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Letter

Oxidative Coupling of Aldehydes with Alcohol for the Synthesis of Esters Promoted by Polystyrene-Supported N-Heterocyclic Carbene: Unraveling the Solvent Effect on the Catalyst Behavior Using NMR Relaxation

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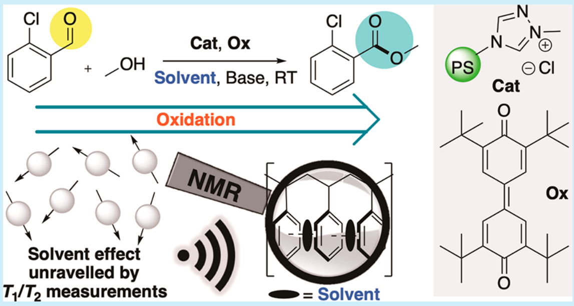
ABSTRACT: Heterogeneous organocatalysts hold great potential as they offer practical advantages in terms of purification and reusability compared with the homogeneous counterpart. A puzzling aspect is the solvent effect on their catalytic performance. Here we propose a new approach whereby T_1/T_2 NMR relaxation measurements are used to evaluate the strength of solvent−surface interactions in the polystyrene-supported N-heterocyclic carbene-promoted oxidation of aldehydes. The results reveal that solvents with high surface affinity lead to a decrease in catalyst activity.



Preparation of esters plays a crucial role in the synthesis of chemicals of interest for both academia and industry due to their ubiquitous presence in natural products and polymers and as APIs (active pharmaceutical ingredients).[1] Traditional routes involve toxic coupling reagents, and their use leads to the production of hazardous waste. Nevertheless, in the past decade, the demand of green protocols in response to the more stringent environmental regulations has encouraged chemists to develop new sustainable methods for the preparation of these compounds.[2] In the toolkit of organic chemists, oxidative coupling of aldehydes is among the most desirable routes due to the high stability of the aldehyde group compared to the acyl halide and the better atom economy of the overall process.[3] A mild and metal-free approach to convert aldehydes into esters in the presence of alcohols employs N-heterocyclic carbene (NHC) in oxidative conditions.[4] External oxidants in stoichiometric amounts (TEMPO, MnO_2 and Kharasch reagent) can be used.[5] However, cooperative systems that employ atmospheric oxygen as terminal oxidant would be more desirable. Surprisingly, after the seminal works of Shinkai and Diederich in 1980 and 1992, respectively, this approach remained uninvestigated until the first decade of the millennium.[6] In fact, in 2015 Sundén and co-workers[7] disclosed an efficient protocol to convert *α*,*β*-unsaturated aldehydes into the corresponding esters employing a triazolium salt (NHC) along with a mediator couple composed of an FePc (iron(II) phthalocyanine) and 2,6-di-*tert*-butylphenol. This mediator couple is able to generate the required oxidant species directly *in situ* working in homogeneous catalytic conditions and using atmospheric oxygen as terminal oxidant.[7] Unfortunately, in organocatalysis a higher catalytic loading is required to efficiently promote the reaction, compared to that for metal catalysis, making this protocol less attractive for industrial purposes.

The most promising approach to overcome this drawback encountered in the homogeneous catalytic process is that of anchoring the catalyst onto an insoluble support and reusing the catalyst several times after a simple filtration.[8] In addition, this approach has the potential to increase the sustainability of the process by facilitating catalyst separation, for example, by avoiding energy-intensive distillation procedures, which can in some cases make catalyst recovery unfeasible. In this context, Massi and co-workers reported the esterification of glycerol and solketal employing the strategy adopted by Sundén, using a simple triazolium salt supported on polystyrene for this purpose.[9] Subsequently, the same authors presented the oxidation of 5-hydroxymethylfurfural (5-HMF).[10]

Unlike homogeneous organocatalytic processes, the behavior of organocatalysts immobilized over a solid support, that is, heterogeneous organocatalysts, still remains puzzling, and this has limited their use and development both in academia and in industry, relative to their homogeneous counterparts.[11] New experimental protocols, in addition to the existing ones, are

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needed to gain new insights into the behavior of such materials, if they are to be developed as alternative, greener catalysts. In particular, unlike reactions in the presence of homogeneous organocatalysts, reactions over solid heterogeneous organocatalysts can be significantly affected by diffusion and adsorption behavior of reaction species over the surface. Yet, the influence of these aspects in heterogeneous organocatalysis remains unexplored. In recent years, NMR relaxation time measurements have emerged as a promising method to investigate and evaluate the adsorption behavior of molecules over porous materials due to the noninvasive nature and the fast acquisition time of the methodology.[12] It was demonstrated that the T_1/T_2 ratio can be used as a robust indicator of an activation energy for surface diffusion, which is intrinsically linked to the strength of molecule−surface interactions. In particular, a higher T_1/T_2 ratio indicates a stronger interaction with the surface. T_1/T_2 measurements have also been applied by Habina et al. to different systems, such as studies of surface interactions in oil and gas shales.[13] In a recent work carried out by D'Agostino and Gladden, NMR T_1-T_2 experiments were successfully used to explain the size effect of gold (Au) nanoparticles on glycerol adsorption over Au/TiO_2 catalysts.[14] Subsequently, these authors applied the same method to rationalize the inhibition effect of additives on catalyst activity in the oxidation of glycerol promoted by Au/TiO_2 catalyst[15] and to explain the solvent effect in aerobic oxidations of polyols over Au/TiO_2 catalysts.[16]

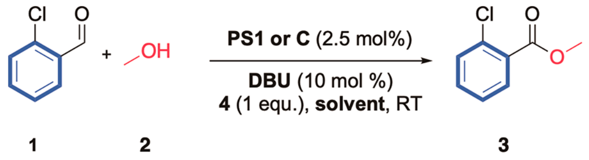
Prompted by these studies conducted over purely heterogeneous inorganic catalysts, we have envisaged that NMR relaxation techniques could play a significant role in starting to unravel the behavior of organocatalysts immobilized over solid surfaces, with solvent effects being among key aspects to understand in these materials. The role of solvent on the reaction rate is well-known, and it can be manifested in several ways: polar solvents may stabilize TSs (transition states) if they are characterized by charge separation; in addition, the polarity of the medium strongly influences the performance of acid−base reactions, and in metal catalysis, solvents can compete with the substrate in the complexation step, affecting the reaction rate dramatically.[17]

Even though several studies have been performed to investigate the solvent effect in heterogeneous catalysis, only inorganic supports have been investigated. Marchi and coworkers disclosed the solvent effect in the hydrogenation of acetophenone promoted by Ni/SiO_2, and they found a correlation between the solvent adsorption energy and the reaction rate concluding that the adsorption of the solvent molecules on the surface may partially block the active sites.[18]

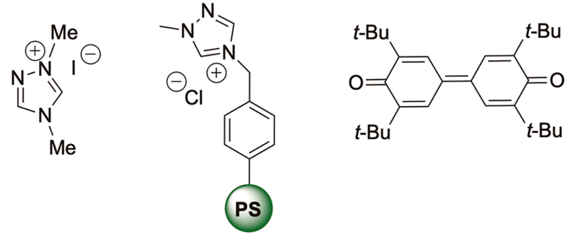
While it is clear that efforts have been made to understand solvent effects in traditional metal-supported catalysts, insights into solvent effects in organocatalysts supported on solids have remained elusive. Herein, we present new insights into how the type of solvent can affect reactivity in heterogeneous organocatalysis. In particular, NMR relaxation time measurements have been used to probe the strength of surface interactions of several solvents over a polystyrene-supported triazolium salt (NHC). In addition, NMR diffusion measurements have also been performed to assess the presence of any mass transport limitations affecting the process.

As we were interested in studying the oxidation of aldehydes into the corresponding esters through heterogeneous NHC catalysis, we chose the reaction between 2-chlorobenzaldehyde **1** and methanol **2** as a benchmark reaction because of its simple monitoring by NMR spectroscopy. The quinone oxidant **4** has been selected as the oxidant for the process and DBU (1,5-diazabiciclo(5.4.0)undec-7-ene) as the base necessary to activate the triazolium salts (as homogeneous catalyst, **C**, and the same salt immobilized over polystyrene, **PS1**) into the corresponding NHC *in situ*. The polystyrene-supported triazolium salt **PS1** was selected as the catalyst due to its well-known broad compatibility in oxidative NHC catalysis, and it was prepared following a previously reported protocol.[9] The average pore size of the porous matrix of this material is approximately 5.4 nm (see Supporting Information, page S2, for details). A homogeneous version of the reaction was performed under the same conditions using the analogous triazolium salt in solution, **C**. Several solvents were used, with different features (results summarized in Table 1). THF (tetrahydrofuran), DMF (dimethylformamide), and DCM (dichloromethane) were chosen as polar solvents, whereas toluene and cyclohexane were chosen as slightly polar and nonpolar solvents, respectively.

Table 1. Solvent Screening for the Oxidative Coupling of 2-Chlorobenzaldehyde with Methanol[a]



catalyst	solvent	TOF[b]
C	THF	$(1.56 \pm 0.04) \times 10^{-3}$
PS1	THF	$(1.51 \pm 0.04) \times 10^{-3}$
C	DMF	$(4.00 \pm 0.10) \times 10^{-4}$
PS1	DMF	$(3.33 \pm 0.08) \times 10^{-4}$
C	DCM	$(2.13 \pm 0.05) \times 10^{-3}$
PS1	DCM	$(1.91 \pm 0.05) \times 10^{-3}$
C	toluene	$(5.28 \pm 0.13) \times 10^{-4}$
PS1	toluene	$(3.11 \pm 0.08) \times 10^{-4}$
C	cyclohexane	$(2.78 \pm 0.07) \times 10^{-4}$
PS1	cyclohexane	$(1.39 \pm 0.03) \times 10^{-4}$



C **PS1** (*f*: 0.59 mmol g^{-1}) **4**

[a]Reaction conditions: Aldehyde **1** (0.5 mmol), alcohol **2** (1.0 mmol), **4** (0.5 mmol), **C** or **PS1** (12.5 μmol), DBU (0.05 mmol), diphenyl ether (0.5 mmol) as internal standard for the NMR yield quantification using a 300 MHz Gemini Varian spectrometer, solvent (4.0 mL). [b]Turnover frequency (TOF) in s^{-1}.

The ratios between TOFs (heterogeneous over homogeneous) were calculated and are summarized in Table 2. Since we are primarily interested in the effect of the solvent inside the pores of the heterogeneous NHC over the porous solid support, the use of this ratio is crucial because it rules out the influence of solvent effects in the homogeneous reaction, that is, removing any effect not caused by molecule−surface interaction or diffusion within the catalyst pores (such as

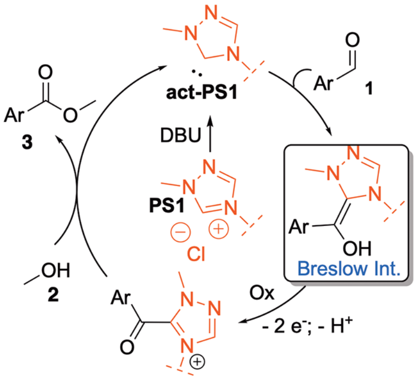
Table 2. TOF Ratio between Heterogeneous and Homogeneous Oxidative Coupling by NHC

solvent	TOF_{hetero}/TOF_{homo}
THF	0.97 ± 0.03
DMF	0.83 ± 0.02
DCM	0.90 ± 0.03
toluene	0.59 ± 0.02
cyclohexane	0.50 ± 0.02

proticity, polarizability, or basicity that could be involved in the stabilization or destabilization of the transition states in the mechanism).

From the data in Table 2, it is possible to observe that a similar reactivity is observed for polar solvents (THF, DMF, DCM) when comparing the heterogeneous reaction with the homogeneous one. This finding is of high relevance as it is often the case that the reactivity of heterogeneous organocatalysts is much lower than that of the homogeneous counterpart, whereas in this case, for those solvents, a comparable reactivity is observed. The drop in TOF ratio appears more remarkable for the slightly polar solvent toluene and for the nonpolar solvent cyclohexane. Scheme 1 shows the general accepted mechanism for the oxidation of aldehydes promoted by NHC and an external oxidant. The Breslow intermediate is the key species involved in the redox step, and it is generated through the nucleophilic addition of the *in situ* formed catalyst **act-PS1**. The catalytic species involved in the process is **act-PS1**, whereas **PS1** is the protonated form in which usually the catalyst is stored for stability purposes. To switch from **PS1** to **act-PS1** *in situ*, a base such as DBU is required. For the NMR experiments, as we were interested in investigating the physical behavior of **act-PS1**, because it is the active form, we treated the precatalyst with a strong base in excess (NaH) before the preparation of the NMR samples (see Supporting Information for details).

Scheme 1. Generally Accepted Mechanism for the Oxidative NHC Catalyzed Reaction[5c]



The activated polystyrene-supported catalyst was soaked in anhydrous solvent for 24 h to allow full saturation of the pores. After this time, the catalyst particles were put onto a presoaked filter paper, the external surface of the catalyst particles was dried to remove any excess bulk solvent around the particles, and the solid was then transferred into a 5 mm NMR tube. The spin−lattice relaxation time, T_1, was measured using an inversion recovery pulse sequence, and the transverse relaxation time, T_2, was measured with the CMPG pulse sequence[19] (see Supporting Information for details on acquired NMR relaxation data and fitting of the data). T_1/T_2 values are summarized in Table 3.

Table 3. Values of T_1/T_2 Ratio of Solvents in the Polystyrene-Supported NHC Catalyst Used in This Work

solvent	T_1/T_2
THF	2.39 ± 0.07
DCM	2.94 ± 0.09
DMF	3.11 ± 0.09
toluene	3.97 ± 0.12
cyclohexane	4.61 ± 0.14

For fast tumbling bulk liquids, such as the solvents used in this work, single values of T_1 and T_2 are higher than for liquids confined in porous materials, and it is well-known that $T_1/T_2 \approx 1$, as also suggested by the theory.[20] Aksnes and Gjerdåker have reported a T_1 significantly different from T_2 for bulk cyclohexane, although this was measured at 400 MHz.[21] We note here that while the T_1 of bulk liquids at room temperature does not depend on frequency,[22] the behavior of T_2 is more complex as it is affected by frequency as well as scalar coupling.[23] Previous experimental results at frequencies below 400 MHz have shown that for cyclohexane $T_1 = T_2 = 2.9$ s,[16a] which is in agreement with the value of 2.8 s reported here (see Supporting Information, Table SI4). We also note that in our case, NMR relaxation times of the bulk liquid are not necessary for our analysis, which is based on the T_1/T_2 of solvents confined in the porous matrix of the catalyst. It is important to highlight here that while single values of relaxation times can be affected by several factors other than the surface influence, such as amount of bulk liquid, degree of pore saturation, and specific surface area of contact, the T_1/T_2 ratio is to a large extent not affected by these factors and is a more direct and robust indication of the influence of surface interactions.[13a] In particular, as mentioned above, the T_1/T_2 ratio value is related to the surface−molecule energy interaction. Higher T_1/T_2 values indicate a stronger affinity of the solvent for the surface, and in our case this occurs for the less polar solvents; this is expected due to the hydrophobic nature of the matrix, which leads to preferential interactions with the less polar solvents. The results reported here give experimental evidence of such effects and provide quantitative metrics to assess them. Diffusion measurements were also performed in order to assess the influence of the pore diffusion on reaction rate, in addition to solvent adsorption effects. The Weisz−Prater criterion was applied to estimate the presence of diffusion limitation. In all cases, the calculated values were below 1; hence pore diffusion limitation can be excluded (see Supporting Information for more details).[24]

A plot of the TOF ratio versus T_1/T_2 of the solvent is shown in Figure 1, and it clearly depicts a remarkable trend showing that solvents with higher affinity for the surface result in lower catalytic activity. This strongly suggests that the decrease in catalytic activity is closely related to a stronger surface affinity of the solvent, which inhibits reactivity by preventing access of reactant molecules to the catalytic sites over the surface. A similar effect has been reported for metal/support catalysts used in oxidation of diols using NMR spectroscopic analysis,[25] and here, for the first time, we observe a similar effect on immobilized organocatalysts. This suggests that solvent selection is a key parameter to consider when optimizing and developing such materials. It is important to highlight that

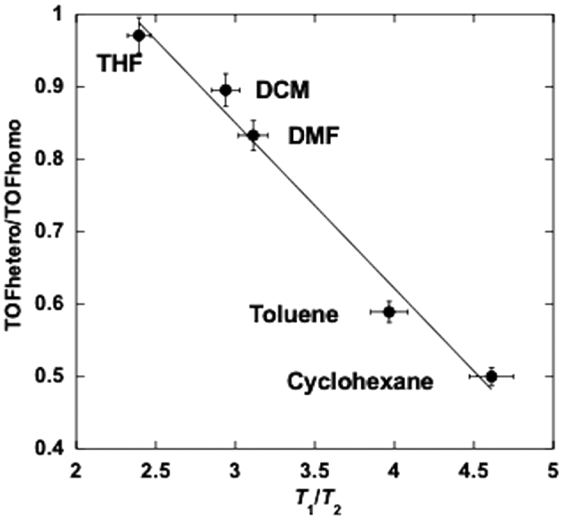


Figure 1. T_1/T_2 of solvents used in the oxidative coupling of 2-chlorobenzaldehyde with methanol versus the $\mathrm{TOF_{hetero}/TOF_{homo}}$. The solid line is a linear fit, which represents a guide for the eyes.

other effects may affect reactivity, most notably diffusion and transition state stabilization; however, as previously discussed, based on our calculations and considerations, such effects have already been ruled out. Hence, the results shown here demonstrate that the solvent interaction with the catalyst surface plays a key role in determining catalyst activity.

In conclusion, we have used NMR relaxation and diffusion studies coupled with reaction screening to rationalize for the first time how solvent−surface interactions can affect the reaction rate of immobilized organocatalysts, using the oxidative coupling of 2-chlorobenzaldehyde with methanol promoted by NHC as a model reaction. Other systems will be studied in the near future by our group in order to expand this approach. The initial findings reported here are of high importance as they suggest that the design of a solid matrix with suitable adsorption properties is a key parameter to take into account when designing these catalysts, which could lead to new and exciting developments in this area of catalysis so far underexploited.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01188.

Experimental procedures, characterization data, and T_1, T_2, and diffusion measurements (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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