

# Sustainable Organocatalyzed Enantioselective Catalytic Michael Additions in Betaine-Derived Deep Eutectic Solvents

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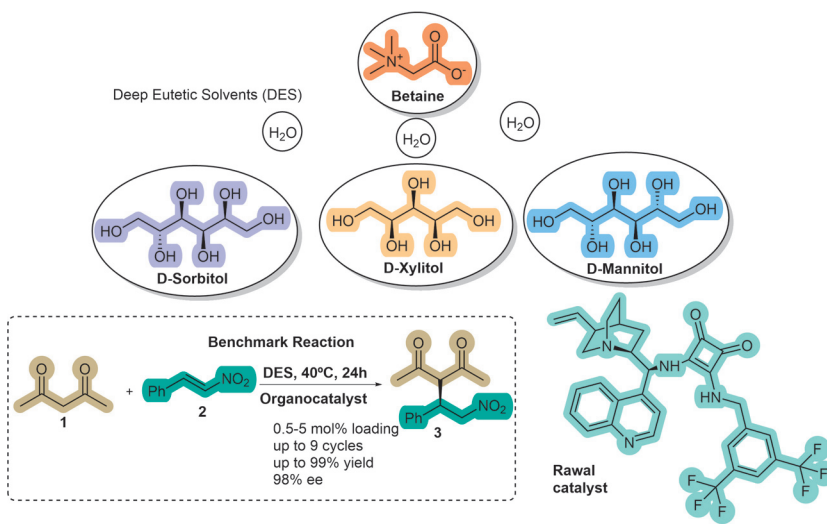
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**Abstract** The organocatalyst cinchonidine-squaramide was immobilized within three different deep eutectic solvents (DESs): betaine:D-sorbitol:water, betaine: D-xylitol:water, and betaine:D-mannitol:water and evaluated in a well-known asymmetric Michael addition. These reactions provided excellent yields (up to 99%) and enantioselectivities (up to 98%) using only 1 mol% of organocatalyst. It was also possible to achieve 9 cycles in reactions with DES (betaine:D-sorbitol:water), proving the high recyclability of this system. In the reactions realized with only 0.5 mol% of organocatalyst, it was possible to achieve 5 cycles, and the products were obtained with high yields (up to 95%) and excellent enantioselectivities (up to 94%), using DES (betaine:D-sorbitol:water).

**Keywords** cinchonidine-squaramide, betaine, deep eutectic solvent (DES), immobilization, organocatalysis

Over the last years, in asymmetric organocatalysis, the use of alternative solvents has increased, contributing to the reduction of waste formation, in many cases from the use of volatile organic compounds as a reaction medium.<sup>2</sup> The development of greener chemistry is necessary and in

this context, deep eutectic solvents (DESs) emerged as a new generation of cheap and readily available solvents which are simple to prepare.<sup>3</sup>

DESs are recyclable, reusable, stable, nonflammable, biodegradable, and nontoxic mixtures. Some of its properties are similar to ionic liquids, however, these can be toxic and are not biodegradable. These excellent properties give DESs the possibility of being used as greener solvents as an alternative to those commonly used in synthesis. Currently, DESs are already known as the solvents of the century.<sup>4</sup> Thanks to their low ecological footprint and attractive prices, plus the fact that they are nontoxic and biodegradable, DESs have garnered significant interest and are now considered as alternative ‘green’ solvents, with application in a wide range of organic reactions.<sup>5</sup> DESs are built from hydrogen-bond donor and hydrogen-bond acceptor components and gratifyingly can be easily adapted for specific applications. The most widely used hydrogen-bond donor components, include: urea, thiourea, phenol, glucose, citric acid, malonic acid, sorbitol, and glycerol. The most commonly used hydrogen bond acceptors are: choline chloride, betaine, glycine, and proline.<sup>6,7</sup>

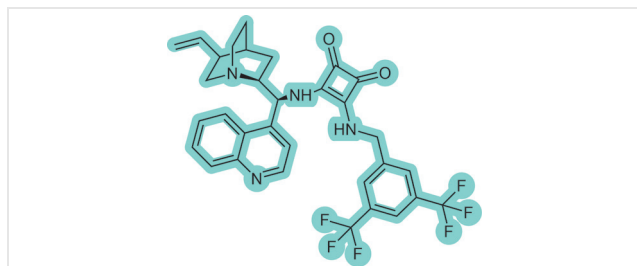
DESs have been applied in numerous chemical sectors, such as polymerizations, biotransformations, such as solvents, in metal-catalyzed reactions, sample preparations, catalytic techniques, and also in the design of new pharmaceutical formulations.<sup>8</sup>

DESs containing betaine and carbohydrates have been studied by Vicente et al.<sup>9</sup> Recently, Gutiérrez and coworkers modelled the interactions between DES constituents using computational methods.<sup>10</sup>

A very peculiar and relevant aspect for asymmetric synthesis is the use of chiral DESs that can be simultaneously used as a reaction medium and a source for asymmetric induction, where the chirality of the solvent itself is very important.<sup>11</sup>

Recently, our group reported the first immobilization of cinchona organocatalysts on porous glass beads and subsequent application in heterogeneous catalysis. We compared their performance in both batch and flow systems.<sup>12</sup> In this paper we report our studies on immobilized cinchona-squaramide catalysts in three different DESs, focusing on both catalytic activity and enantioselectivity of the organocatalyst and its recyclability over several reaction cycles.

Considering the excellent enantioselective and catalytic properties that the cinchonidine-squaramide catalyst<sup>13</sup> (Figure 1) previously provided, a standard Michael reaction was tested, in order to evaluate the enantioselectivity, yield, and number of catalytic cycles. This benchmark reaction is easy to perform and provides an excellent measure of the efficiency of the system under the parameters discussed above.<sup>13,14</sup>

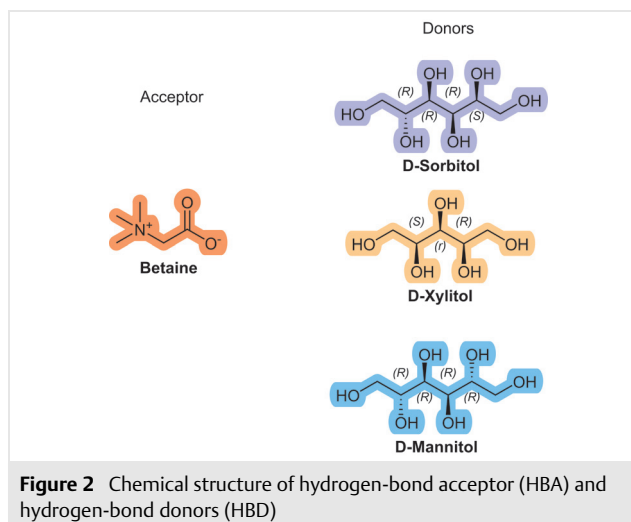


**Figure 1** Structure of the cinchonidine-squaramide catalyst

In the first part of this work, we selected a set of DESs, in which one of its components is a chiral compound, and these compounds can be linear or cyclic (see the Supporting Information, Tables I–III). All DESs presented in Tables I–III of the Supporting Information were tested in the chosen Michael reaction. Figure 2 shows the chemical structures of the components of the DESs that were studied.

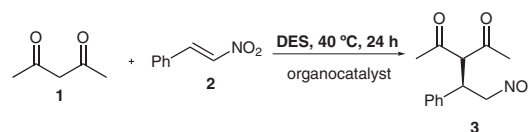
In order to study the recyclability and performance of the catalyst, three different quantities (5, 1, and 0.5 mol%) of the cinchonidine-squaramide organocatalyst were tested in the Michael addition using the selected DESs, starting with the DES containing D-sorbitol (DES A). The results obtained at a catalyst loading of 5 mol% are presented in Table 1.

After nine reaction cycles, there was a noticeable drop in both the yield and the enantioselectivity (Table 1, entry 9), which suggested loss of catalytic activity. The yields were generally consistent throughout, whilst there were some irregularities with the enantioselectivity measure-



**Figure 2** Chemical structure of hydrogen-bond acceptor (HBA) and hydrogen-bond donors (HBD)

**Table 1** Results of Michael Reactions (Acetylacetone (**1**) and *trans*- $\beta$ -Nitrostyrene (**2**)<sup>a</sup>) Catalyzed by 5 mol% Cinchonidine-Squaramide Immobilized in DES A (Betaine:D-Sorbitol:Water)



Entry	DES A	Catalyst loading	Cycle	Yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	betaine: D-sorbitol: water	5 mol%	1	≥99	97
2			2	≥99	62
3			3	≥99	70
4			4	≥99	95
5			5	97	82
6			6	98	90
7			7	≥99	94
8			8	95	90
9			9	88	62

<sup>a</sup> Reaction conditions: **1** (0.275 mmol), **2** (0.25 mmol), DES A (2 mL), 40 °C, 24 h.

<sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy using mesitylene as a standard.

<sup>c</sup> Determined by HPLC with a chiral stationary phase column.

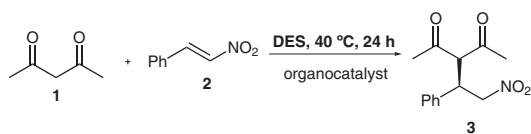
ments, which may have been due to sampling errors (for instance, entry 2, 62% ee, entry 3, 70% ee and then entry 4, 95% ee) or due to the chiral nature of the sorbitol component that can potentially compete with the organocatalyst (see below for further study of this effect). According to Alonso and co-workers, one of the factors that influences the results is the partial solubility of DES or the catalyst in the extraction solvents Hex:AcOEt (1:1) used to isolate the reaction product.<sup>2</sup> It is not easy to explain this observation, but it is a strong indication of a complex dynamic system. This oscillation in enantioselectivity could be the result of

dynamic processes occurring in solution, i.e., the formation of several transient species between the reagents, the DES constituents, and the organocatalyst. It is likely that these transient species are chiral and influence the enantioselectivity of the reaction (see below for further discussion). There were no indications of the structure of these transient species, but they are probably formed through hydrogen bonds and other noncovalent interactions, such as ion-dipole interactions and  $\pi$ - $\pi$  interactions.

The reactions were run at 40 °C, as opposed to room temperature, for the purpose of maintaining the DES in the liquid state (it tends to solidify at the latter temperature).

The use of 5 mol% of immobilized catalyst in the DESs containing D-sorbitol showed a high catalytic activity over nine cycles. Based on these excellent results, we decided to decrease the catalytic loading to 1 mol%, and the results obtained are shown in Table 2.

**Table 2** Results of Michael Reactions (Acetylacetone (**1**) and *trans*- $\beta$ -Nitrostyrene (**2**)<sup>a</sup>) Catalyzed by 1 mol% Cinchonidine-Squaramide Immobilized in DES (Betaine:D-Sorbitol:Water)



Entry	DES A	Catalyst loading	Cycle	Yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1			1	≥99	98
2			2	≥99	69
3			3	≥99	66
4			4	94	79
5	betaine: D-sorbitol:water	1 mol%	5	95	93
6			93	75	
7			99	60	
8			94	29	
9			81	17	

<sup>a</sup> Reaction conditions: **1** (0.275 mmol), **2** (0.25 mmol), DES B (2 mL), 40 °C, 24 h.

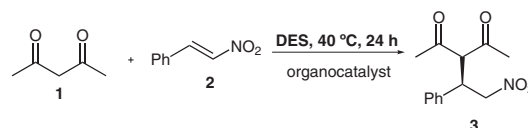
<sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy using mesitylene as a standard.

<sup>c</sup> Determined by HPLC with a chiral stationary phase column.

Table 2 shows that 1 mol% of organocatalyst provided nine reaction cycles, the same number of cycles achieved with 5 mol% of the same catalyst. From entry 1 to 9, Table 2, the yields were quantitative during the first three cycles and then decreased slightly for the next 5 cycles, before bottoming out to 81% after the 9th cycle. Again, there was an oscillatory trend with the enantioselectivities, which was probably due to the dynamics of the chiral components (see below), but eventually bottomed out after the 8th cycle falling to 29% ee and then 17% ee after the 9th cycle.

Since with only 1 mol% of catalyst we obtained nine reaction cycles, it was of interest to decrease the loading to only 0.5 mol% catalyst (Table 3). In this case the results were less encouraging, it was impossible to obtain quantitative yields and although the yields remained consistent throughout the five cycles, the enantioselectivity bottomed-out at 43% ee after the 5th cycle.

**Table 3** Results of the Michael Reactions (Acetylacetone (**1**) and *trans*- $\beta$ -Nitrostyrene (**2**)<sup>a</sup>) Catalyzed by 0.5 mol% Cinchonidine-Squaramide Immobilized on DES A (Betaine:D-Sorbitol:Water)



Entry	DES A	Catalyst loading	Cycle	Yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1			1	82	94
2			2	94	87
3	betaine: D-sorbitol:water	0.5 mol%	3	95	68
4			95	74	
5			88	43	

<sup>a</sup> Reaction conditions: **1** (0.275 mmol), **2** (0.25 mmol), DES A (2 mL), 40 °C, 24 h.

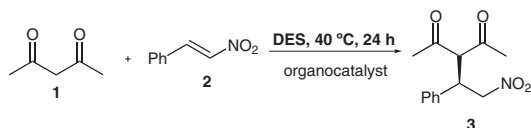
<sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy using mesitylene as a standard.

<sup>c</sup> Determined by HPLC with a chiral stationary phase column.

From these studies we concluded that our organocatalyst performs best at 5 and 1 mol% loading. Since these results were obtained using DES A, we also decided to study other DESs containing D-sorbitol analogues: such as D-xylitol (DES B) and D-mannitol (DES C; Tables 4 and 5). On using DES B and C it was also possible to obtain a high number of catalytic cycles with catalyst loadings of 1 and 0.5 mol%, respectively. In a similar fashion to what happened upon using DES A these catalyst loads also presented the most promising results. In the case of DES B (Table 4), best results were obtained at 1 mol% catalyst loading; after 4 cycles both the yield and enantioselectivity remained high (86% and 84% ee). However, in the case of the system using 0.5 mol% catalyst, the enantioselectivity bottomed out at 10% ee after the 4th cycle, although the yield was quantitative. This was a strong indication of the competing or the antagonistic effects of the organocatalyst and the DES chiral component (D-xylitol) (see below for DFT calculations).

Finally, Table 5 shows the results of the reactions catalyzed by 0.5 and 1 mol% of cinchonidine-squaramide (catalyst A) in the DES containing D-mannitol (DES C). The results shown in Table 5 correspond to loadings of 0.5 and 1 mol% of the catalyst. A 5th reaction cycle was also performed with 0.5 mol% catalyst but unfortunately the DES solidified, a clear indication of the increased density of the DES most likely due to increased hydrogen-bonding net-

**Table 4** Results of Michael Reactions (Acetylacetone (**1**) and *trans*- $\beta$ -Nitrostyrene (**2**)<sup>a</sup>) Catalyzed by 0.5 and 1 mol% Cinchonidine-Squaramide Immobilized on DES B (Betaine:D-Xylitol:Water)



Entry	DES B	Catalyst loading	Cycle	Yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	betaine: D-xylitol:water	0.5 mol%	1	96	87
2			91	93	
3			89	63	
4			98	10	
5		1 mol%	1	98	92
6			93	67	
7			90	93	
8			86	84	

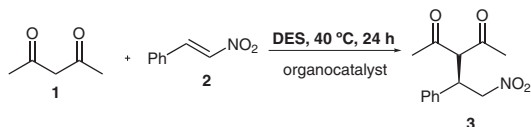
<sup>a</sup> Reaction conditions: **1** (0.275 mmol), **2** (0.250 mmol), DES B (2 mL), 40 °C, 24 h.

<sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy using mesitylene as a standard.

<sup>c</sup> Determined by HPLC with a NOT A chiral stationary phase column.

work formation. The same also happened on the fourth reaction cycle using 1 mol% catalyst. The yields obtained were good, albeit the enantioselectivities generally lower than those obtained using DES A and B. It should be noted that DES C was partially soluble in the solvent used in the extraction of the product.

**Table 5** Results of Michael Reactions (Acetylacetone (**1**) and *trans*- $\beta$ -Nitrostyrene (**2**)<sup>a</sup>) Catalyzed by 0.5 and 1 mol% Cinchonidine-Squaramide Immobilized in DES C (Betaine:D-Mannitol:Water)



Entry	DES C	Catalyst loading	Cycle	Yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	betaine: D-mannitol:water	0.5 mol%	1	57	83
2			35	73	
3			55	99	
4		1 mol%	4	67	≥99
5			1	19	52
6			2	64	78
7			3	87	87

<sup>a</sup> Reaction conditions: **1** (0.275 mmol), **2** (0.25 mmol), DES C (2 mL), 40 °C, 24 h.

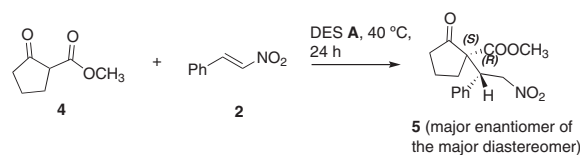
<sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy using mesitylene as a standard.

<sup>c</sup> Determined by HPLC with a chiral stationary phase column.

The best enantioselectivities were obtained using both DES A and C, which are C6 sugars (and epimers in the C-5 position; sorbitol C-(S)5 and mannitol C-(R)5), with the former giving the best results, probably due to the configuration of the C-5 stereocenter. The C-5-sugar D-xylitol was the worst performer, probably due to the length of its backbone and its influence on reactant solubility and transition-state stabilization.

Based on the best results that were obtained for DES A, to measure the scope of the reaction, we decided to evaluate the reaction of cinchonidine-squaramide (1 mol%) immobilized in DES A for the asymmetric Michael addition of methyl 2-oxocyclopentane-1-carboxylate (**4**) and *trans*- $\beta$ -nitrostyrene (**2**). Table 6 shows the results and gratifyingly shows that the catalytic system was active up to ten cycles, maintaining the enantioselectivities, diastereoselectivities, and yields. The diastereoselectivities increased significantly from the 1st to the 2nd cycles and remained more or less constant until the 10th cycle, up to 97% de. Surprisingly, the enantioselectivity of the major diastereomer (*S,R*) had very small variation over the 10 cycles, in the 1st cycle 94% ee and in the last cycle 93% ee. The yields were almost quantitative during all the cycles, with the exception of the 6th cycle, where the yield dropped to 56%, which may have been a mixing issue.

**Table 6** Results of the Michael Reactions with Methyl 2-Oxocyclopentane-1-carboxylate (**4**) and *trans*- $\beta$ -Nitrostyrene (**2**)<sup>a</sup> Catalyzed by 1 mol% Cinchonidine-Squaramide Immobilized on DES A



Entry	DES A	Catalyst (loading)	Cycle	Yield (%) <sup>b</sup>	de (%) <sup>c</sup>	ee (%) <sup>c</sup>
1	betaine: D-sorbitol:water	no	–	99	58	rac
2		1 mol%	1	99	73	94
3			2	99	92	86
4			3	99	93	84
5			4	99	92	92
6			5	99	94	88
7			6	56	94	96
8			7	98	94	93
9			8	97	97	94
10			9	98	97	95
11			10	97	97	93

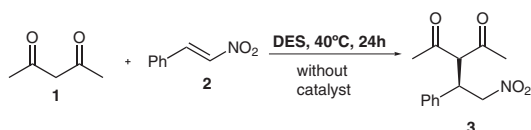
<sup>a</sup> Reaction conditions: **4** (0.275 mmol), **2** (0.25 mmol), DES A (2 mL), 40 °C, 24 h.

<sup>b</sup> Determined by isolated mass.

<sup>c</sup> Determined by HPLC with a chiral stationary phase column.

As an interesting side study, to determine if the chiral DES had an impact on the asymmetric induction, some reactions were carried out in the absence of catalyst. Gratifyingly, the reaction showed for DES A a large enantioselectivity of 75% ee (Table 7, entry 1), but interestingly when the reactions were performed using DES B and C only an enantioselectivity of 3% ee was obtained and the yields were about 30% lower (Table 7, entries 2 and 3).

**Table 7** Results of Michael Reactions Carried Out in the Absence of Catalyst in DESs between Acetylacetone (**1**) and *trans*- $\beta$ -Nitrostyrene (**2**)<sup>a</sup>



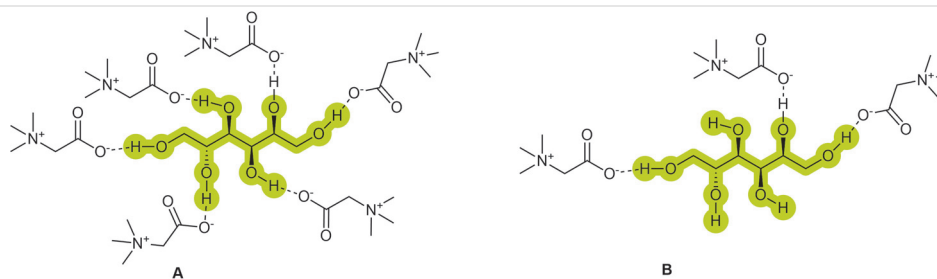
Entry	DES	Ratio	Yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	betaine:D-sorbitol:water (DES A)		81	75
2	betaine:D-xylitol:water (DES B)	1:1:3	53	3
3	betaine:D-mannitol:water (DES C)		51	3

<sup>a</sup> Reaction conditions: **1** (0.275 mmol), **2** (0.25 mmol), DES (2 mL), 40 °C, 24 h.

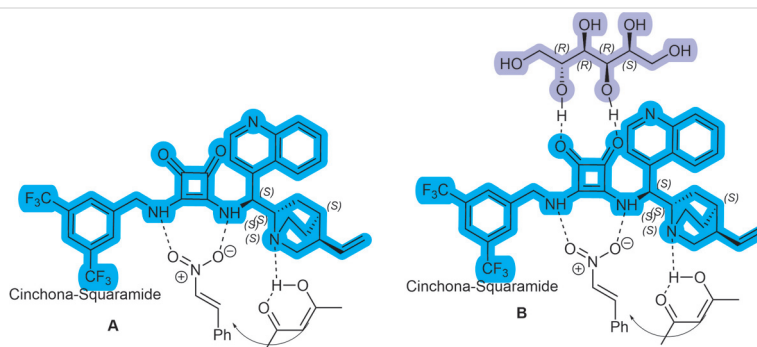
<sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy using mesitylene as a standard.

<sup>c</sup> Determined by HPLC with chiral stationary phase column.

It's hard to understand the exact role of the chiral DES in these reactions. It appears to have a specific role in establishing key hydrogen bonding networks with the reagents and the catalyst. Some possible interactions are described in Figure 3. In Figure 3A, a possible interaction between D-sorbitol and betaine is shown, however, due to steric hindrance it is more likely that the ratio between sorbitol and betaine would be 1:2 or 1:3 at most. In Figure 3B, the possible stabilization of the Michael addition transition state by sorbitol and betaine is shown. For simplicity, water is not included, but for sure it must also be a key component in stabilizing this transition state via specific H-bonding interactions. Fluctuations in the enantioselectivities between cycles may be explained via disruptions and changes in the H-bonding networks during the reaction cycles; for example, the nitro groups of the various Michael addition intermediates shown in the drawing in Figure 3B may alternate between different hydroxyl groups of the sorbitol unit, which can affect the bulk enantioselectivity. The oscillations in the enantioselectivities could be due to dynamic matching and mismatching interactions. In the case of the catalyst's role, a purported mode of action is outlined in Figure 4B<sup>13,15</sup> where it is suggested that the sorbitol component can form stable H-bonding interactions with the two carbonyls of the squaramide unit, possibly lowering the energy of the transition state. In fact, it's very likely that the TS shown in Figure 4B competes with that shown in Figure 4A and might explain these oscillations.

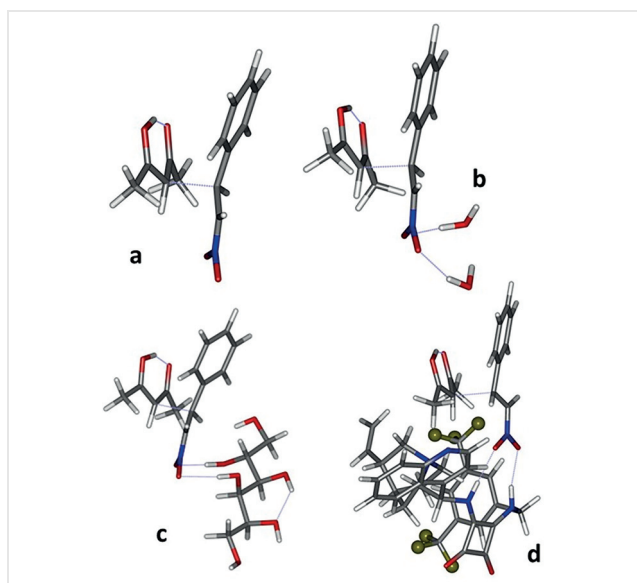


**Figure 3** (A) Possible interactions between D-sorbitol and betaine. (B) Possible stabilization of the reaction transition state (TS) by the key DES A components. The water molecules are not shown but they may act as a bridge between the betaine and sorbitol components and perhaps also between the DES components and the TS structure.



**Figure 4** (A) Purported transition-state mechanism for the cinchona-squaramide catalyzed Michael addition.<sup>13,15</sup> (B) Postulated role of the DES sorbitol component in stabilizing the transition state (for clarity the betaine component is omitted).

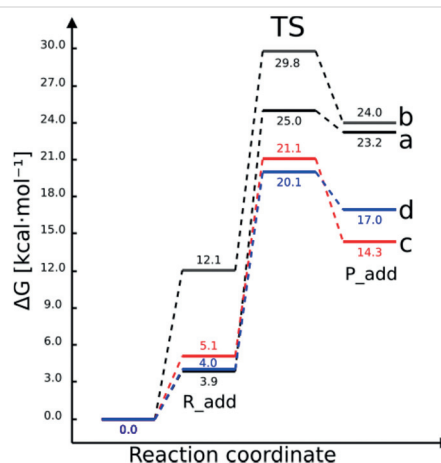
To gain deeper insights into the mechanism of this reaction in these systems we performed DFT computational studies on a very simplistic model system at M06-2X/6-31G(d,p) level using the Gaussian 16 software package.<sup>16</sup> Solvent effects were considered by the SMD continuum solvation model.<sup>17</sup> Four models were considered for the reaction between acetylacetone and *trans*- $\beta$ -nitrostyrene environment (Figure 5): (a) implicit water, (b) implicit water plus explicit water molecules, (c) implicit water and sorbitol, (d) and implicit water and cinchona-squaramide catalyst.



**Figure 5** Transition-state structures calculated (DFT) for the studied models displaying relevant H-bonds with the TS structure

Transitions states for the different models shown in Figure 5 were found and the free energy profiles show an important reduction on the barrier height (activation energy) when compared with the water models, not only for the cinchona-squaramide case, but also on the sorbitol system. We found that it was the cinchona-squaramide catalyst that gave the lowest TS energy (d, blue line Figure 6) followed by the sorbitol system (c, red line Figure 6) and, interestingly, it was the system composed of intrinsic and extrinsic water that showed the highest energy barrier (grey line Figure 6). This study shows clearly that the DES component sorbitol has a significant positive effect on reaction transition state, probably at a catalytic level, supporting the observed experimental results.

Of all the DESs used in the standard reaction, DES A (betaine:D-sorbitol:water) was the one that gave the best results.<sup>18–21</sup> The use of low loads of catalyst, namely 5 and 1 mol%, provided the Michael adduct with the best yields, ees, and greatest number of cycles, five and nine cycles, respectively, in the case of acetylacetone and ten cycles in the case of methyl 2-oxocyclopentane-1-carboxylate. The differenc-



**Figure 6** Free-energy profile for the different studied system. Free-energy profiles for the different studied systems. Calculated energies relative to the energy of separated reactants. Reactant adducts, transition states, and product adducts are represented by R\_add, TS and P\_add, respectively.

es in the results with the various DESs may be accounted for by the different sugar components used. The structure of D-mannitol is also very similar to that of D-sorbitol and the only aspect that distinguishes them is the orientation of one of the hydroxyl groups. Some oscillations in the ees from one cycle to the next were recorded, this can be due to various H-bonding modes between the DES components, the reactants, and the catalyst (see above) but also the mixing may also have an influence, poor mixing of the viscous DES may lead to a nonuniform or asymmetric distribution of the components, including elements of the DES and the organocatalyst provoking these oscillations in the enantioselectivity. DFT studies showed that sorbitol appears to have a catalytic effect on the reaction through specific H-bonding effects. Furthermore detailed experimental studies will be conducted in due course to understand more fully the mechanistic nature of the reactions in these systems.

## Conflict of Interest

The authors declare no conflict of interest.

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## Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/a-2117-9971>.

## References and Notes

- (1) Current address: Faculty Pharmacy, University of Coimbra, Pólo das Ciências da Saúde, Azinhaga de Santa Comba, 3000-548 Coimbra, Portugal; e-mail: [ajburke@ff.uc.pt](mailto:ajburke@ff.uc.pt).
- (2) Alonso, D. A.; Burlingham, S.; Chinchilla, R.; Guillena, G.; Ramón, D. J.; Tiecco, M. *Eur. J. Org. Chem.* **2021**, 29, 4065.
- (3) Zhang, Q.; De Oliveira Vigier, K.; Royer, S.; Jérôme, F. *Chem. Soc. Rev.* **2012**, 21, 7108.
- (4) Flores-Ferrándiz, J.; Chinchilla, R. *Tetrahedron: Asymmetry* **2017**, 2, 302.
- (5) Paiva, A.; Craveiro, R.; Aroso, I.; Martins, M.; Reis, R. L.; Duarte, A. R. C. *ACS Sustainable Chem. Eng.* **2014**, 5, 1063.
- (6) Smith, E. L.; Abbott, A. P.; Ryder, K. S. *Chem. Rev.* **2014**, 21, 11060.
- (7) Hansen, B. B.; Spittle, S.; Chen, B.; Poe, D.; Zhang, Y.; Klein, J. M.; Sangoro, J. R. *Chem. Rev.* **2020**, 3, 1232.
- (8) Cui, Y.; Li, C.; Bao, M. *Green Process. Synth.* **2019**, 8, 568.
- (9) Vicente, F. A.; Bradic, B.; Novak, U.; Likozar, B. *Biopolymers* **2020**, 10, 152.
- (10) Gutiérrez, A.; Alcalde, R.; Atilhan, M.; Aparicio, S. *Ind. Eng. Chem.* **2020**, 25, 11880.
- (11) Fanjul-Mosteirín, N.; Del Amo, V. *Tetrahedron* **2021**, 2, 131.
- (12) Amorim, A. C.; Fonseca, D.; Carreiro, E.; Hermann, G. J.; Federsel, H.-J.; Burke, A. J. *Synlett* **2022**, 33, 1756.
- (13) Hagihara, K.; Rawal, V. H.; Malerich, J. P. *J. Am. Chem. Soc.* **2008**, 44, 14416.
- (14) Massolo, E.; Palmieri, S.; Benaglia, M.; Capriati, V.; Perna, F. M. *Green Chem.* **2015**, 3, 792.
- (15) Burke, A. J.; Hermann, G. J. *3-Amino-Cinchona Derivatives*, In *Organocatalysis: Stereoselective Reactions and Applications in Organic Synthesis*; Benaglia M., De Gruyter: Berlin, Boston, **2021**, 85–126.
- (16) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A. Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian 16*, Rev. B.01; Gaussian, Inc.: Wallingford **2016**.
- (17) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B.* **2009**, 113, 6378.
- (18) **General Procedure for Producing DESs**  
In general, DESs result from the mixture of several components in the appropriate amounts to obtain the DES in the desired ratios. The conditions presented were optimized for each DES. The specific DES resulted from mixing 1 equiv of betaine with 1 equiv of the desired sugar and 3 equiv of water, in the case of DESs produced in the ratio 1:1:3.
- (19) **General Procedure for Asymmetric Catalytic Michael Additions**  
2 mL of DES solvent was added to a 25 mL round-bottom flask containing a magnetic stirring bar. 1 equiv of *trans*- $\beta$ -nitrostyrene (**2**, 0.25 mmol) and 1.1 equiv of acetylacetone (**1**) or methyl 2-oxocyclopentane-1-carboxylate (**4**, 0.275 mmol) were added to the DES. Finally, **5**, **1**, or 0.5 mol% of cinchonidine-squaramide (catalyst **A** in the Supporting Information) were added to the mixture and allowed to react for 24 h at 40 °C under sufficient stirring (this is very important as the DES by nature is viscous). The reaction was monitored by TLC and after total consumption of the starting material, extraction was performed with Hex:AcOEt (1:1, 2  $\times$  2 mL). The crude products **3** (yellowish solid) or **5** (colorless opaque oil) isolated from the reaction mixture were directly analyzed by <sup>1</sup>H NMR spectroscopy and HPLC without further purification. The previously described procedure was repeated for several reaction cycles until the catalyst no longer showed catalytic activity.
- (20) **Product 3**  
Yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.35–7.16 (m, 5 H, ArH), 4.65 (m, 2 H, CH<sub>2</sub>), 4.38 (m, 1 H, CH), 4.27 (m, 1 H, CH), 2.29 (s, 3 H, CH<sub>3</sub>), 1.94 (s, 3 H, CH<sub>3</sub>) ppm. <sup>13</sup>C APT-NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 201.80 (C), 201.03 (C), 135.99 (CH), 129.36 (2  $\times$  CH), 128.58 (CH), 127.95 (2  $\times$  CH), 78.20 (CH<sub>2</sub>), 70.74 (CH), 42.80 (CH), 30.45 (CH<sub>3</sub>), 29.55 (CH<sub>3</sub>) ppm.
- (21) **Product 5**  
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.81–2.07 (m, 4 H, 2 CH<sub>2</sub>), 2.31–3.39 (m, 2 H, CH<sub>2</sub>), 3.75 (s, 3 H, CH<sub>3</sub>), 4.08 (dd, *J* = 4, 12 Hz, 1 H, CH), 4.98–5.04 (m, 1 H, CH<sub>2</sub>), 5.14–5.18 (m, 1 H, CH<sub>2</sub>), 7.23–7.33 (m, 5 H, ArH) ppm.<sup>12</sup> HPLC: Daicel Chiralpak OD-H column, *n*-hexane/*i*-propanol = 95/5, 1 mL/min, 220 nm. Retention times: *t*<sub>major</sub> = 15.747 min, *t*<sub>minor</sub> = 26.280 min (minor diastereomer); *t*<sub>major</sub> (*S,R*) = 19.040 min, *t*<sub>minor</sub> = 27.487 min (major diastereomer).<sup>12</sup>