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A Mild, Efficient and Sustainable Tetrahydropyranylation of Alcohols Promoted by Acidic Natural Deep Eutectic Solvents

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Introduction

Although the implementation of protecting-group free (PGF) strategies in synthesis offers some undeniable advantages both from an economic and an environmentally standpoint,[1] the development of novel methodologies for the introduction/removal of protecting groups which ideally fulfill the sustainability requirements (quantitative yields, use of environmentally responsible solvents, low E-factor and high atom economy) is of great significance and represents nowadays a urgent challenge of industrial research. In this context, the protection of hydroxy groups is of fundamental importance in almost every multi-step synthetic approach to complex molecular architectures of industrial interest, such as (glyco)peptides,[2] oligosaccharides,[3] nucleotides[4] and/or active pharmaceutical ingredients (APIs).[5] As a matter of fact, the introduction of a -OH protecting group is often essential to avoid undesired reaction pathways induced by the acidic and nucleophilic character of the hydroxy functionality. Among the myriad of hydroxy-protecting groups described so far, the tetrahydropyranyl moiety (THP) has attracted a considerable attention owing to the high stability of THP ethers under strongly basic reaction conditions, as well as in the presence of highly

nucleophilic (i.e. organometallics), oxidizing (metal oxides, peroxides) or reducing (molecular hydrogen, hydrides) agents.[6] The introduction of the THP protecting group (tetrahydropyranylation reaction) usually entails the addition of alcohols, thiols or phenols to the inexpensive and commercially available 3,4-dihydro-2*H*-pyran (DHP) at room temperature under Brønsted or Lewis acid catalysis (Figure 1A). To this purpose, several greatly diversified methods have been developed over the last three decades,[7] however these approaches often require the use of aprotic volatile organic solvents (VOCs), toxic and expensive reagents, broad excesses of chemicals, long reaction times and/or high temperatures.

Methods for the introduction of the tetrahydropyranyl moiety in a more sustainable fashion have been deeply investigated (Figure 1B). These approaches mainly rely on the use of acidic ionic liquids,[8] heterogenous catalytic systems[9] and organocatalysts[10] as promoters, or on the use of catalyst-free conditions.[11] Solvent-related issues have been addressed indeed by replacing the common VOCs with more environmentally friendly alternatives such as cyclopentyl methyl ether (CPME) and 2-methyltetrahydrofuran (2-MeTHF),[12] water[13] or working under solvent-free conditions.[14]

Since the seminal report by Abbott and co-workers,[15] many efforts have been devoted in the last decade to the development of Deep Eutectic Solvents (DESs) as new media for a wide range of uses. Owing to their peculiar physical properties, such as low volatility, flammability, and vapor pressure, increased chemical and thermal stability, DESs have been exploited as a superior class of improved solvents with impressive performances, both in terms of sustainability and reactivity, in a plethora of applications.[16] DESs are obtained by combining in eutectic molar ratio, specific Hydrogen bond Donors (HBDs) and Acceptors (HBAs), and the large pool of bio-derived and bio-inspired components available offers almost unlimited possibilities to formulate new DESs with remarkable and tunable properties. DESs composed only by primary metabolites and naturally occurring compounds (aminoacids, organic acids, sugars among others) are designated as Natural Deep Eutectic Solvents (NADESs) and constitute a relevant subclass of DESs.[17] The special features of NADESs, such as biodegradability and biocompatibility,[18] suggest that they potentially represent the ultimate alternative to traditional organic solvents (VOCs), and are now foreseen as promising contributors to more sustainable industrial processes.[19] Several eutectic mixtures of bioderived compounds have been prepared and employed for various applications,[20] ranging from organic synthesis and natural product research,[18] to drug formulation[21] and biocatalytic transformations.[22]

Among the impressive number of reports on the application of (NA)DESs in organic synthesis,[23] those involving the strong participation of one (or more) component of the NADES into the transformation, i.e. by reacting with other molecules present in the environment or by actively promoting the process, appear as the most appealing. Recently, acidic NADESs have been significantly employed as non-innocent reaction media in several transformations,[24] including the preparation of functionalized materials[25] and biomass valorization,[26] owing to their excellent physico-chemical properties, which can be easily tailored according to specific purposes. In this context, we recently reported the first application of carboxylic acid-based NADESs as environmentally benign reaction media to perform a versatile and high-yielding Nazarov cyclization of divinyl ketones, operating under simple aerobic reaction conditions and avoiding the use of strong Brønsted or Lewis acids.[27] Despite the potential of acidic NADESs as active reaction media in acid-catalyzed transformations, their use as solvents and promoters in protecting group chemistry remains hitherto unexplored and, to the best of our knowledge, the overall employment of NADESs as sustainable reaction media in functional group protection reactions is currently limited to few examples.[28]

On the basis of these considerations and motivated by our ongoing interest in the development of new sustainable synthetic methodologies,[29] we herein report a systematic study on the usefulness of acidic NADESs as non-innocent reaction media to promote the tetrahydropyranylation of alcohols, working under air and under mild reaction conditions (Figure 1C). Notable features of our report includes: a) the unprecedented use of bioinspired acidic deep eutectic systems as active reaction media for the introduction of a hydroxy-protecting group in a simple synthetic operation, b) the possibility to telescope tetrahydropyranylation/S_NAc transformations in a one-pot procedure using the same eutectic mixture and c) the easy scale-up of the methodology and the efficient recycle of the NADES, which are of great value in terms of efficiency and environmental sustainability.

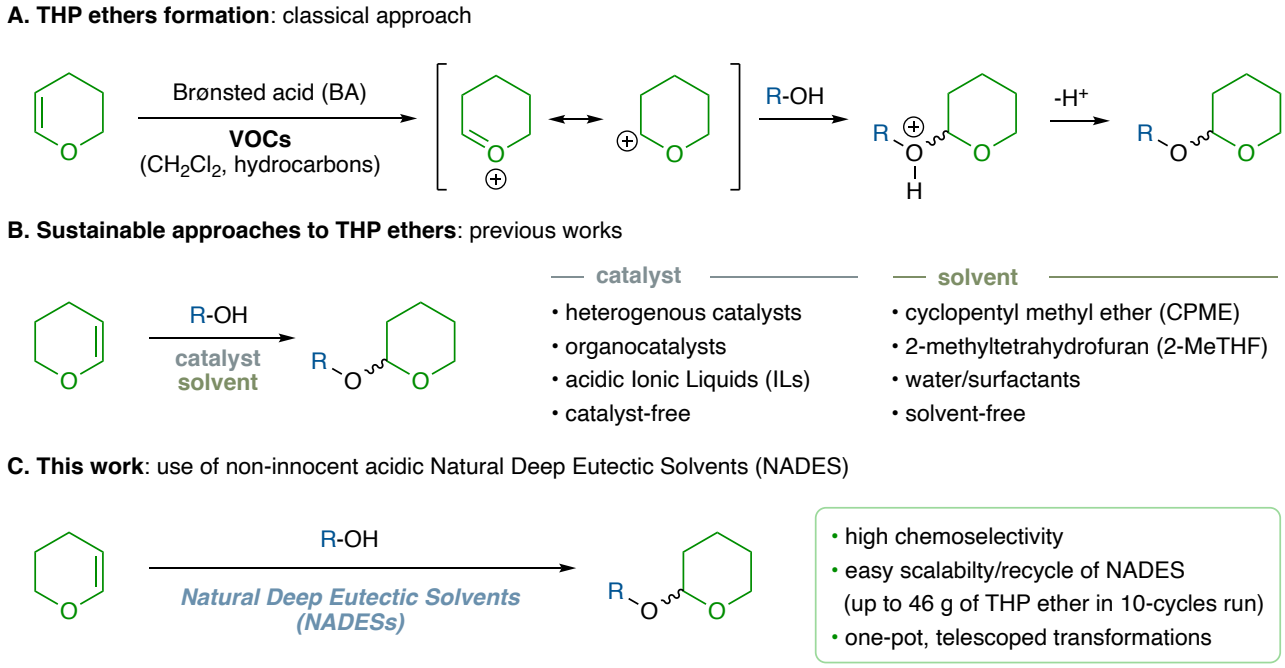


Figure 1. (A-B) State-of-the-art of the tetrahydropyranylation of alcohols and (C) aim of the work.

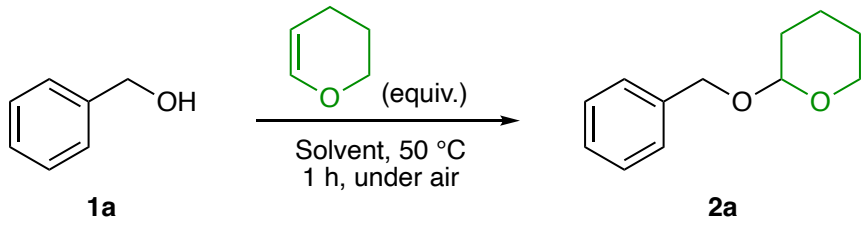
Results and discussion

Reaction development

We started our preliminary investigations using phenylmethanol **1a** as a model substrate. Based on our previous results,[27] a homogenous solution of **1a** (1 mmol) and DHP (1.5 equiv.) in a prototypical ChCl/malonic acid (1:1 mol mol^{-1}) eutectic mixture (400 mg) was vigorously stirred at 50 °C and under air for 1 h (Table 1, entry 1). After a simple workup procedure using the environmentally responsible CPME[30] as extraction solvent (see Supporting Information for details), the tetrahydropyranyl ether **2a** was recovered in quantitative yield, disclosing the unique mild catalytic activity of the acidic NADESs as non-innocent reaction media. Less satisfactory results were obtained lowering the temperature (entry 2) or the amount of DHP (entry 3), while other ChCl/carboxylic acid based NADESs containing oxalic (entry 4), L-(-)-malic (entry 5), glutaric (entry 6) or L-(+)-lactic acid as HBDs were less effective to promote the tetrahydropyranylation reaction, although ether **2a** was produced in slightly lower but reasonable yields (86-96%). As expected, less acidic NADESs based on glycerol (entry 8), urea (entry 9) and water (entry 10) as HBD were ineffective in promoting the reaction, indicating that the presence of an acidic component in the composition of the NADES is required.

Other environmentally friendly reaction media, such as water (entry 11), 2-MeTHF (entry 13) and 4-MeTHP (entry 14) also gave satisfactory results, however a stoichiometric amount of malonic acid as catalyst (1.5 equiv.) was required. Noteworthy, the use of a classical VOCs as dichloromethane (entry 15) was less effective than the above-mentioned sustainable media to promote the tetrahydropyranylation of **1a** under these conditions. With CPME as solvent (entry 12) a moderate yield of **2a** (65%) was obtained, which is likely due to the low solubility of malonic acid in this highly hydrophobic reaction media.

Table 1. Tetrahydropyranylation of benzyl alcohol **1a** under different conditions.[a]



1a **2a**

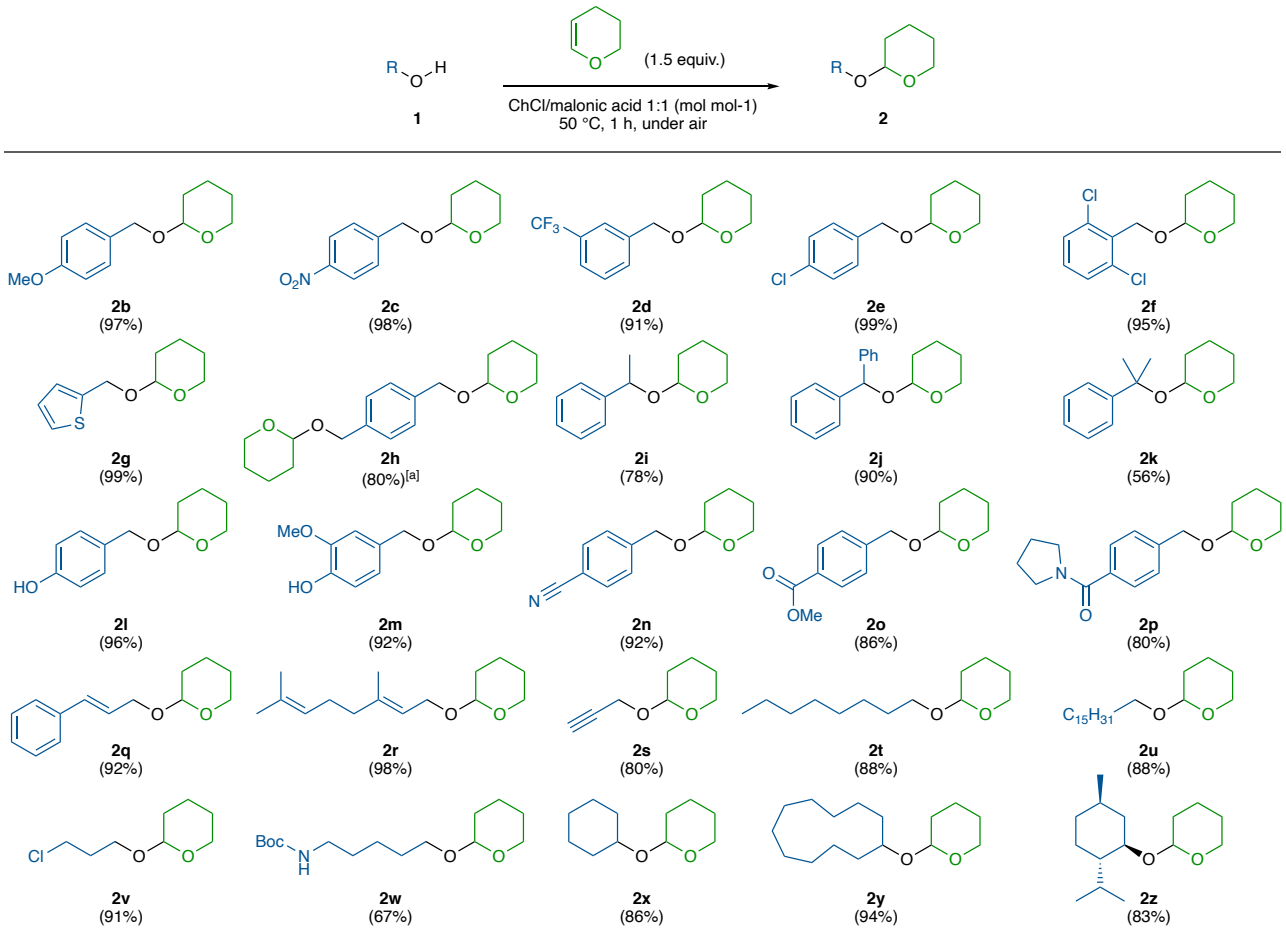
Entry	Solvent	DHP (eq.)[b]	**2a** (yield %)[c]
1	ChCl/malonic acid 1:1	1.5	99
2	ChCl/malonic acid 1:1	1.5	59[d]
3	ChCl/malonic acid 1:1	1.0	88
4	ChCl/oxalic acid 1:1	1.5	88
5	ChCl/L-(-)-malic acid 1:1	1.5	91
6	ChCl/glutaric acid 1:1	1.5	96
7	ChCl/L-(+)-lactic acid 1:1	1.5	86
8	ChCl/Gly 1:2	1.5	-
9	ChCl/H_2O 1:2	1.5	-
10	ChCl/urea 1:2	1.5	-
11	H_2O[e]	1.5	91
12	CPME[e]	1.5	65
13	2-MeTHF[e]	1.5	97
14	4-MeTHP[e]	1.5	95
15	CH_2Cl_2[e]	1.5	87

[a] Reaction conditions: **1a** (1.0 mmol), DES (400 mg) *or* solvent (0.500 mL), 1 h, 50 °C, under vigorous stirring. [b] DHP = 3,4-dihydro-2*H*-pyran. [c] Determined by

quantitative GC-FID analyses using calibration curves of **2a**. [d] T = 25 °C. [e] 1.5 equiv. of malonic acid were added as catalyst.

Scope and applications

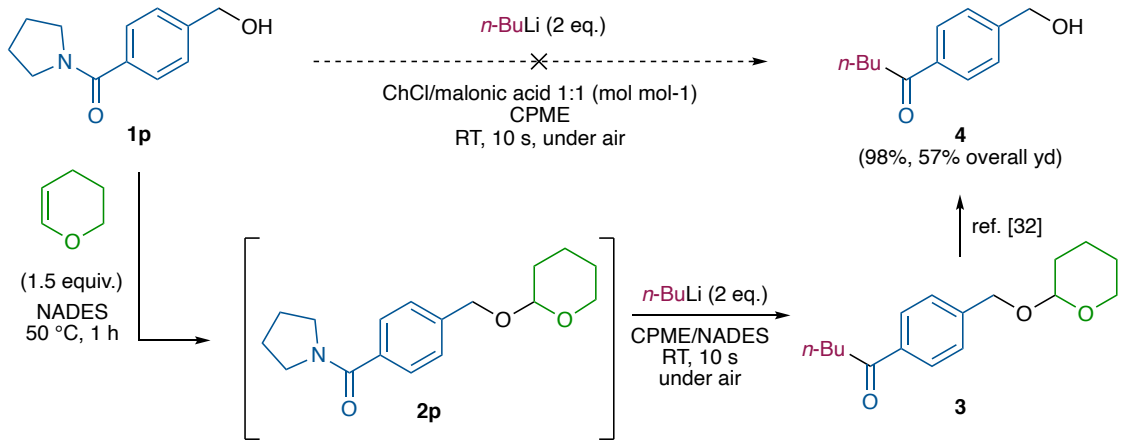
With satisfactory conditions in place, the scope and limitations of this transformation were evaluated for a series of functionalized primary, secondary and tertiary alcohols **1** exploiting the mild catalytic activity of the ChCl/malonic acid 1:1 (mol mol^{-1}) deep eutectic mixture as privileged reaction medium (Scheme 1). Pleasingly, the reaction proceeded smoothly *en route* to a variety of substituted (hetero)benzyl THP ethers **2b-g** bearing electron-donating (**2b**) and electron-withdrawing (**2c-f**) groups on the aromatic ring in excellent yields after workup (91-99%). Secondary alcohols were also efficiently converted into the corresponding tetrahydropyranylated products **2i-j**, whereas the sterically hindered ether **2k** was recovered only in moderate yield (56%) upon treatment of the parent tertiary alcohol under these conditions. The simultaneous protection of two hydroxyl groups was easily achieved by increasing the amount of 3,4-dihydro-2*H*-pyran, providing the bis-THP ether **2h** in good overall yield (80%) in a single synthetic operation. Remarkably, the use of the ChCl/malonic acid 1:1 (mol mol^{-1}) eutectic system as catalyst/solvent allowed the chemoselective introduction of the THP moiety a) on a primary alcohol in the presence of a competitive phenolic group (**2l-m**), and b) in the presence of several acid sensitive functional groups such as nitriles (**2n**), carboxylic acid derivatives (**2o-p**) and multiple C-C bonds (**2q-s**) without competitive pathways. Assorted (cyclo)alkyl derivatives served as competent reaction partners as well, thereby delivering the desired THP ethers **2t-z** in 67–96% yield.



Scheme 1. Tetrahydropyranylation of alcohols **1** in ChCl/malonic acid (1:1 mol mol^{-1}) deep eutectic mixture. Reaction conditions: **1** (1 mmol), 3,4-dihydro-2*H*-pyran (1.5 mmol), NADES (400 mg), 50 °C, 1 h. Yields of **2** refer to isolated products after flash column chromatography. [a] 3.0 equiv. of 3,4-dihydro-2*H*-pyran were used.

An attractive strategy to improve the efficiency of a chemical reaction in terms of efficiency and environmental sustainability is the design of telescoped, one-pot processes involving multiple sequential synthetic operations.[31] To further highlight the utility and the robustness of our methodology, we designed a telescoped approach for the preparation of the hydroxymethylated valerophenone **4** based on a preliminary tetrahydropyranylation of benzyl alcohol **1p**, followed by an *in situ* nucleophilic acyl substitution reaction promoted by *n*-BuLi (2 equiv.) on *N*-acylpyrrolidine **2p** in a heterogeneous CPME/NADES mixture (Scheme 2),[29d, 29e] using environmentally benign reaction media under bench-type reaction conditions. Whereas the direct treatment of **1p** with *n*-BuLi was unsuccessful due to the predominant lithium alkoxide formation, the introduction of the THP moiety as protecting group easily allowed the preparation of ketone **3**, which was

finally subjected to classical deprotection conditions[32] (see Supporting Information) to release the target hydroxylated valerophenone **4** in 57% yield over three steps.



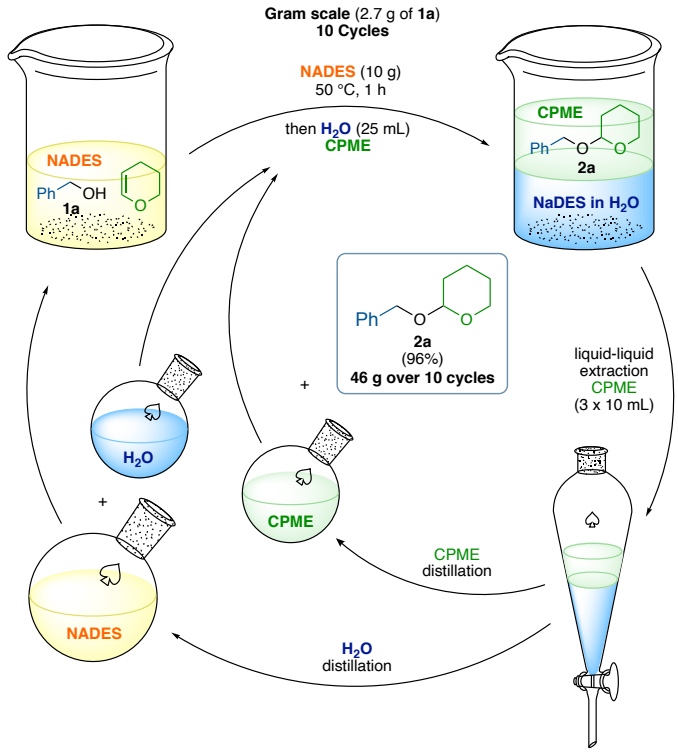
Scheme 2. Telescoped tetrahydropyranylation-S_NAc sequence for the synthesis of hydroxymethylated valerophenone **4**. NADES: ChCl/malonic acid (1:1 mol mol^{-1}).

Scalability and recycle

With the aim to assess the sustainability of this new synthetic protocol, we finally investigated the scalability of the process and the recyclability/reusability of the solvent (Figure 2A). To this end, we set up a gram scale synthesis of **2a** starting from 2.7 g of **1a** and 10 g of ChCl/malonic acid (i.e. 2.5 mmol of substrate per g of NADES) under the optimized reaction conditions. The tetrahydropyranylation proceeded smoothly in 1 h at 50 °C and, upon completion of the reaction, water (25 mL) was added to dilute the eutectic mixture. Liquid-liquid extraction using CPME (3 x 10 mL) allowed the isolation of **2a** from the reaction mixture. Removal of CPME by distillation from the organic layer allowed the recovery of **2a** in 88% yield (4.22 g), while water was removed under reduced pressure from the aqueous layer to restore the ChCl/malonic acid (1:1 mol mol^{-1}) eutectic mixture. Remarkably, the NADES was recovered and reused in subsequent recycling steps without further purification.[33] Both water (20 g out of 25 g) and CPME (28 mL out of 30 mL) were also recycled to increase the sustainability of the whole process. As shown in Figure 2B, the catalytic activity of the ChCl/malonic acid (1:1 mol mol^{-1}) eutectic mixture remains essentially unchanged up to ten cycles, leading to nearly quantitative yields of **2a** for each recycling step. Overall, this recycling procedure allowed the

preparation of 46.1 g of desired product, with an overall yield of 96% over 10 cycles (see Supporting Information for full experimental details).

A)



B)

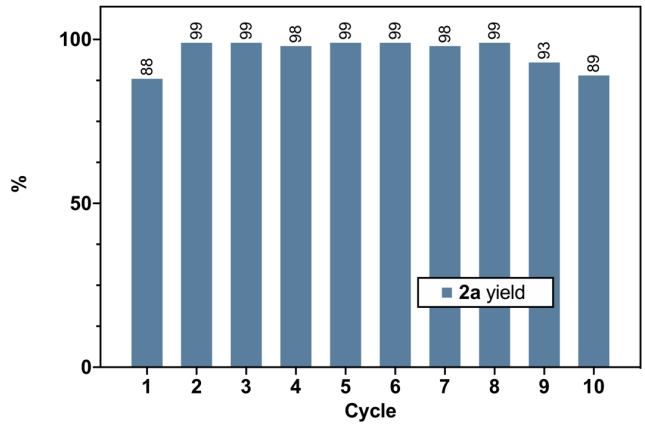
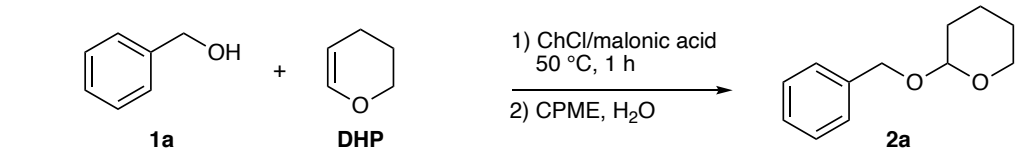


Figure 2. (a) Gram-scale reaction and recycling procedure. (b) Recyclability of the ChCl/malonic acid (1:1 mol mol^{-1}) deep eutectic mixture. Yields refer to isolated product.

The sustainability of the procedure has been evaluated by the calculation of green metrics such as the environmental factor (E-factor) and the process mass intensity (PMI).[34] The overall low impact of the NADES-based tetrahydropyranylation reaction herein described is clearly illustrated by the excellent atom economy of the reaction (100%) combined with the results shown in Figure 3, with optimal calculated E-factors of 14.7 for a single run and 2.9 for the overall 10-steps recycling sequence.[35]



single run:

2.70 g	3.15 g (1.5 eq.,1.05 g excess)	10 g NADES 25 g H_2O 25.89 g CPME	4.22 g (88%)

PMI = (2.70 + 3.15 + 10 + 25 + 25.89) g / 4.22 g = 15.8

E-factor = (1.05 + 10 + 25 + 25.89) g / 4.22 g = 14.7

10-cycles run:

27.0 g	31.5 g (1.5 eq.,10.5 g excess)	10 g NADES 25 g H_2O (5.0 g loss/cycle) 25.89 g CPME (1.73 g loss/cycle)	46.1 g (96%)

PMI = (27.0 + 31.5 + 10 + 70 + 41.46) g / 46.1 g = 3.9

E-factor = (10.5 + 10 + 70 + 41.46) g / 46.1 g = 2.9

Figure 3. Green metrics calculated for the tetrahydropyranylation of **1a** in NADES.

Conclusions

In summary, our report discloses that acidic Natural Deep Eutectic Solvents can be efficiently employed as effective reaction media to catalyze the tetrahydropyranylation of alcohols under mild reaction conditions. This methodology allows the preparation of several THP-ethers starting from primary, secondary and tertiary alcohols in short reaction times, and the products can be isolated resorting to a simple workup procedure using the environmentally responsible CPME as the extraction solvent. Remarkably, the reaction proceeds with excellent chemoselectivity in the presence of competitive hydroxy groups such as phenols, and well tolerates the presence of acid-labile functional moieties such as nitriles, esters or multiple C-C bonds. The utility and the versatility of this new synthetic protocol have been further highlighted by its scalability and the easy recyclability/reusability of the NADES, CPME and water, which are of great value in terms of efficiency and environmental sustainability. This allow multigram preparations of THP-protected alcohols using simple synthetic operations without any loss of the catalytic activity of the reaction media up to ten recycling steps,

lowering the overall environmental impact of the whole process. Overall, our methodology represents one of the few examples on the use of bioinspired deep eutectic solvents as sustainable reaction media in functional group protection, and constitutes the first application of bioinspired acidic DESs as catalytic systems in protecting group chemistry.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: tetrahydropyranylation • protecting group • deep eutectic solvents • sustainable chemistry • acid catalysis

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