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This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1717748> since 2022-12-07T14:56:14Z

Published version:

DOI:10.1039/C9GC03465J

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Natural Deep Eutectic Solvents as an Efficient and Reusable Active System for the Nazarov Cyclization

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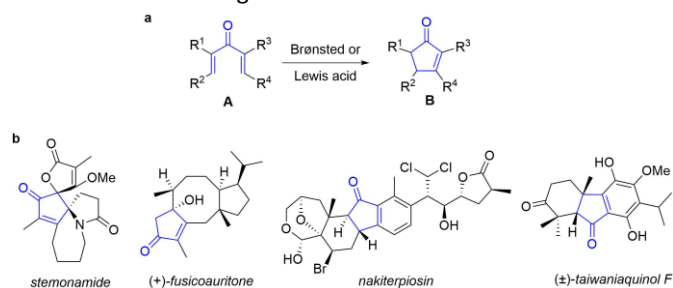
Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Natural Deep Eutectic Solvents have emerged as alternative non-toxic, non-aqueous solvents for an increasing number of synthetic transformations. Remarkably, in some cases one (or more) components of the NaDES plays an active role in the reaction mechanism and directly participates as either a catalyst or as a reagent in the reaction. In this paper, we tested several NaDESs in which one of the components is a carboxylic acid as medium to perform Nazarov cyclizations on divinyl ketones to obtain cyclopentenones, a widespread motif in natural compounds. The reaction conditions were optimized and the scope investigated on *C*-, *O*- and *N*-derived compounds. To assess the full sustainability of the proposed approach, the recyclability and scalability of the process were investigated, thus proving that multi-grams preparations are possible with complete recycle of the medium.

1. Introduction

The Nazarov reaction or Nazarov cyclization (NC) was first reported in 1942 and consists in the 4π conrotatory electrocyclicization of divinyl ketones to cyclopentenones in the presence of Brønsted or Lewis acids (Scheme 1).¹ The reaction is tolerant to substituents on the dienone skeleton (Scheme 1, **A**), and thus allows for the facile synthesis of functionalized cyclopentenones **B**, including relatively simple non-annulated structures as well as complex polynuclear cyclopentenoid skeletons annulated with one or more non-aromatic, aromatic or heteroaromatic rings.



Scheme 1. a. The Nazarov reaction. b. Examples of the occurrence of the cyclopentenone motif in natural compounds

During the years, the Nazarov reaction has found a wide application in synthesis and has become one of the most useful tools for the preparation of various cyclopentenone motifs.^{1b, 2} The study of the torquoselectivity of the reaction allowed for a stereochemical control of the substituted cyclopentenones

obtained,³ and enantioselective versions of the NC were reported.⁴ Modern protocols for the facile generation of the pentadienyl cation intermediate include a wide number of precursors beyond the traditional divinyl ketones **A**,⁵ including oxiranes,⁶ unsaturated carbinols,⁷ allene ethers⁸ and propargylic esters.⁹ Besides strong Brønsted acids, the NC can be catalysed by Lewis acids, such as main-groups Lewis acids and transition metals: successful data are for example reported for $\text{BF}_3 \cdot \text{Et}_2\text{O}$,¹⁰ $\text{Pd}(0)$,¹¹ Ag ,¹² $\text{Au}(I)$,¹³ $\text{Au}(III)$ ^{9b, 14} and halides.¹⁵ Remarkably, organocatalytic versions of the NC were also reported in which chiral phosphoric acid derivatives,¹⁶ diamines,¹⁷ thioureas,¹⁸ cinchona alkaloids¹⁹ were also used.²⁰ Despite its importance as a synthetic tool for the preparation of natural and pharmaceutically active compounds, and its undeniable potential as a synthetic tool which fulfills green chemistry principles in terms of atom economy, the NC still presents some drawbacks related to sustainability. Indeed, strong Brønsted acids (e.g. TFA, TfOH, MsOH), which are toxic and corrosive, are usually employed and are often required in a stoichiometric or super-stoichiometric amount.²¹ On the other hand, the use of Lewis acids is affected by the cost and air-sensitivity of the metal catalyst. Furthermore, volatile organic solvents (VOCs), and in particular chlorinated solvents, are by far the most common solvent system for the NC.^{2e} Up to now, only few references report on more sustainable versions of the NC, in which non-toxic and recyclable homogeneous²² and heterogeneous²³ catalysts were used. A remarkable example in this sense is represented by the cellulose- SO_3H catalyst reported by Rostami.²⁴ Finally, a Nazarov cyclization performed in water in the presence of surfactants (and Lewis acids) was reported.²⁵

Deep eutectic solvents (DESs) have emerged as a new promising class of green solvents, since they are non-flammable, non-toxic, biodegradable and very easily prepared from cheap and

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

readily accessible components.²⁶ An appropriate choice of the constituents pave the way to the design of different matrix with specific physicochemical properties.²⁷ When the compounds that constitute the DESs are primary metabolites and in general natural compounds, namely aminoacids, organic acids, sugars or choline derivatives, the DESs are called natural deep eutectic solvents (NaDESs). NaDESs totally fulfill green chemistry principles and are now foreseen as potential contributors to more sustainable industrial processes.²⁸

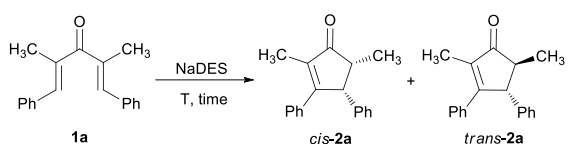
Since the first report by Abbot,²⁹ DESs have been successfully employed in several fields of application,^{26c, 27} including organic synthesis.³⁰ It has been shown that, apart from constituting a more sustainable alternative to traditional solvents, DESs often behave as non-innocent reaction medium and can have an active role in promoting organic reactions, by improving the reaction rate, the yield and allow for milder conditions. This has been attributed to the supramolecular structure of these mixtures, characterized by an extensive hydrogen bonding pattern.^{30c-e}

In this work, we wish to report on our study on the Nazarov cyclization in deep eutectic solvents, open-air and under mild conditions. Naturally occurring carboxylic acids are employed as component of the DES, allowing for mild conditions in a renewable active solvent system, which combines the lower toxicity and good biodegradability³¹ with its low cost. As to our knowledge, this is the first example of a NC promoted by weak carboxylic acids. Remarkably, the medium can be recycled up to 4 times without considerable loss in its activity.

2. Results and Discussion

To start our project and investigate the feasibility of the NC in NaDESs, we chose the symmetric tetra-substituted dienone **1a** as a model substrate.³² Various choline chloride (ChCl)-carboxylic acid based NaDESs were tested on the base of their ability to convert **1a** into the product cyclopentenone **2a** (Table 1). At first, ChCl/L-(+)-lactic acid in 1:2 molar ratio was tested and revealed ineffective in promoting the reaction at room temperature, even after 24 h (Table 1, entry 1). On the other hand, ChCl/oxalic acid 1:1 partially converted the substrate at the same temperature (entry 2). Raising the temperature up to 60 °C resulted in an improvement of the reaction yield to 91% after 16 h (entry 3). NaDESs based on L-(-)-malic acid (entry 4), citric acid (entry 5) and L-(+)-tartaric acid (entry 6) were less effective, as lower yields were obtained with these NaDESs under the same experimental conditions. Conversely, malonic acid (entry 7) and maleic acid (entry 8) based NaDESs performed well, affording **2a** with a yield of 92% and 87% respectively. ChCl/*p*-toluenesulfonic acid (TsOH) in 1:2 molar ratio was also tested, and in this case a yield up to 99% was obtained (entry 9).^{21, 31} NaDESs based on betaine (entry 11) and L-proline (entry 12), instead of ChCl, were found to be ineffective in promoting the reaction. We then performed some control experiments, which are summarized in Table 1, entries 13-16. A DES not containing an acid, such as ChCl/H₂O 1:2 (entry 13), or a polar organic solvent, such as ethanol (entry 14), were ineffective in promoting the reaction, indicating that an acid-containing DES is required.

Table 1. Study of the reaction conditions for the Nazarov cyclization of substrate **1a** in NaDESs.



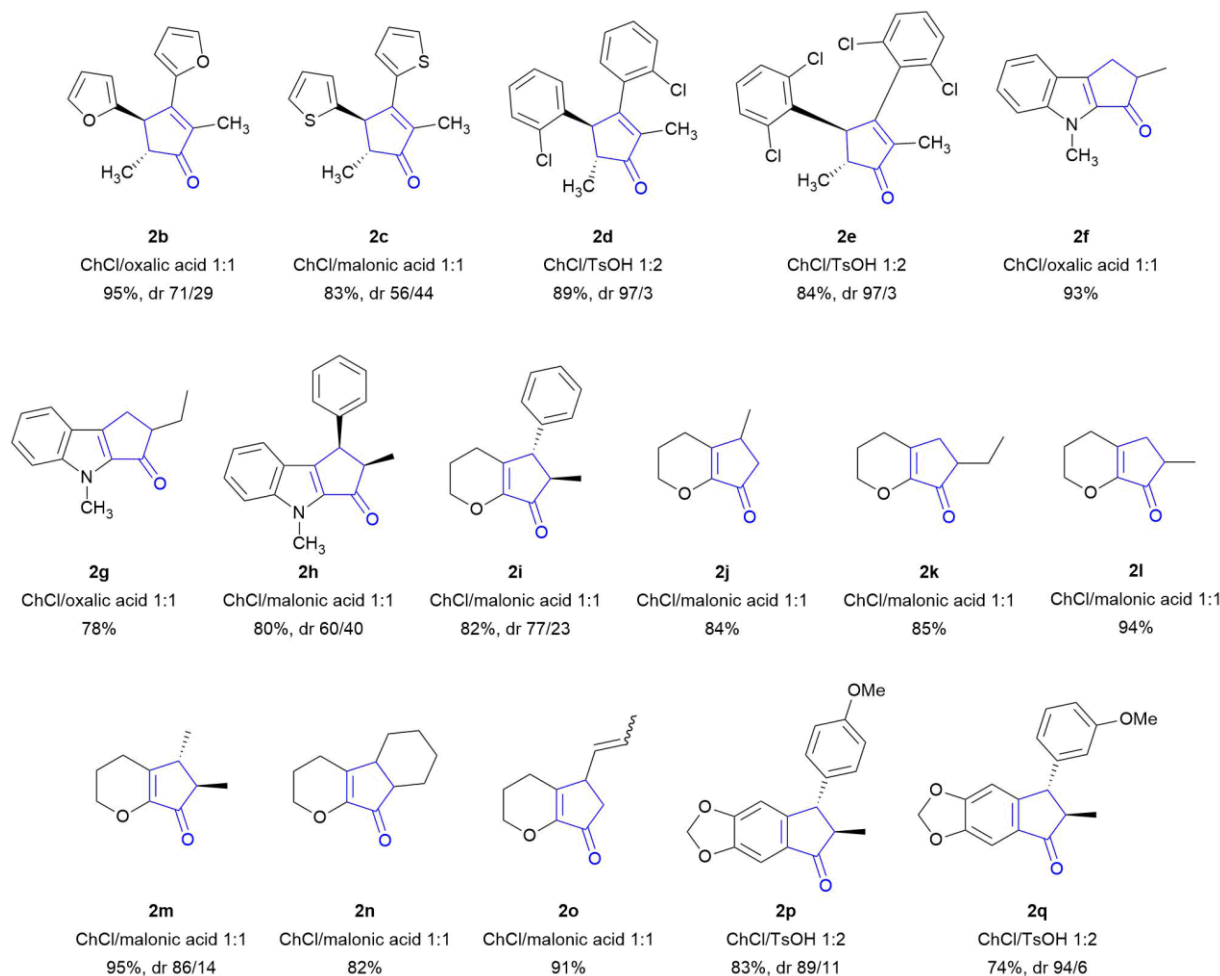
entry	solvent	T (°C)	time	2a (%) ^a	<i>cis/trans</i> ^b
1	ChCl/L-(+)-lactic acid 1:2	rt	24 h	traces	-
2	ChCl/oxalic acid dihydrate 1:1	rt	16 h	30%	57/43
3	ChCl/oxalic acid dihydrate 1:1	60	16 h	91%	14/86
4	ChCl/L-(-)-malic acid/H ₂ O 1:1:2	60	16 h	22%	26/74 ^d
5	ChCl/citric acid 1:1 + 2% H ₂ O	60	16 h	36%	67/33
6	ChCl/L-(+)-tartaric acid 1:1 + 2% H ₂ O	80 ^c	16 h	67%	17/83 ^d
7	ChCl/malonic acid 1:1	60	16 h	92%	17/83
8	ChCl/maleic acid 1:1	60	16 h	87%	16/84
9	ChCl/TsOH monohydrate 1:2	60	16 h	99%	15/85
10	ChCl/R-(-)-mandelic acid 1:1	60	16 h	59%	20/80 ^d
11	betaine/malonic acid 1:2	60	16 h	-	-
12	L-proline/oxalic acid dihydrate 1:1	60	16 h	-	-
13	ChCl/H ₂ O 1:2	60	16 h	-	-
14	EtOH	60	16 h	-	-
15	EtOH (10 eq malonic acid)	60	16 h	33%	24/76
16	DCE (10 eq malonic acid)	60	16 h	traces	-
17	H ₂ O (10 eq malonic acid)	60	16 h	23%	30/70

Reaction conditions: **1a** (0.2 mmol), in 1 g of the appropriate DES. ^a Yield of isolated product. ^b Determined by ¹H-NMR analysis of purified compounds. ^c Higher temperature was required due to the viscosity of the medium. ^d 0% enantiomeric excess.

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The acidic component of the eutectic mixture, malonic acid, was tested in either polar and apolar solvents such as ethanol (entry 15), 1,2-dichloroethane (entry 16) and water (entry 17), but very low yields were obtained in these cases, suggesting that the activity is a peculiar property of the eutectic mixture, and does not derive from its acidic component per se.³³ Considering that in general the acidity of the DES is governed by the acidity of the HBD, we then tried to rationalize these results, taking into consideration the pKa of the acidic component of the NaDES. The NaDESs containing malic acid (pKa 3.40), citric acid (2.92, 4.28 and 5.21) and tartaric acid (2.99) were almost ineffective, while the best results were obtained with oxalic (1.23), malonic (2.83) and maleic acid (1.93),³⁴ with malonic acid better performing (see entry 7, Table 1) than maleic (entry 8, Table 1). Taken together, these data do not account for a direct correlation between performance in the NC and pKa of the acidic component of the DES. According to a recently published

study,³⁵ the acidic properties of DES mixtures can differ from those of their components alone, and moreover they can be significantly affected by the temperature. This behaviour suggests the crucial role played by the supramolecular interactions in the eutectic mixture and is particularly relevant in the case of ChCl/oxalic acid 1:1 and ChCl/malonic acid 1:1, where a drop in the pH values are observed as the temperature increases.³⁶ These observations are in line with our results, which showed how in ChCl/oxalic acid 1:1 and ChCl/malonic acid 1:1 (entries 3 and 7 of Table 1) at 60 °C **2a** was obtained in both case in 92% yield despite the different pKa of the HBD component (1.23 for oxalic acid and 2.83 for malonic acid). The diastereoselectivity of the reaction was also evaluated in terms of *cis/trans* ratio. At room temperature (entry 2) the cyclization is not diastereoselective. At 60 °C the selectivity improves in favour of *trans-2a* to a 14/86 ratio in the case of ChCl/oxalic acid (entry 3).



Scheme 2. Scope of the Nazarov Cyclization in NaDES. All reactions were performed at 60 °C for 16 h and extracted with cyclopentyl methyl ether (CPME), as described in the SI.

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Similar results have been obtained with ChCl/malonic acid and ChCl/maleic acid (entries 7 and 8) thus proving that the most efficient NaDES are also those inducing the best diastereoselectivity. It should be noted that in the case of ChCl/citric acid (entry 5) the diastereoselectivity is in favour of *cis*-**2a**. A proposed mechanism to account for the diastereoselectivity either in favour of the *cis* or the *trans* cyclopentenone and based on the acidic character of the melt might involve multiple key activation roles of the solvent (Brønsted acid and hydrogen bond formation), as well as a plausible structure of the eutectic mixture. Further computational and physicochemical investigations are needed to elucidate these aspects. Regarding the enantioselectivity of the reaction, when we employed NaDESs composed of a chiral carboxylic acid (entries 4, 6 and 10) we did not observe any induction of chirality in the product.

Based on the optimization study, we extended the scope of the reaction to different substrates, choosing ChCl/malonic acid, ChCl/oxalic acid or ChCl/TsOH as possible reaction media (entries 7, 3 and 9 of Table 1). The results reported in Scheme 2 refer to the best score we obtained for each of the substrates. Symmetrical dienones bearing electron-rich or electron-poor aryl substituents were successfully cyclized to the corresponding cyclopentenones **2b-e** with very good yields (Scheme 2). Sterically encumbered substrates leading to **2d** and **2e** afforded the corresponding products with almost complete diastereoselectivity for the *trans* isomer.

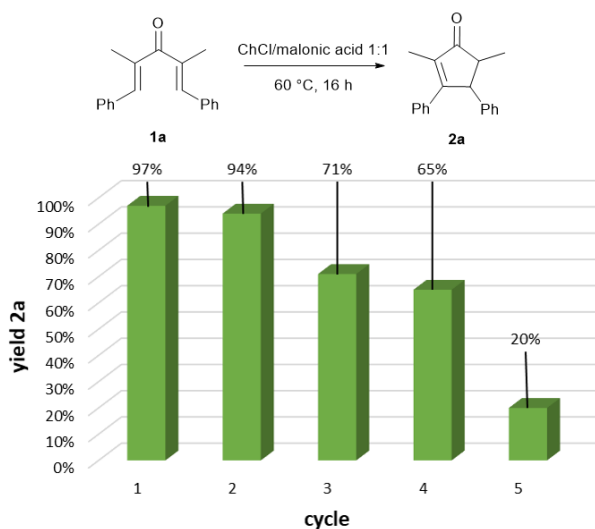


Figure 1. Recyclability of the ChCl/malonic acid DES for the Nazarov cyclization of **1a**. Yields were determined by quantitative ^1H NMR analysis using CH_3NO_2 as internal standard.

Since one of the most synthetically useful aspects of the NC is represented by the possibility to access fused (hetero)polycyclic

molecular scaffolds, and due to our own research interest for the synthesis of heterocyclic natural compounds,³⁷ we investigated the reactivity of several dienones whose structure is embedded in an indole or dihydropyran moiety. With our delight, for all the substrates the reaction proceeded smoothly to afford cyclopentenones **2f-o** in 78% to 95% yields. Finally, we showed that also aryl vinyl ketones, which are less prone to undergo the cyclization due to the interruption of the aromatic system as a consequence of the cyclization,³⁸ are converted into the corresponding Nazarov products **2p** and **2q** in good yield and diastereoselectivity.

One of the most attractive features of a catalytic system is undoubtedly the recyclability. We tested the possibility to recycle the ChCl/malonic acid eutectic mixture for the cyclization of dienone **1a**, at a concentration of 0.2 mmol/g (i.e. mmol of substrate per g of NaDES). The procedure for the recovery of the NaDES, shown in Figure 3, is highly feasible and involves the addition of water to the reaction mixture upon completion of the reaction, causing the precipitation of the product, which can be collected by filtration. Water is then evaporated to restore the eutectic mixture, which is used without further manipulations for another run. As shown in Figure 1, the activity of the NaDES remains essentially unchanged for the first two cycles and is acceptable up to the fourth one, while in the fifth run a drop in the yield of product **2a** is observed.

The activity of the NaDES strongly depends on the dynamic behaviour of its molecules and possibly in this case on the intermolecular interactions in which the COOH of the NaDES is involved. It seems then reasonable that the protic nature of the carboxylic acid component becomes stronger or weaker either in a more restricted or more disordered supramolecular network. To investigate how the activity of the NaDES changes at each recycling cycle we decided to evaluate the structure of the NaDES ChCl/malonic acid by ^1H and ^{13}C NMR (see SI for full size spectra).³⁹

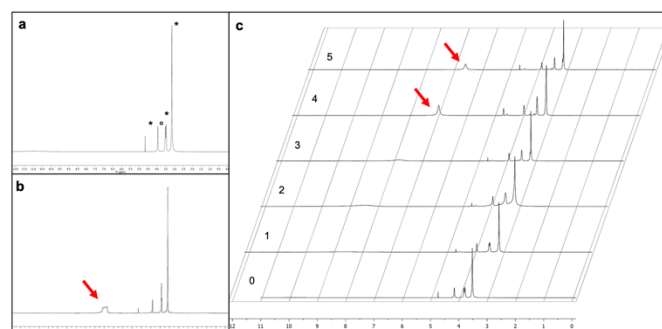


Figure 2. ^1H NMR of NaDES ChCl/malonic acid after recycling. a. ChCl/malonic acid ($^*\text{ChCl}$; $^*\text{malonic acid}$). b. ChCl/malonic acid with 10% water w/w. c. ChCl/malonic acid after the first (1), second (2), third (3), fourth (4) and fifth (5) cycle.

In Figure 2 the ^1H NMR spectra of pure NaDES ChCl/malonic acid are reported. The ^1H NMR signals at 3.1 (9H), 3.4 (2H) and 4.1 ppm (2H) are attributable to ChCl (*), while at 3.5 ppm the CH_2 of malonic acid is detectable (*). The COOH proton of malonic acid is entrapped in the tight network of intermolecular H bonds and is detectable in the ^1H NMR spectrum as a very broad signal between 10 and 11 ppm. In Figure 2, **b**, the ^1H NMR of ChCl/malonic acid in which a 10% of water has been added on purpose is reported. A signal at around 7 ppm is detectable and assigned to water entrapped in the NaDES, while free water is detectable at 4.7 ppm. In Figure 2, **c**, the ^1H NMR spectra of the NaDES recovered after each cycle are reported. It is evident that the structure of the NaDES remains substantially unchanged after the first cycle (Figure 2, **c**, 1), compared to the freshly prepared one (Figure 2, **c**, 0). In these cases yields of **2a** of 94% and 97% respectively were obtained (see Figure 1). Starting from the NaDES recovered from the second cycle, a broad signal around 8 ppm starts to appear and becomes progressively more evident after the fourth and fifth cycle, shifting towards 7 ppm. The presence of some other minor peaks might indicate that the structure of the DES is partially decomposed.⁴⁰ To rationalize these results, it should be worthwhile to recall that the activity of the NaDES ChCl/malonic acid is higher than that of malonic acid alone (see entries 13-15 in Table 1), as a confirm that the supramolecular structure of the DES might enhance the polarizability of COOH groups and facilitate the reactivity. The increase in the amount of water contained in the DES (and not removable by simple evaporation) is apparently correlated with the observed drop in yield. Further investigations are needed to assess how the supramolecular structure of the NaDES is modified at each cycle.⁴¹

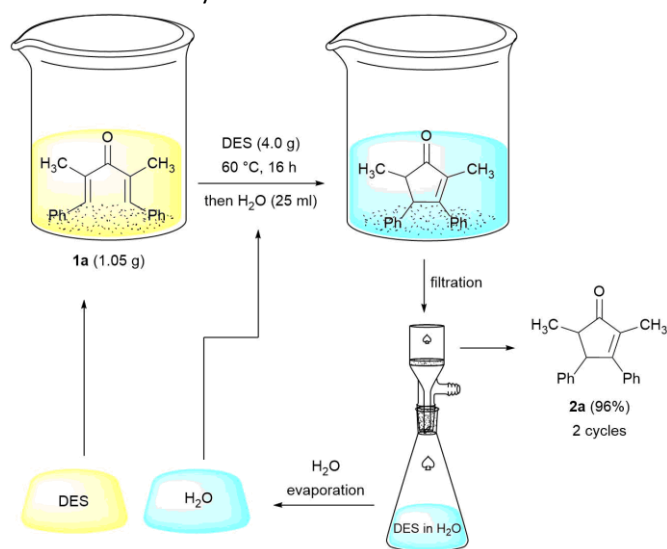


Figure 3. Two-cycles, gram-scale reaction.

The successful recycling procedure prompted us to further increase the efficiency of the process, with a view to its scalability. To this aim, we tested various substrate concentrations in NaDES, in order to find the highest concentration at which the yield of product yield remains unaltered, which was found to be 1 mmol/g, provided that the substrate was well dispersed in the medium and the stirring of

the mixture was effective. Therefore, we set up a gram-scale reaction starting from 1.05 g (4.0 mmol) of substrate **1a** and 4.0 g of ChCl/malonic acid (Figure 3). The NaDES was recovered and used again for a second run through the above described procedure. To minimize waste at this scale preparation, the water recovered at the rotavapor after the first cycle was used again for the second cycle.

The overall process afforded 2.01 g of cyclopentenone **2a** by using only 4.0 g of ChCl/malonic acid 1:1. The E-factor parameter for the process is 19.5, a value that confirms the green chemistry credentials of our protocol (see SI for the calculations).⁴²

3. Conclusions

In this paper, for the first time we have disclosed a conceptually new, flexible, versatile, and high-yielding Nazarov cyclization of divinyl ketones performed in deep eutectic solvents, in which the reaction medium acts in a dual role both as a solvent and as a promoter of the cyclization. The combination of divinyl ketones and NaDESs composed by carboxylic acids as an environmentally benign reaction medium enables access to the targeted compounds with excellent yields and good stereocontrol, at moderate temperature. The scope of the reaction is wide and several substituents on the divinyl ketone framework are well tolerated.

Furthermore, the potential of this reaction in terms of Green Chemistry principles coherence was addressed and several sustainable features of this transformation have been developed. In particular, we demonstrated that the process is scalable and multi-gram preparations are accessible. A practical and easy work-up allows for the recovery of both the NaDES and water. We demonstrated that 4 cycles of reaction are tolerated with an overall acceptable yield. The beneficial effect of the DES is further showcased by its ability to obtain, in some cases, pure compounds, thus avoiding purification by column chromatography.

4. Experimental section

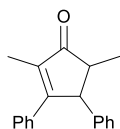
4.1 Materials. Flasks and all equipment used for the generation and reaction of moisture-sensitive compounds were dried by electric heat gun under nitrogen. Unless specified, all reagents were used as received without further purifications. Anhydrous THF was obtained by distillation over LiAlH₄, followed by distillation over Na-benzophenone; benzaldehyde was distilled under vacuum. Flash column chromatography was performed over silica gel (40-63 μm, 230-400 mesh); *R_f* values refer to TLC carried out on silica gel plates. ^1H NMR and ^{13}C NMR spectra were recorded on a Jeol ECZR600, in CDCl₃, using residual solvent peak as an internal standard (CHCl₃, ^1H : 7.26 ppm, ^{13}C : 77.16 ppm). NMR spectra of DESs were recorded in a capillary tube, using D₂O as locking solvent. Multiplicities are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet), m (multiplet), br (broad). GC-MS spectra were recorded at an ionizing voltage of 70 eV. Deep eutectic solvents were prepared by methods reported in the literature (see SI for

details). Divinyl ketone substrates **1a-q** were synthesized according to the literature (see SI for details).

4.2 General procedure for the Nazarov cyclization in DES. A vial was charged with the dienone substrate (0.2-0.5 mmol), then the DES (5 g per mmol of substrate) was added and the mixture was stirred at 60 °C for 16 h. Water was added and the mixture was extracted three times with cyclopentyl methyl ether (CPME); the combined organic layers were dried over anhydrous Na₂SO₄, filtered and the solvent was evaporated under reduced pressure. When required, the crude product was purified by flash column chromatography.

4.3 General procedure for recycling cycles. A vial was charged with the dienone **1a** (1.0-4.0 mmol), then ChCl/malonic acid 1:1 (5 g or 1 g per mmol of substrate) was added and the mixture was stirred at 60 °C for 16 h. Water was added, causing the precipitation of the product. The solid product was recovered by filtration, while water was evaporated under reduced pressure to afford the eutectic mixture, which was used for the next reaction cycle.

2,5-dimethyl-3,4-diphenylcyclopent-2-en-1-one (**2a**)²⁴



Synthesized according to the general procedure with ChCl/malonic acid 1:1. White solid, 92% yield, *trans/cis* ratio 83:17. R_f 0.25 (PE/Et₂O 9:1). **trans-2a** ¹H NMR (600 MHz) δ (ppm): 7.34-7.24 (m, 5H), 7.23-7.19 (m, 2H), 7.15-7.11 (m, 1H), 7.09-7.06 (m, 2H), 3.98 (quin, 1H, $J = 2.2$ Hz), 2.41 (qd, 1H, $J = 7.3, 2.8$ Hz), 2.03 (d, 3H, $J = 2.0$ Hz), 1.36 (d, 3H, $J = 7.5$ Hz). ¹³C NMR (150 MHz) δ (ppm): 211.1 (Cq), 167.2 (Cq), 142.2 (Cq), 136.9 (Cq), 135.3 (Cq), 129.1 (CH), 128.9 (CH), 128.5 (CH), 128.4 (CH), 127.7 (CH), 126.8 (CH), 56.5 (CH), 51.4 (CH), 15.4 (CH₃), 10.3 (CH₃). **GC-MS** m/z (%): 262 [M]⁺ (100), 247 (88), 219 (38), 115 (36). **cis-2a** ¹H NMR (600 MHz) δ (ppm): 7.40-7.37 (m, 2H), 7.34-7.24 (m, 4H), 7.24-7.19 (m, 2H), 7.18-7.16 (m, 1H), 7.00 (br s, 1H), 4.63-4.60 (m, 1H), 2.92 (quin, 1H, $J = 7.4$ Hz), 2.09 (d, 3H, $J = 1.7$ Hz), 0.76 (d, 3H, $J = 7.5$ Hz). ¹³C NMR (150 MHz) δ (ppm): 211.6 (Cq), 166.4 (Cq), 139.3 (Cq), 137.1 (Cq), 135.9 (Cq), 129.1 (CH), 128.5 (CH), 128.5 (CH), 128.4 (CH), 127.7 (CH), 127.0 (CH), 52.7 (CH), 45.6 (CH), 12.4 (CH₃), 10.4 (CH₃). **GC-MS** m/z (%): 262 (100), 247 (92), 219 (40), 115 (40).

Conflicts of interest

There are no conflicts to declare

Acknowledgements

The authors acknowledge Prof. Vito Capriati for helpful discussions and advice, Dr. Matteo Tiecco for providing betaine/malonic acid DES, Huvepharma srl, CRT (Cassa di Risparmio di Torino), Regione Piemonte and the Italian Ministry of Research for financial support.

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