulting oil was purified via chromatography on silica gel (hexanes/AcOEt=2:1) affording the pure product **5** (0.39 g, 75%) as a solid, mp=65–67 °C. R_f (hexanes/AcOEt=2:1)=0.2; [α]²⁰ +10.0 in

CHCl₃; ¹H NMR (CDCl₃, 300 MHz): δ=1.51 (s, 9H), 2.97–3.13 (m, 2H), 3.71 (s, 3H), 4.57–4.68 (m, 1H), 5.09 (s, 2H), 5.21 (d, J=8.2 Hz, 1H), 7.00 (d, J=8.5 Hz, 2H), 7.27 (d, J=8.2 Hz, 2H), 7.30–7.44 (m, 5H), 7.30–7.39 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz): δ=28.3, 37.5, 52.4, 54.8, 67.0, 80.6, 118.6, 128.1, 128.2, 128.6, 129.9, 130.1, 136.2, 137.4, 152.7, 155.6, 172.0; LR-MS (ESI/DCM/MeOH + 10 mmol/L NH₄OAc): m/z=446 [(M+NH₄)⁺], 429 [(M+H)⁺], 373 [(M+H–C₄H₈)⁺], 329 [(M+H–Boc)⁺].

Anal. Calcd for C₂₃H₂₈N₂O₆ (428.49): C 64.47, H 6.59, N 6.54; found C 64.30, H 6.27, N 6.19.

Z-p-Me(IDA-OMe)-Phe-OtBu 6.

A Schlenk flask was charged with 9 (0.30 g, 1.2 mmol), Pd₂(dba)₃ (40 mg, 2.5 mol%), P(o-tol)₃ (47 mg, 10 mol%), CuBr·DMS (32 mg, 0.1 equiv), 2 mL of HMPT, and 2 mL of THF. At -10 °C a solution of the organozinc derivate of Z-I-Ala-OtBu (1.2 mmol) in 4 mL of THF was added. The reaction mixture was slowly allowed to warm to room temperature over night. The reaction mixture was concentrated under argon and the solvent was removed under vacuum. AcOEt was added and the organic phase was washed twice with water and brine. The collected organic layers were dried over MgSO₄ and concentrated. The crude resulting oil was purified via chromatography on silica gel (hexanes/AcOEt=7:3) affording the pure product 6 (0.41 g, 65%) as a glass. R_f (hexanes/AcOEt=7:3)=0.18; [α]_D²⁰ +14.6 in CHCl₃; ¹H NMR (CDCl₃, 600 MHz): δ=1.42 (s, 9H), 3.09 (d, J=5.7 Hz, 2H), 3.57 (s, 4H), 3.72 (s, 6H), 3.91 (s, 2H), 4.51–4.57 (m, 1H), 5.12 (s, 2H), 5.25 (d, J=7.7 Hz, 1H), 7.13 (d, J=7.5 Hz, 2H), 7.31 (d, J=7.6 Hz, 2H), 7.32–7.40 (m, 5H), 7.30–7.39 (m, 5H); ¹³C NMR (CDCl₃, 150 MHz): δ=27.9, 38.1, 51.5, 53.9, 55.2, 60.4, 66.8, 82.3, 128.1, 128.2, 128.5, 129.1, 129.6, 135.3, 136.0, 136.4, 155.6, 170.5, 171.5; LR-MS (ESI/DCM/MeOH+10 mmol/L NH₄OAc): m/z=529 [(M+H)⁺], 473 [(M+H–C₄H₈)⁺].

Anal. Calcd for C₂₈H₃₆N₂O₈ (528.61): C 63.62, H 6.86, N 5.30; found C 63.79, H 6.91, N 5.20.

Z-p-Me(3-Boc-Cyc)-L-Phe-OMe 7.

A Schlenk flask was charged with 8 (0.19 g, 0.28 mmol), Pd₂(dba)₃ (10 mg, 2.5 mol%), P(o-tol)₃ (12 mg, 10 mol%), CuBr·DMS (8 mg, 0.1 equiv), 2 mL of HMPT, and 2 mL of THF. At -10 °C a solution of the organozinc derivate of Z-I-L-Ala-Ome (0.35 mmol) in 2 mL of THF was added. The reaction mixture was slowly allowed to warm to room temperature over night. The reaction mixture

was concentrated under argon and the solvent was removed under vacuum. AcOEt was added and the organic phase was washed twice with water and brine. The collected organic layers were dried over MgSO₄ and concentrated. The crude resulting oil was purified via chromatography on silica gel (hexanes/AcOEt=3:2) affording the pure product **7** (0.19 g, 86%) as a solid, mp=56–57 °C. R_f (hexanes/AcOEt=3:2)=0.16; [α]²⁰ +40.4 in CHCl₃; ¹H NMR (CDCl₃, 300 MHz): δ=1.42 (s, 9H), 1.47 (s, 18H), 2.53–2.79 (m, 4H), 3.03–3.11 (m, 2H), 3.11–3.50 (m, 8H), 3.57 (br s, 4H), 3.69 (s, 3H), 4.57–4.70 (m, 1H), 5.08 (s, 2H), 5.21 (d, J=7.7 Hz, 1H), 7.02 (d, J=8.0 Hz, 2H), 7.16 (d, J=8.0 Hz, 2H), 7.30–7.44 (m, 5H), 7.30–7.38 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz): δ=28.5, 28.7, 37.9, 47.3, 48.9, 49.5, 50.0, 52.3, 54.8, 56.9, 67.0, 79.3, 79.4, 128.1, 128.2, 128.6, 129.1, 130.3, 130.6, 134.7, 136.7, 155.6, 155.8, 156.1, 171.9; HR-MS (EI/70 eV): m/z=calcd for C₄₂H₆₃N₅O₁₀ 797.4575; found 797.4559±0.62 ppm.

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Supporting information

Z-I-Ala-OtBu (1a):

A 10 ml Schlenk flask was charged under Argon with 300 mg Z-OH-Ala-OtBu, 2,5 ml dry DMF and 1,4 eq. (PhO)₃PMeI. The mixture was stirred over night. After at mixture water/ice was added the DMF solution and Na₂S₂O₄ until the yellow colour disappeared; n-Pentane was added and the mixture washed with a 1 eq. NaOH (solution 1%). After the organic phase washed three time with water and concentrated in vacuum.

The crude product was purified via flash chromatography (8 : 2 n-Pentane AcOEt) affording the pure product 1a (yield 85%).

¹H NMR (CDCl₃, 300MHz): δ = 1.5 (s, 9H), 3.55 (d, 2H), 4.4 (m, 1H), 5.1 (s, 2H), 5.6 (d, 1H), 7.4 (m, 5H); ¹³C (CDCl₃, 75 MHz): δ = 28.0, 54.0, 67.2, 83.5, 128.1, 128.2, 128.5, 136.1, 155.4, 168.1.

LR-MS (ESI/DCM/MeOH + 10 mmol/l NH₄Ac): m/z = 406 [(M+H)], 423 [(M+NH₄Cl)].

Z-I-Ala-OMe (1b):

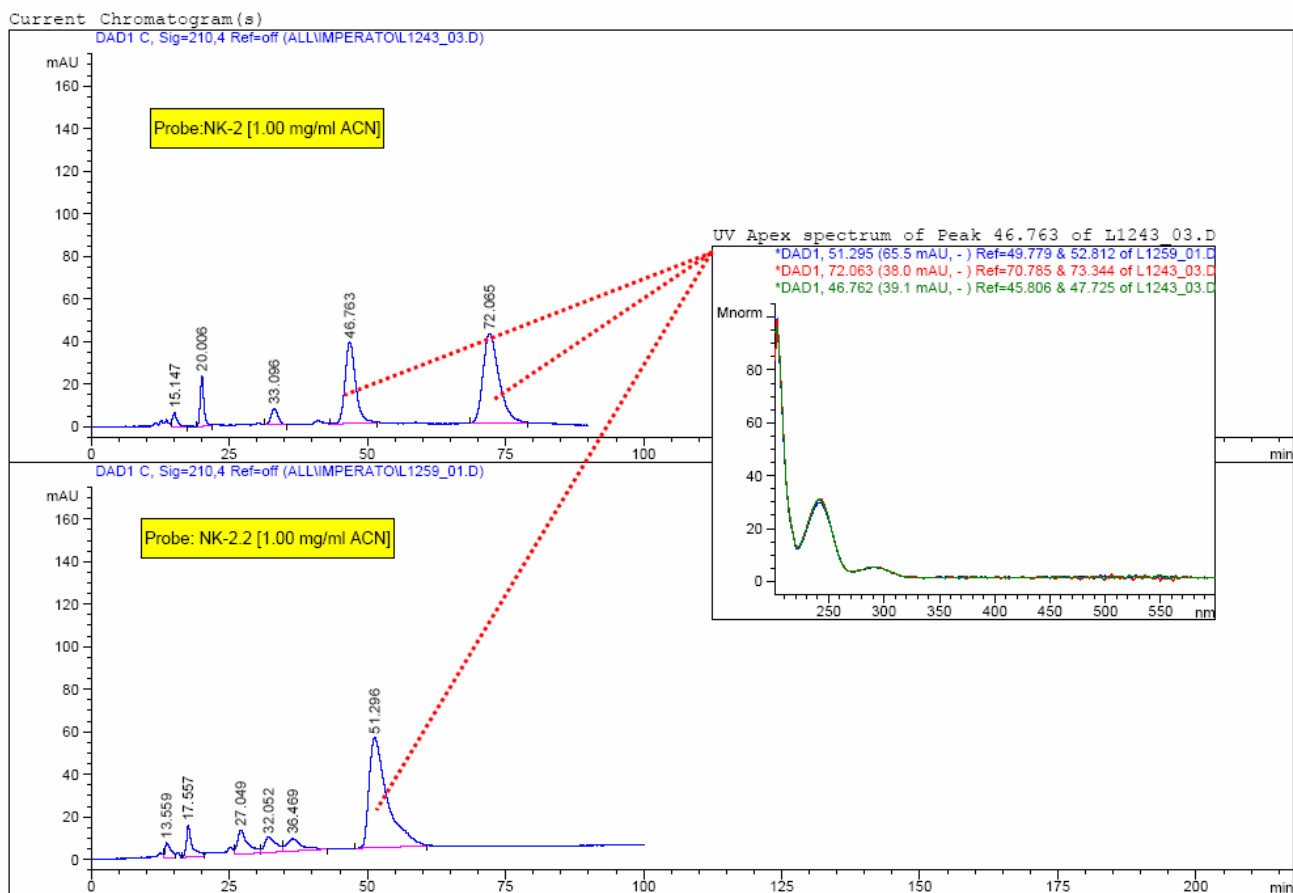
A 10 ml Schlenk flask was charged under Argon with 300 mg Z-OH-Ala-OMe, 2,5 ml dry DMF and 1,4 eq. (PhO)₃PMeI. The mixture was stirred over night. After at mixture water/ice was added the DMF solution and Na₂S₂O₄ until the yellow colour disappeared; n-Pentane/AOEt was added and the mixture washed with a 1 eq. NaOH (solution 1%). After the organic phase washed three time with water and concentrated in vacuum.

The crude product was purified via flash chromatography (8 : 2 n-Pentane AcOEt) affording the pure product 1b (yield 68%).

¹H NMR (CDCl₃, 300MHz): δ = 3.55 (m, 2H), 3.8 (s, 3H), 4.6 (m, 1H), 5.1 (s, 2H), 5.65 (d, 1H), 7.5 (m, 5H); ¹³C (CDCl₃, 75 MHz): δ = 10.5, 53.2, 67.4, 128.8, 129.5, 129.9, 135.9, 155.0, 170.0.

LR-MS (ESI/DCM/MeOH + 10 mmol/l NH₄Ac): m/z = 364 [(M+H)], 375 [(M+NH₄Cl)].

Column: Daicel Chiracel OD-H 250mm. Solution: 30% n-Hexane 70% water. Inj. 3ul/0.3 ml/min. Flow 0.300 ml/min.



Appendix A

Aldol reaction in sugar melting solutions

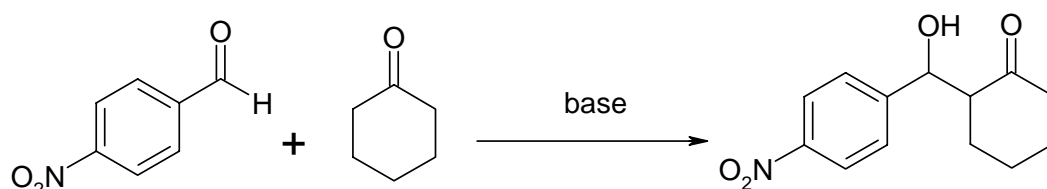
The adol reaction is one of the most important reactions in organic synthesis for the formation of C-C bonds. It is therefore not surprising that a large number of methods have been developed for this transformation.

Aldol reaction has been classically conducted in the presence of strong base or acid. However under such strong conditions the synthesis of desired aldol product is plagued by the concomitant α,β -unsaturated ketone, formed through aldol dehydration, and other side products from, self-condensation of the ketone. Alkali and earth alkali metal salts including Na_2CO_3 have been used to promote aldol reaction and recently prolin, prolin-functionalized and amines catalyzed aldol reaction have been reported.

In general, most methodologies available for the asymmetric adol reaction fall in one of the following categories: (a) the chiral auxiliary-assisted aldol reaction based on the use of stoichiometric quantities of the chiral appendage; (b) chiral Lewis acid-catalyzed Mukaijama-type and chiral Lewis base-catalyzed aldol reaction; (c) heterobimetallic bifunctional Lewis acid/Brønsted base-catalyzed direct aldol reactions; and (d) aldol reaction catalyzed by Aldolase enzymes and antibodies. A significant characteristic of the latter two methodologies is the employment of unmodified carbonyl compounds as donor substrates.

Herein we present the aldol reaction of unmodified ketone with reactive aldehyde bearing strong electron-withdrawing groups in melting sugar solutions catalysed by NaCO_3 , prolin and prolin-salts.

Table 4: Exploration of various sugar melting mixture as solvents of the direct aldol addition reaction of cyclohexenone and 4-Nitrobenzaldehyde



entry	“Solution”	Na ₂ CO ₃	Prolin	Prolin K	Prolin Li
A	Fruct/Urea/NaCl 70:20:10	yield 47% syn : anti 1.25 : 1	yield 30% syn : anti 3.2 : 1	-----	yield 30% syn : anti 3.5 : 1
B	Glucose/Urea/NH₄Cl 60:30:10	yield 52% syn : anti 1,25 : 1	-----	-----	-----
C	Sorbit/DMU 40 : 60	-----	yield 15% syn : anti 10 : 1	yield 15% syn : anti 11 : 1	-----
D	water	yield 98% syn : anti 1 : 7	yield 85% syn : anti 1 : 3	-----	-----
E	[bmim]PF₆ ^{1,a}	-----	yield 91% syn : anti 1 : 20	-----	-----
F	water	yield 94% ^b syn : anti 1 : 5	yield 65% ^c syn : anti 1 : 2	yield ^{2,d} syn : anti 1 : 5.5	
G	PBS ^{3,e}	-----	yield 50% syn : anti 1 : 1		
H	SDS ^f	-----	yield 78% syn : anti 1 : 3		

¹ aldolisation of *p*-CF₃-benzaldehyde with cyclohexenone

² base zn-Prolin

³ 0.01M phosphate buffer, 2.7 mM KCl, 137 mM NaCl, pH = 7.4, 0.1 equivalent SDS

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^c K. Sakthivel, W. Notz, T. Bui, C.F. BarbasIII; *J. Am. Chem. Soc.*; **2001**; 5260-5267

^d Yin-Su Wu, Wei-Yan Shao, Chuan-Qi Zheng, Zhong-Li Huang, Jiwen Cai, Qui-ying Deng; *Helvetica Chimica Acta*; **2004**; 1377-1384

^e A. Cordova, W. Notz, C.F. BarbasIII; *Chem. Comm.*; **2002**; 3024-3025

^f Yi-Yuan Peng, Qiu-Ping Ding, Zucheng Li, Peng George Wang, Jin-Pei Cheng, *Tetrahedron Letter*; **2004**; 3871-3875

As shown in table 4 we have aldol reaction only in Fructose, Glucose mixture (entry A and B) using as base NaCO_3 and proline; instead of in the mixture Sorbit/Dimethylurea the reaction run only using proline as base (entry C). In all case the yield are low, we can suppose that at 90°C the retro aldol reaction take place. Otherwise no α,β -unsaturated ketone, formed through aldol dehydration other polycondensation product is observed.

Is important note too that in the melting sugar mixture independently as the used base the syn diastereoisomer is always the major product, the ratio syn : anti change between 1.25 : 1 using mixture Fruct/Urea/ NaCl or Glucose/Urea/ NH_4Cl (base NaCO_3 , entry A and B) and 10 : 1 using Sorbit/ NH_4Cl (base prolin entry C).

Recently reports have been appeared to explain the mechanism of the aldol reaction of cyclohexenone and substituted bezaldehyde catalyzed with several base. All this study demonstrates that in the sterically controlled transition state the thermally stable anti isomer is preferable.

We explain the fact that in our experiment the syn is the major product by a re-equilibration at high temperature. In figure 5 the NMR spectra at room temperature showing the ratio syn : anti is 1 : 7 is reported; while in figure 6 shows the NMR spectra after heating at 80°C in presence of NaCO_3 as base the ratio syn : anti is 1 : 3.

Careful amounts of the products gave an indication for chiral induction from the chiral melt to reaction product.

Fig.5 NMR spectrum at room temperature in CDCl₃ of diastereoisomeric mixture of **4** and **5**

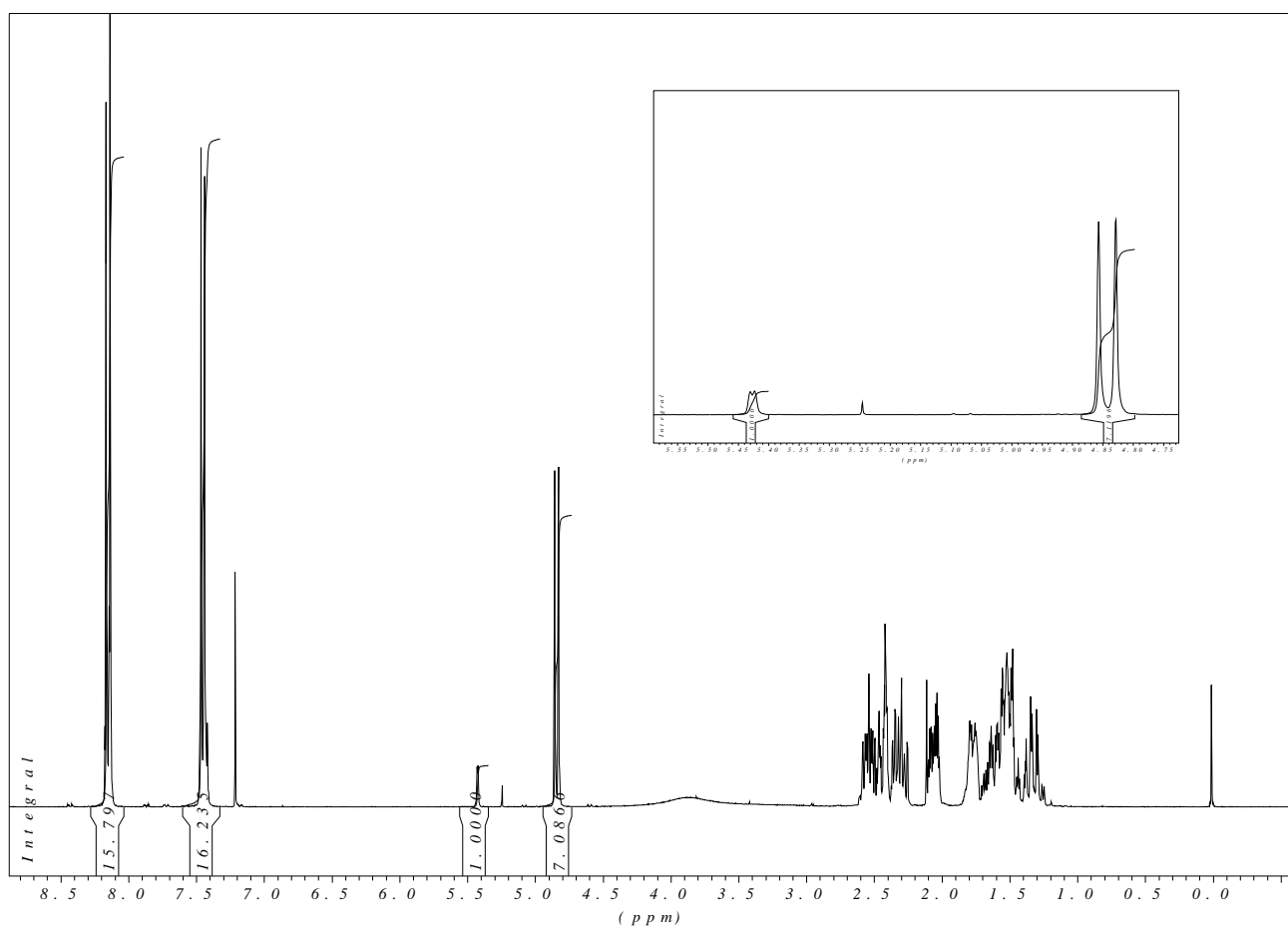


Fig.6 NMR spectrum after heating at 80°C in CDCl₃ of diastereoisomeric mixture of **4** and **5** in presence of NaHCO₃

