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Low melting mixtures based on β-cyclodextrin derivatives and *N*,*N*′-dimethylurea as solvents for sustainable catalytic processes†

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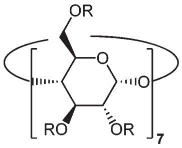
β-Cyclodextrin series and *N*,*N*′-dimethylurea formed low melting mixtures able to immobilize organometallic species based on sulfonated phosphanes. Hydroformylation and Tsuji–Trost reactions were efficiently performed in these new solvents which led to new recyclable catalytic systems.

Introduction

Recently, a new family of solvents, so-called deep eutectic solvents (DESs) or low melting mixtures (LMMs), have emerged in the current literature.[1–5] They are prepared by mixing high-melting-point starting materials, which form a liquid by hydrogen-bond interactions. They are generally cheap and easy to prepare from readily available materials. Among them, LMMs based on carbohydrates have been also described.[6] The latter are environmentally benign, because they are easily biodegradable, relatively non-toxic, and are available from bulk renewable resources without numerous energy consuming modification steps. Some LMMs based on carbohydrates and organometallic catalysis have already been combined with success. In 2006, König and co-workers investigated the palladium-catalyzed Suzuki coupling of phenyl boronic acid with aryl bromides in different carbohydrates–urea–inorganic salts mixtures.[7] In the same publication, they have also reported the hydrogenation of methyl α-cinnamate in various carbohydrate–urea melts in the presence of Wilkinson's catalyst. The Stille cross-coupling in various sugar–urea–salt melts was also investigated.[8] Next, the same group highlighted that palladium-catalyzed Heck coupling can be successfully performed in low melt composed of D-mannose and *N*,*N*′-dimethylurea (DMU).[9] In this context, we propose a new family of LMMs based on DMU and β-cyclodextrin (β-CD) derivatives for an organometallic catalysis application. Indeed, β-CD is a cyclic carbohydrate composed of seven D-glucopyranose units some of whose hydroxyl groups could form hydrogen bonds with DMU. In addition, the CD family allowed increasing catalytic activity and/or selectivity during organometallic processes by playing the role of mass transfer agents[10,11] or ligands.[12–14] In this article, we described new LMM mixtures easily obtained by the simple association of β-CD or its derivatives (Scheme 1) and DMU. Some of these mixtures were evaluated as solvents in rhodium-catalyzed hydroformylation reaction and in palladium-catalyzed cleavage of allylcarbonates (Tsuji–Trost reaction).



β-CD: R = -H (100 %)
CRYSME-β-CD: R = $-CH_3$ (23 %) or -H (77 %)
RAME-β-CD: R = $-CH_3$ (60 %) or -H (40 %)
TRIME-β-CD: R = $-CH_3$ (100 %)
HP-β-CD: R = $-CH_2CHOHCH_3$ (20 %) or -H (80 %)
HTMAP-β-CD: R = $-CH_2CHOHCH_2N(CH_3)_3^+$, Cl^- (16 %) or -H (84 %)

Scheme 1 Structure of CDs used.

Results and discussion

DMU was mixed with different CDs at a weight ratio of 70/30 by using a mortar and pestle. Each preparation was then introduced into a Schlenk tube with a stirring bar and gradually heated with an oil bath until the melting of the mixture was visually observed (see Fig. 1 as an illustration). Note that the melting points of all the CDs are superior to 200 °C whereas that of DMU is equal to 104 °C. Table 1 summarizes the melting temperatures of these mixtures. For TRIME-β-CD, no melt was observed. This behaviour could be due to the inability of this CD to form hydrogen bonds with DMU. All other mixtures gave a clear melt around 90 °C. These temperatures were also determined by differential scanning calorimetry (DSC; see Table 1 and ESI†). The obtained temperatures by the two methods are in accordance. To evaluate the thermal

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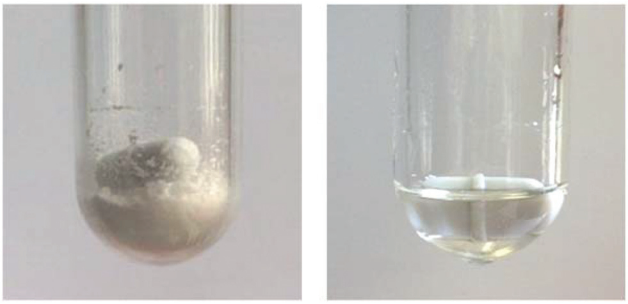


Fig. 1 DMU–RAME-β-CD (w/w (%): 70/30) at room temperature (left) and at 90 °C (right).

Table 1 Description of the various solvents based on DMU–CDs mixture (70/30, w/w (%))[a]

CD	Melting point[b] (°C) (visually)	Melting point[b] (°C) (DSC)	Viscosity (cP) at 90 °C
β-CD	90	91	1165
CRYSME-β-CD	90	92	445
RAME-β-CD	90	91	235
TRIME-β-CD	No melt	No melt	—
HP-β-CD	85	91	205
HTMAP-β-CD	80	87	495

[a] All these CDs are commercially available except HTMAP-β-CD synthesized as described in the literature. These CDs were used without drying (see the Experimental part). [b] Melting points are at normal pressure in air.

stability of the melts, all the mixtures were heated overnight at 90 °C and then the mixtures were left at room temperature for 10 hours. This cycle was repeated for 7 days without any decomposition of DMU or CD. The viscosities of the LMMs are important data that need to be addressed for application in a catalytic process. Consequently, these viscosities were determined at 90 °C (Table 1).

The highest value was obtained for the melt DMU–β-CD whereas the lowest for DMU–HP-β-CD. These viscosities are relatively high (>100 cP). These values are attributed to the presence of an extensive hydrogen bond network between each component. As the viscosities are mainly affected by the water content, viscosity measurements were performed by varying the percentage of water in the LMMs (up to 10% – Fig. 2). As expected, the value decreased when water was added. All the values of viscosity are in the same order above 8% of water in the LMMs.

Hydroformylation and Tsuji–Trost reactions have been selected to demonstrate the interest of these new solvents. For both these reactions, the widespread water-soluble ligand tris(*m*-sulfonatophenyl)phosphine trisodium salt (TPPTS) has been chosen to maintain the transition metal (rhodium or palladium) in the catalytic layer.[15] Note that this polar ligand is well soluble in all the mixtures based on DMU–CD (up to 3% w/w). The integrity of this ligand in these solvents was controlled by ^{31}P NMR experiments by heating–cooling cycles. As an illustration, a fraction of the solvent DMU–RAME-β-CD containing TPPTS was dissolved in D_2O after 10 heating–cooling cycles (from room temperature to 90 °C and then to room temperature) under nitrogen. The ^{31}P{^{1}H} NMR spectrum exhibited a singlet at −6.9 ppm in the mixture DMU–RAME-β-CD–D_2O (see ESI†). This spectrum showed no modification of NMR signal before and after these heating–cooling cycles. These experiments demonstrated that TPPTS is not oxidized in these media.

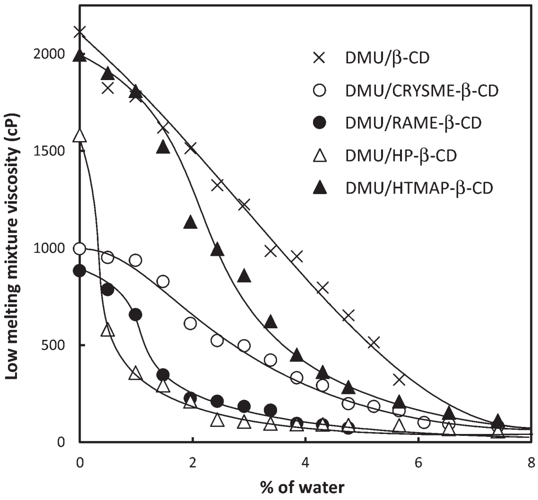
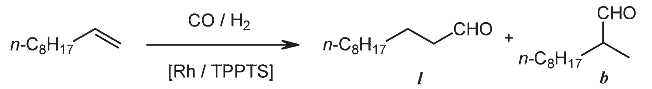


Fig. 2 Viscosity of DMU–CD (w/w (%): 70/30) low melting mixtures at 90 °C *vs.* percentage of water in DMU–CD.

First, the role played by various solvents based on DMU and CD (w/w (%): 70/30) was investigated in a hydroformylation reaction catalyzed by the Rh/TPPTS combination at 90 °C (Table 2). 1-Decene was chosen as a solvent-insoluble substrate in order to obtain a biphasic system.[16] For the combination DMU–CD (Table 2, entries 1–5), the conversions after one hour were situated between 37% and 99%. The values clearly depended on the nature of the CDs. In the presence of a cationic CD (HTMAP-β-CD), the conversion was the lowest (entry 1). The best results were obtained with native and methylated CDs. More precisely, the methylation degree of the CD affected the outcome of the reaction since the more the CD was methylated, the more the conversion was. The best result was obtained in the case of DMU–RAME-β-CD with a conversion of 99% (entry 5). It is worth mentioning that addition of water to the DMU–RAME-β-CD mixture has no beneficial effect on the conversion (compare entry 5 with entries 6 and 7). Indeed, when 10% or 20% of the DMU–RAME-β-CD mixture was replaced by water, the conversion decreased. This behavior was surprising since addition of water decreased the viscosity. The selectivity in aldehydes was high (91–95%) in each case and the linear to branched aldehydes ratio (l/b) was equal to 2.3 (compare entries 1–5). This value is classical for hydroformylation experiments performed with TPPTS as a ligand in polar media and indirectly proved the integrity of the catalytic system.[17] In order to ensure that the reactants and/or products did not react with the solvent, ^{1}H NMR experiments were performed at the end of the reaction. The data clearly

Table 2 Rhodium-catalyzed hydroformylation of 1-decene in various solvents[a]

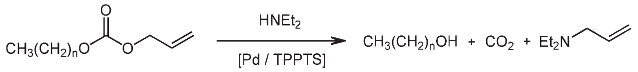


Entry	Solvent (w/w (%): 70/30)	C[b] (%)	S[c] (%)	l/b[d]
1	DMU–HTMAP-β-CD	37	91	2.3
2	DMU–HP-β-CD	43	92	2.3
3	DMU–β-CD	66	93	2.3
4	DMU–CRYSME-β-CD	76	94	2.3
5	DMU–RAME-β-CD	99	95	2.3
6[e]	DMU–RAME-β-CD	76	96	2.4
7[f]	DMU–RAME-β-CD	34	96	2.3
8[g]	DMU–RAME-β-CD	99	90	2.6
9	DMU–choline chloride	36	90	2.4
10	DMU–water	27	86	2.6
11	Water–RAME-β-CD	17	88	1.9
12[h]	Water	9	42	2.9

[a] *Experimental conditions*: $Rh(acac)(CO)_2$ = 21 μmol (1 eq.), TPPTS = 105 μmol (5 eq.), 1-decene = 42 mmol (2000 eq.), solvent = 6 g, 90 °C, 50 bar CO–H_2 (1/1), 1500 rpm, reaction time = 1 h. All CDs were used without drying (see Experimental part). [b] C = 1-decene conversion. [c] S = aldehydes selectivity. [d] Branched aldehyde (b) is racemic. [e] 10% of the DMU–RAME-β-CD mixture was replaced by 0.6 g of water. [f] 20% of the DMU–RAME-β-CD mixture was replaced by 1.2 g of water. [g] TPP was used instead of TPPTS – reaction time = 30 min. [h] Only 6 g of water.

indicated that no cross reaction was observed. This point is very important since the integrity of each partner is preserved during the catalytic experiments in these new solvents. Another experiment was performed in DMU–RAME-β-CD solvent by using triphenylphosphane (TPP) instead of TPPTS as a ligand (entry 8). The reaction is completed after only 30 minutes instead of 1 hour in the case of TPPTS. Nevertheless, the organic layer was coloured, suggesting the presence of catalytic species. This observation was confirmed by ^{31}P NMR experiments performed on an organic layer which revealed that 30% of the initial amount of TPP was transferred to the organic layer. These experiments undoubtedly showed that a part of rhodium was lost in the organic layer. This behaviour is not in accordance with the specifications required for an application in a biphasic organometallic catalytic process since the product is polluted by the catalyst. This result showed that the use of a polar ligand such as TPPTS is preferable since the extraction of this ligand in the organic layer is completely avoided as demonstrated by ^{31}P NMR experiments. As comparative data, another set of experiments was performed in DMU–choline chloride, DMU–water, water–RAME-β-CD or water (entries 9–12) as a solvent. In each case, the conversion was lower compared to the experiments performed in DMU–CD mixtures. So, the composition of the solvent significantly affected the outcome of the reaction and the best result in terms of catalytic activity and selectivity was obtained in the case of the DMU–RAME-β-CD mixture (entry 5).

Secondly, the palladium-catalyzed cleavage of allylcarbonates (Tsuji–Trost reaction) was chosen to extend the scope of DMU–RAME-β-CD as a solvent for catalytic processes. The cleavage of allyloctylcarbonate was carried out at 90 °C under nitrogen with diethylamine as an allyl scavenger (Scheme 2).[18] Quantitative conversion of allyloctylcarbonate was observed in only five minutes. NMR control experiments were performed and no side-product was observed. In order to evaluate the stability of the catalytic system, recycling experiments were performed. The work-up was extremely simple. At the end of the reaction, the biphasic system was cooled down to room temperature. The DMU–RAME-β-CD phase became solid and the organic layer was simply removed under air-atmosphere without special precaution (Fig. 3). The new fresh organic layer was added to the remaining DMU–RAME-β-CD phase and this mixture was heated at 90 °C under nitrogen to perform the recycling experiment (Fig. 4 – Exp. Cond. 1). The catalytic layer remained active without loss of activity during 4 cycles. Then to test the robustness of the catalytic system, this DMU–RAME-β-CD phase containing the catalyst was left overnight in the solid state under air-atmosphere and was used the next day for another set of recycling experiments performed with allyloctadecylcarbonate instead of allyloctylcarbonate (Fig. 4 – Exp. Cond. 2). Interestingly, the catalytic layer remained active without loss of activity during 4 cycles. This result showed not only the stability of the catalytic system under air-atmosphere in the solid state but also the efficiency of this system even if a more apolar substrate was used. A third condition was tested to evaluate the stability of the catalyst under more drastic conditions. After removing the organic layer, the DMU–RAME-β-CD phase used for the first 8 runs and containing the catalyst was stirred and heated under air-atmosphere at 90 °C for 15 minutes. Then, a new fresh organic layer of allyloctadecylcarbonate was added to the DMU–RAME-β-CD phase and this mixture was heated at 90 °C under air-atmosphere instead of a nitrogen atmosphere (Fig. 4 – Exp. Cond. 3). The conversion dramatically decreased up to 15% and became null for the



Scheme 2 Palladium catalyzed cleavage of allyloctylcarbonate (*n* = 7) or allyloctadecylcarbonate (*n* = 17).

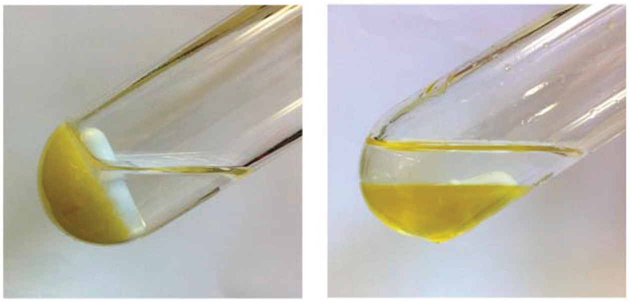


Fig. 3 Reaction media of Tsuji–Trost reaction at room temperature (left) and at 90 °C (right).

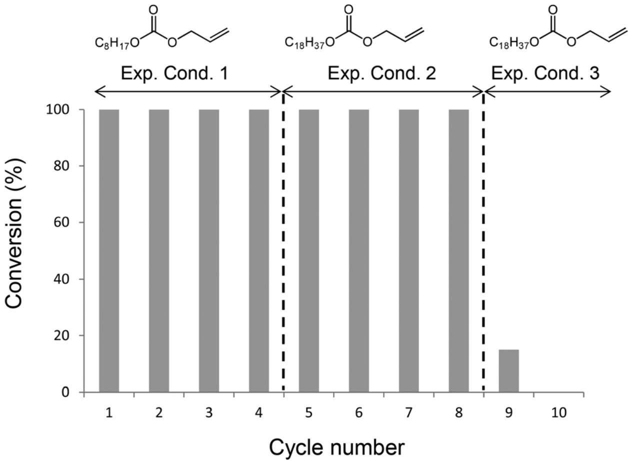


Fig. 4 Recycling experiment for palladium catalyzed cleavage of allylalkylcarbonates. *Experimental condition* 1: $Pd(OAc)_2$ = 8 μmol (1 eq.), TPPTS = 70 μmol (9 eq.), allyloctylcarbonate = 800 μmol (100 eq.), diethylamine = 2.4 mmol (300 eq.), DMU–RAME-β-CD (w/w (%) = 70/30) = 1.4 g, heptane = 1.4 g, 90 °C, 1200 rpm under N_2, reaction time = 5 minutes. *Experimental condition* 2: The same conditions as in 1 except allyloctadecylcarbonate instead of allyloctylcarbonate. *Experimental condition* 3: The same conditions as in 2 except under air instead of under N_2.

following experiment. In this case, due to the heating under air, O_2 dramatically diffused into the DMU–RAME-β-CD phase and TPPTS was transformed to its oxide. Consequently, the latter was unable to stabilize palladium species that led to a deactivation of the catalytic system. These experiments highlighted two interesting behaviours. Firstly, the catalyst species dissolved in DMU–RAME-β-CD is recyclable at least 8 times without loss of activity and allows the change of substrates. Secondly, at room temperature, the catalyst species maintained in the solvent in the solid state was protected against degradation. So, the recycling work-up is very convenient and this kind of solvent offers very simple handling under protective conditions for the catalytic system.

Experimental

Materials

All chemicals were purchased from Fisher Scientific and Aldrich Chemicals in their highest purity. All chemicals were used as supplied without further purification. β-CD and CRYSME-β-CD were provided by Roquette Frères and RAME-β-CD was furnished by Wacker. HTMAP-β-CD was obtained by a chemical modification of β-CD described by Deratani *et al.*[19] HP-β-CD was purchased from Aldrich Chemicals. As commercial CDs are known to contain water, we have determined the percentage of water for each CD.[20] The percentage of water in each CD was determined by heating CD in a Schlenk tube under vacuum (2 h at 80 °C, 2 h at 100 °C and then 2 h at 120 °C). The difference of the weight allowed obtaining the quantity of water. The β-CD, CRYSME-β-CD, RAME-β-CD, HP-β-CD and HTMAP-β-CD contained 10%, 10%, 7%, 6% and 12% of water, respectively. These values corresponded to a percentage of water equal to 3%, 3%, 2.1%, 1.8% and 3.6% for the LMMs based on DMU–β-CD, DMU–CRYSME-β-CD, DMU–RAME-β-CD, DMU–HP-β-CD and DMU–HTMAP-β-CD, respectively.

Organic layers obtained after catalysis experiments were analyzed by ^1H-NMR on a Bruker DRX300 spectrometer (300 MHz for ^1H nuclei) and by gas chromatography on a Shimadzu GC-17A gas chromatograph equipped with a polydimethylsiloxane capillary column (30 m × 0.32 mm) and a flame ionization detector. Perkin-Elmer DSC Pyris 1 apparatus was used for differential scanning calorimetry analysis. All experiments were performed in the temperature range 65–105 °C, at a heating/cooling rate of 5 °C min^{-1}. Three successive cycles were done following the same program. Temperature and heat flow rates were calibrated with a very pure indium standard, whose melting temperature and enthalpy are well known. Data acquisition (onset of the (solid + liquid) equilibria temperatures) and processing were done with Perkin-Elmer's Pyris™ software. A Brookfield Model LVDVII+Pro viscometer with the SC4-25 spindle at 200 rpm was used in this study. Viscosity was measured at 90 °C in a SC4-13RPY sample chamber with an embedded RTD temperature probe. The temperature was controlled with a TC502 circulating bath refrigerated using a programmable controller. The sample volume was slightly adapted to the volume of the sample chamber. The program parameters and results analysis were controlled with the Rheocalc@PC software.

Catalytic experiments

In a typical hydroformylation experiment, $Rh(acac)(CO)_2$ (5.5 mg; 21 μmol; 1 eq.), TPPTS (60 mg; 105 μmol; 5 eq.) and solvent constituents in the solid state (4.2 g of *N*,*N*′-dimethylurea and 1.8 g of RAME-β-CD (w/w(%) = 70/30) for example) were charged into a 25 mL autoclave. Air was replaced by 20 bar of CO–H_2 (1/1), and after heating at 90 °C, the mixture was stirred using a multipaddle unit (1500 rpm) for 1 hour for an incubation period. The stirring was then stopped, and after cooling and depressurization, 1-decene (6 g; 42 mmol; 2000 eq.) was introduced under nitrogen into the autoclave. The medium was heated at 90 °C and then stirred (1500 rpm) for 1 hour at this temperature under 50 bar of CO–H_2 (1/1).

In a typical Tsuji–Trost experiment, $Pd(OAc)_2$ (1.75 mg; 8 μmol; 1 eq.), TPPTS (40 mg; 70 μmol; 9 eq.), *N*,*N*′-dimethylurea (0.98 g) and RAME-β-CD (0.42 g) (w/w (%) = 70/30) were introduced into a Schlenk tube. Then, the reaction mixture was stirred under nitrogen for 1 hour in an oil bath at 90 °C and at 1200 rpm for an incubation period during which the medium became fluid and limpid. After cooling at room temperature, this catalytic layer became quickly solid, and allyloctylcarbonate (0.167 g; 800 μmol; 100 eq.) and diethylamine (0.171 g; 2.4 mmol; 300 eq.) dissolved in heptane (1.4 g) were added to it. After immersion of the Schlenk tube in the oil bath at 90 °C, the solid catalytic layer became quickly liquid again and the biphasic system was then stirred for 5 minutes at 90 °C. After cooling, the organic layer was very easily recovered under air-atmosphere without special precaution and the solid catalytic layer was then recycled after introduction under nitrogen of a new solution of allyloctylcarbonate and diethylamine in heptane.

Conclusions

To summarize, we have reported for the first time the use of LMMs based on β-CD series and DMU as solvents for hydroformylation and Tsuji–Trost reactions. These solvents can be formed by simply mixing the starting materials (commercially available), thus by-passing all problems of purification and waste disposal. They are not volatile solvents and not flammable, making their storage convenient. They are easily recoverable due to the nonexistence of chemical reaction during their formation. They can be prepared from cheap, readily available and toxicologically well characterized starting materials. Thanks to these positive points, these LMMs have now become of growing interest in organometallic catalysis. In both catalytic reactions, the transition metal is efficiently maintained in the solvent by using TPPTS as a polar ligand. In hydroformylation reaction, the use of the solvent DMU–RAME-β-CD allowed to reach higher catalytic activities than those reported for classical systems based on CD in water as a solvent. In the case of Tsuji–Trost reaction, both high catalytic activity and recyclability are obtained. In addition, this solvent offered simple handling and protection of the catalytic species confined in this solvent in the solid state. We are currently further studying other LMMs based on various CDs by varying the size (α- or γ-CD) and/or the nature of the substituents for applications in organometallic catalysis. We will also explore the capacity of CDs to form inclusion complexes with organic substrates in these LMMs.

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