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NMR relaxation time measurements of solvent effects in an organocatalysed asymmetric aldol reaction over silica SBA-15 supported proline†

Graziano Di Carmine,[ab] Luke Forster,[b] Simeng Wang,[b]
Christopher Parlett,[bcde] Armando Carlone[*f] and Carmine D'Agostino[*b]

Immobilisation of organocatalysts onto solid supports represents a very promising solution to tackle their low productivity by enabling their reuse. Herein, the use of NMR relaxation measurements, coupled with reaction screening, was used to investigate the effect of solvent interactions with the immobilised catalyst matrix on reactivity in an asymmetric organocatalysed aldol reaction. Important insights for the further development of such complex, yet promising catalytic systems are provided.

Introduction

Organocatalysis has nowadays consolidated its role as an advanced approach to access complex molecules, in a sustainable manner.[1] The field grew at a dramatic pace with a plethora of new reactions and activation modes being developed.[2] Unfortunately, albeit sometimes counterbalanced by economic and environmental factors, the low turnover number (TON) is often a drawback for industrial applications. Researchers have tried to overcome this setback by immobilising catalysts,[3] or recycling them, by engineering highly active catalysts, and combining different types of catalysts synergistically.[4] Among the different approaches, the most promising way seems to be the heterogenisation of the organocatalyst itself. By anchoring the organocatalyst onto an inert, mechanically-stable, insoluble support,[5] it can be reused and implemented in a flow reactor.[6] In the last two decades a large number of organocatalysts have been heterogenised on both organic and inorganic supports.[7–17] Reactions and conditions cannot be simply translated from homogeneous to heterogeneous catalysis; adsorption effects due to the presence of a solid surface have to be taken into account.[18] In fact, in the transition state (TS), the environment around the reacting partners experiences a drastic change with new interactions taking place.[19] For example, SBA-15 and silica-based materials that exhibit a strong external acidity can be involved in the mechanism of enamine catalysis; Katz *et al.* reported that the silanol groups on the silica surface act as hydrogen bond donor towards some substrates.[20] This dual activation mechanism was studied also relatively to silica functionalised with stronger acidic groups to investigate how variation in pK_a affects the kinetics of aldol reactions.[21] This suggests that a deeper understanding of the factors involved would aid the design of catalysts and supports. Characterising interactions within the pore space of such catalysts is challenging. In this context, NMR relaxation has recently emerged as a rapid and non-invasive tool to explore the chemical and morphological effects of solid surfaces in catalysis[22–25] and to investigate the solvent effect in metal-catalysed homogeneous reactions.[26] In particular, the ratio of the NMR relaxation times, T_1/T_2, has been proven to be a robust parameter to characterize surface interactions; strong molecule-surface interactions are characterised by a high T_1/T_2 ratio. In bulk liquids, spin–lattice T_1 and spin–spin T_2 relaxation times are similar and the $T_1/T_2 \sim 1$. Within porous materials, they both decrease due to a more limited mobility of the molecules confined in the pore space. However, T_2 experiences translational and rotational limitations associated with the surface diffusion to a higher degree than T_1 and T_1/T_2 becomes greater than 1; thus, the T_1/T_2 ratio can be correlated with the molecule-surface affinity.[27] For example, T_1/T_2 measurements have been

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[a] *Department of Chemical, Pharmaceutical and Agricultural Sciences (DOCPAS), University of Ferrara, Via Luigi Borsari 46, I-44121, Ferrara, Italy*
[b] *Department of Chemical Engineering and Analytical Science (CEAS), The University of Manchester, M13 9PL, Manchester, UK. E-mail: carmine.dagostino@manchester.ac.uk*
[c] *Diamond Light Source, Harwell Science and Innovation Campus, OX11 0DE, Didcot, Oxfordshire, UK*
[d] *The University of Manchester at Harwell, Harwell Science and Innovation Campus, OX11 0DE, Didcot, Oxfordshire, UK*
[e] *Catalysis Hub, Research Complex at Harwell, Rutherford Appleton Laboratory, OX11 0FA, Harwell, Oxfordshire, UK*
[f] *Department of Physical and Chemical Sciences, Università degli Studi dell'Aquila, Via Vetoio, 67100 L'Aquila, Italy. E-mail: armando.carlone@univaq.it*

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successfully used to rationalize solvent effects in Au/TiO_2 catalysts.[28,29] It was shown that surface morphology may affect affinity of reaction species with the catalyst and influence catalytic performances. Recently, we used this approach to investigate the solvent effect in oxidative coupling of aldehydes mediated by polystyrene-supported NHCs.[30]

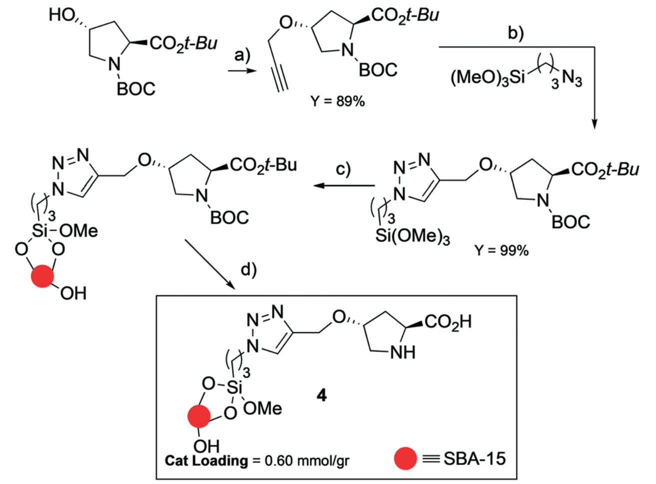
There is a number of reports where organocatalysts are supported on silica; however, the effect of the support on the reactivity remains largely unexplored.[31] Herein, we combine reaction studies with NMR relaxation measurements to investigate the behaviour of a heterogenised proline organocatalyst over a structured silica support, SBA-15, widely used for its tuneable properties and high surface area, in a selection of the solvents, catalysing an aldol reaction between benzaldehyde and hydroxyacetone.

Results and discussion

The aldol reaction between benzaldehyde **1** and hydroxyacetone **2** was chosen as a benchmark reaction. Hydroxyacetone is an α-ketoalcohol, available in large quantities from the biofuel industry, produced by partial hydrogenolysis of glycerol.[32] The aldol product **3** is a key diol intermediate for the synthesis of polyol species.[33] A proline supported organocatalyst on SBA-15 mesoporous silica was selected to investigate the solvent effect in the proline-organocatalysed aldol reaction. Catalyst **4** was prepared according to previously reported procedures[34] (Scheme 1, see ESI† for further information).

The benchmark reaction, taking the conditions from the literature report,[1e] was then run in different solvents comparing the behaviour of catalyst **4** and L-proline (Table 1).

In agreement with previous reports, the reaction was slower over the heterogeneous catalyst with respect to the homogeneous counterpart.[7a] The heterogenised proline catalyst **4** performed best in the absence of solvent (neat, TOF = 0.51×10^{-5} s^{-1}, entry 2), whereas L-proline worked better in solution (DMSO, TOF = 2.91×10^{-5} s^{-1} *vs.* neat, TOF = 2.0×10^{-5} s^{-1}, entries 3 and 1). In the accepted mechanism of proline-catalysed aldol reaction, a key step is the addition of the catalyst-substrate enamine adduct to the electrophilic aldehyde.[35] The solvent may play an important role in this transition state through weak non-covalent interactions.[19–21] Reactions performed in water and ethanol (entries 5–8) show that the solvent effect is dramatically different in homogeneous and heterogeneous catalysis. In fact, homogeneous L-proline is not able to catalyze the reaction in these two solvents, whereas it works when supported (H_2O, TOF = 0.37×10^{-5} s^{-1}; EtOH, TOF = 0.45×10^{-5} s^{-1}).[36] Thus the local combined environment of the organocatalysts and support imparts a great influence, potentially through control over the arrangement of the solvent molecules in the active site. The transition state of the enamine-aldehyde pair may therefore be different and affected by a distinct network established between the solvent and the silanol groups of the silica.[20]

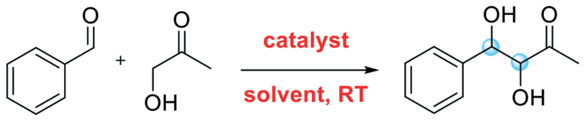


Scheme 1 Synthesis of the immobilised proline catalyst **4**. Reagents and conditions: a) NaH, propargyl bromide, −25 °C then RT, DMF, 16 h; b) (3-azidopropyl)trimethoxysilane, triethyl amine, CuI, RT, THF, 21 h; c) SBA-15, reflux, toluene, 48 h; d) TFA, 0 °C to RT, DCM, 32 h.

Although an effect of water in the aldol reaction promoted by proline has been previously reported, this effect has not yet been studied when hydroxyacetone is used as a pro-nucleophile. Previous works suggest that traces of water in organic solvents may have a beneficial effect by suppressing substrate inhibition.[20c,37] However, this aspect has not yet been elucidated when water is the main solvent and our results here suggest that the use of water as a solvent for such reactions may also be beneficial. The solvent significantly affects the enantioselectivity, not only using proline, but also using the supported catalyst **4**. The best results are obtained with polar aprotic solvents (DMSO and DMF); these findings may suggest that more polar aprotic solvents are able to establish similar interactions regardless of the presence of the silica-based support. Leaching of the organocatalyst into solution was investigated by running the reaction in deuterated solvents and looking for leached moieties, and ruled out.

NMR relaxation measurements were used to investigate the solvent-matrix surface interactions. A high T_1/T_2 ratio represents high affinity and strong interactions between the solvent and the solid support. Relaxation measurements of the solvents and reactants, over **4** and the unfunctionalised matrix SBA-15 were performed (Fig. 1 and Table 2, see ESI† for further details). It can be clearly seen that functionalisation of silica with proline may have a marked effect on surface interactions with different solvents. Affinity of polar solvents decreases when silica is functionalised with the catalyst (Table 2, T_1/T_2 ratio for SBA-15 *vs.* **4**, entries 3–8), which can be rationalised by considering the replacement of silanol groups by the proline group. The loss of silanol groups decreases the interaction of the surface of silica and the H-bond donors and acceptors of the solvent. Indeed, a minimal change in T_1/T_2 was observed in the case of cyclohexane, which is incapable of forming H-bond

Table 1 Aldol reaction between benzaldehyde **1** and hydroxyacetone **2** promoted by either L-proline or **4** in different solvents[a]



1 **2** **3**

Entry	Catalyst	Solvent	TOF (s^{-1})	d.r.	ee/%
1	L-Proline	Neat	2.00×10^{-5}	1/2	18
2	**4**	Neat	0.51×10^{-5}	1/1.3	Rac
3	L-Proline	DMSO	2.91×10^{-5}	1 : 2	76
4	**4**	DMSO	0.36×10^{-5}	1 : 2	72
5	L-Proline	H_2O	n.r.	—	—
6	**4**	H_2O	0.37×10^{-5}	1/1.3	Rac
7	L-Proline	EtOH	n.r.	—	—
8	**4**	EtOH	0.45×10^{-5}	1/1.3	Rac
9	L-Proline	DMF	2.80×10^{-5}	1 : 2.3	62
10	**4**	DMF	0.25×10^{-5}	1/1.8	60
11	L-Proline	DCM	0.98×10^{-5}	1/1.5	36
12	**4**	DCM	0.28×10^{-5}	1/1	Rac
13	L-Proline	THF	2.14×10^{-5}	1/3.5	76
14	**4**	THF	0.29×10^{-5}	1/2	23
15	L-Proline	CyHex	2.10×10^{-5}	1/2	28
16	**4**	CyHex	0.51×10^{-5}	1/1.3	Rac

[a] Reaction conditions: L-proline (Pro, 30 mol%) or **4** (40 mol%), hydroxyacetone (2.9 mmol, 29 eq.), benzaldehyde (0.1 mmol) in DMSO (800 μL). Reaction time: 24 h (L-proline) or 5 days (**4**). TOF and d.r. were determined by ^{1}H-NMR of the crude reaction mixture; ee values are reported for the major diastereoisomer and were determined by HPLC on a chiral stationary phase. The TOF was calculated from the averaged rate over the course of reaction (1 day for the homogeneous catalyst and 5 days for the immobilised catalyst) as $mmol_{product}/(mmol_{cat} \times$ time in seconds).

interactions (entry 9). Conversely, water exhibits the most prominent decrease in T_1/T_2, as it is known to form strong and extensive hydrogen bonding (entry 4). Ethanol, cyclohexane and hydroxyacetone **2**, showed the lowest values of T_1/T_2 ratios in functionalised silica **4** (entries 5, 9, and 1).

It is intriguing to note the lower interaction with **4** showed by ethanol compared to DCM or THF. Whilst a more detailed study on the surface science, possibly with the aid of DFT calculations, is out of the scope of the current work, we may suggest some insights. Molecules such as THF are known to often act as catalyst poisons and this is attributed to their ability to adsorb strongly onto the surface;[38] we believe this might be associated to the ability of the unpaired electrons on the oxygen atom of THF to act as a Lewis base and bind to positive charges on the catalyst surface. Kamlet–Taft solvatochromic parameters may also play a role in determining the T_1/T_2 values; for example, the solvent polarizability of DCM and THF is greater than that of ethanol

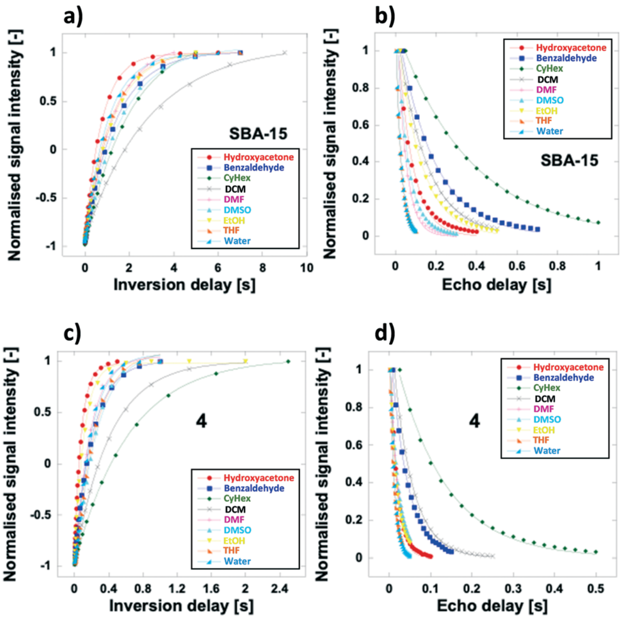


Fig. 1 a) T_1 inversion recovery plots for solvents adsorbed within SBA-15; b) T_2 CPMG decay plots for solvents adsorbed within SBA-15; c) T_1 inversion recovery plots for solvents adsorbed within **4**; d) T_2 CPMG decay plots for solvents adsorbed within **4**.

Table 2 T_1/T_2 relaxation measurements for different solvents in **4** and SBA-15

		4	SBA-15
Entry	Solvent	T_1/T_2	T_1/T_2
1	Hydroxyacetone	5.6 ± 0.2	10.2 ± 0.3
2	Benzaldehyde	5.3 ± 0.2	7.8 ± 0.2
3	DMSO	7.5 ± 0.2	24.4 ± 0.7
4	H_2O	10.0 ± 0.3	38.4 ± 1.2
5	EtOH	6.5 ± 0.2	11.0 ± 0.3
6	DMF	9.4 ± 0.3	30.3 ± 0.9
7	DCM	9.1 ± 0.3	20.8 ± 0.6
8	THF	12.6 ± 0.4	44.6 ± 1.4
9	CyHex	5.2 ± 0.2	5.7 ± 0.2

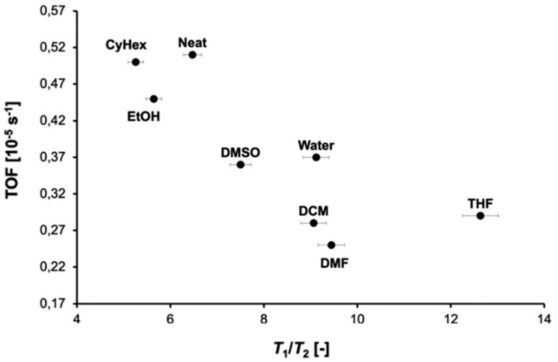


Fig. 2 T_1/T_2 of solvents (adsorbed within catalyst **4**) used in the aldol reaction between benzaldehyde **1** and hydroxyacetone **2** *versus* TOF.

and cyclohexane. Indeed, the highest reactivity occurs in ethanol and cyclohexane, which are also the solvents with the lowest polarizability values among those studied. This is in agreement with the low T_1/T_2 values reported for such solvents; hence, this parameter, whilst not being the only one responsible for determining the T_1/T_2 values, certainly plays a significant role in determining this trend.[39]

By combining the observations from Tables 1 and 2, the highest reactivity is measured in solvents with low affinity with the solid catalyst (cyclohexane, ethanol and hydroxyacetone **2**, the latter roughly comparable to a solvent when used in large excess in neat conditions). Relaxation measurements show that such solvents interact less strongly to the surface and make the catalytic site more accessible to substrates. Surprisingly, no stereoselectivity is observed in these solvents. As mentioned previously, the reaction proceeds only in heterogeneous conditions when water and ethanol were used as the solvent (Table 1, entries 5–8); this corroborates the assumption that the presence of solid surface changes the environment around catalytic sites, as evidenced by the change in T_1/T_2.

A plot of the T_1/T_2 ratio against the TOF of the examined reaction is reported in Fig. 2. The results in Fig. 2 show that in general solvents with a higher T_1/T_2, hence a higher surface affinity, lead to a lower reactivity, as indicated by the lower TOF. This trend is in agreement with previous findings reported for more traditional metal catalysts.[40] The results in Fig. 2 suggest that the T_1/T_2 ratio is a useful indicator to differentiate solvents based on strength of surface interactions and that solvents with a preferential interaction with the solid matrix inhibit access of reactants to the active sites. The solvent affinity for the surface of the solid matrix, therefore, is a key parameter to consider when designing catalytic materials, while the T_1/T_2 ratio is a useful and easily accessible indicator for the affinity.

We note that the solvent is likely to impact not only the TOF but also the enantioselectivity. However, such effects would be much more complex to unravel purely based on competitive adsorption effects as they would involve other aspects, such as adsorption geometry and changes in transition states. Other approaches, such as computational DFT, could be useful in this regard, which are however out of the scope of this work.

Conclusions

Silica-supported organocatalysts are a potential solution to increase productivity by enabling easy separation and reuse of such catalysts. However, the effect of the solid matrix on the reactivity has largely remained unexplored. We have assessed reactivity and adsorption phenomena, *via* NMR relaxation measurements, in an aldol reaction promoted by SBA-15 immobilised proline organocatalyst. The results show that solvents with a high surface affinity lead to a lower reactivity and this may be ascribed to the inability of reactant molecules to access active sites. This study suggests that the solvent interaction with the solid surface is an important parameter to consider when screening heterogenised organocatalysts and NMR relaxation can be used as a fast screening method for solvent evaluation (typical data acquisition time is of the order of tens of minutes). A further significant finding was that in water and ethanol the reaction is catalysed by the immobilised organocatalyst, in sharp contrast with the behaviour of the homogeneous organocatalyst. This observation opens up the potential for the use of more environmentally benign, less hazardous solvents for these transformations, while simultaneous employing an easy-to-separate immobilised catalyst, with critical implications for industrial applications. More work is underway to study this phenomenon and will be the subject of further studies.

Author contributions

Graziano Di Carmine: Conceptualisation, data curation, investigation, methodology, writing-original draft, writing-review & editing. Luke Forster: Data curation, formal analysis, writing-review & editing. Simeng Wang: Data curation, investigation, methodology. Christopher Parlett: Methodology, formal analysis, writing-review & editing. Armando Carlone: Conceptualisation, supervision, writing-review & editing. Carmine D'Agostino: Conceptualisation, funding acquisition, project administration, resources, supervision, writing-review & editing.

Conflicts of interest

There are no conflicts to declare.

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