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Deep eutectic solvent-catalyzed Meyer–Schuster rearrangement of propargylic alcohols under mild and bench reaction conditions†

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The Meyer–Schuster rearrangement of propargylic alcohols into α,β-unsaturated carbonyl compounds has been revisited by setting up an atom-economic process catalyzed by a deep eutectic solvent $FeCl_3{\cdot}6H_2O$/glycerol. Isomerizations take place smoothly, at room temperature, under air and with short reaction times. The unique solubilizing properties of the eutectic mixture enabled the use of a substrate concentration up to 1.0 M with the medium being recycled up to ten runs without any loss of catalytic activity.

The last decades have witnessed extraordinary advances in synthetic organic chemistry. Today, extensive compound libraries are prepared by using combinatorial chemistry–robotics and even the most complex natural products can be synthesized in a laboratory. However, the environmental concerns imposed by society today are forcing chemists to reshape the long-established paradigms, while concepts such as biorenewable resources, sustainability or circular economy are being rapidly implemented in the chemical industry.[1] Thus, besides the high yield and selectivity, a new synthetic process preferably must: (*i*) be safe for both human beings and the environment, (*ii*) take place under mild reaction conditions, (*iii*) be catalytic, and (*iv*) be performed using inexpensive and sustainable solvents. As a matter of fact, solvents account for about 80–90% of the total mass used in any organic reaction, and 80–85% of the waste produced.[2]

In this context, the use of non-conventional media has brought new perspectives in many research fields.[3] Deep eutectic solvents (DESs) are binary or ternary mixtures comprising at least one hydrogen bond acceptor (HBA) and at least one hydrogen bond donor (HBD) with a melting point much lower than that of either of the individual components and that of an ideal liquid mixture. DESs whose components come from renewable sources have emerged as green solvents due to their low toxicity and volatility and have been progressively replacing toxic and volatile organic compounds (VOCs) in many fields such as catalysis, main-group chemistry, electrochemistry, solar technology, and food and pharmaceutical formulations.[4] DESs showing Lewis type or Brønsted type acidity as well as other types of catalytic influence in various reactions have been found to display key roles in several cornerstone organic transformations such as oxidations, aldol or pericyclic reactions as well as condensation and multi-component reactions.[5] Among all the DESs, there is growing interest in those containing metallic salts acting as either HBDs or HBAs because of their inherent catalytic properties. For example, a DES consisting of $FeCl_3{\cdot}6H_2O$ and mono-ethylene glycol (MEG) (2 : 1) was shown to enable the conversion of cellulose into gluconic acid *via* sequential acidic hydrolysis and further oxidation of the transiently formed glucose.[6]

First described in 1922,[7] the Meyer Schuster (MS) rearrangement is the atom economical chemical transformation of propargyl alcohols into α,β-unsaturated carbonyl compounds. It usually requires harsh conditions with strong acids as catalysts, thereby competing with the Rupe reaction if the propargylic alcohol has C–H bonds at the β-position.[8] Independent studies by the Cadierno and García-Álvarez groups have shown that this rearrangement can take place with excellent selectivity and result in neat water when mediated by Lewis acid catalysts (*e.g.*, In- and Ag(I)-based catalysts) (Scheme 1). It required, however, temperatures up to 160 °C even with the use of microwave irradiation.[9] Milder conditions have been used successfully with a Re(I)-based catalyst in neat [BMIM][PF_6] as ionic liquid (IL), at 80 °C and under a nitrogen atmosphere, although the scope was restricted to terminal

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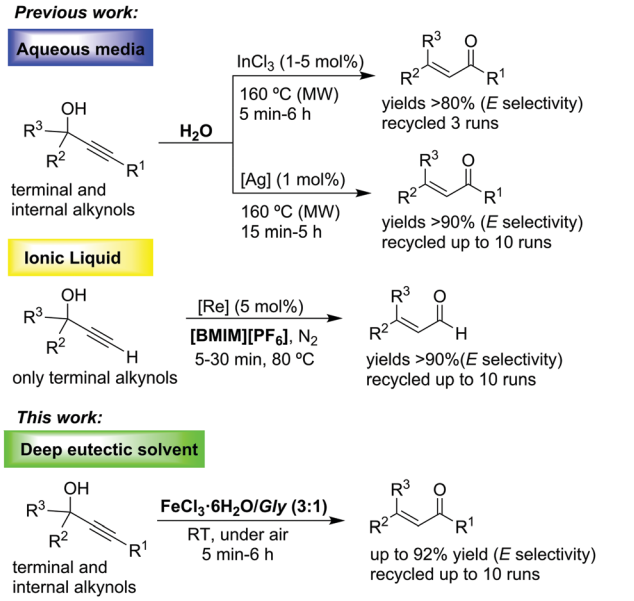

Scheme 1 Meyer–Schuster rearrangement of propargylic alcohols in aqueous media or alternative non-conventional solvents.

alkynes.[10] Herein, we unveil the unique catalytic properties of the eutectic mixture $FeCl_3{\cdot}6H_2O$/glycerol (Gly) (3 : 1 mol mol^{-1}) to promote smooth MS rearrangements, working at room temperature (RT, 25 °C) and under air.

From the extensive list of Lewis acidic DESs (LADESs) available,[11] we selected 8 mixtures bearing metal halides as HBDs or HBAs (Table 1). The MS rearrangement has been traditionally monopolized by using noble metal-containing complexes based on Au, Ag or Ru working in toxic VOCs.[12]

Table 1 MS rearrangement of 1,1-diphenyl-2-propyn-1-ol (**1a**) catalyzed by metallic LADES or solvents at RT and under air[a]

1a **1b**

Entry	LADES or solvent[b]	Catalyst (% mol)	Time (min)	c^c (%)
1	ChCl/$ZnCl_2$ (1 : 2)	—	240	—[d]
2	ChCl/$FeCl_3{\cdot}6H_2O$ (1 : 2)	—	240	—[d]
3	ChCl/$MnCl_2{\cdot}4H_2O$ (1 : 2)	—	240	—[d]
4	ChCl/$CuCl_2{\cdot}2H_2O$ (1 : 2)	—	240	—[d]
5	$ZnCl_2$/Gly (2 : 1)	—	240	20[e]
6	$FeCl_3{\cdot}6H_2O$/Gly (3 : 1)	—	10	>99
7	$FeCl_3{\cdot}6H_2O$/MEG (2 : 1)	—	10	>99
8	$MnCl_2$/Gly (2 : 1)	—	240	—[d]
9	$CuCl_2{\cdot}2H_2O$/Gly (2 : 1)	—	240	—[d]
10	Gly	$FeCl_3$ (10)	240	—[d]
11	Gly	$FeCl_3$ (40)	240	10
12	ChCl/Gly (1 : 2)	$FeCl_3$ (10)	240	—[d]
13	ChCl/MEG (1 : 2)	$FeCl_3$ (10)	240	—[d]
14	ChCl/H_2O (1 : 2)	$FeCl_3$ (10)	240	—[d]
15	H_2O	$FeCl_3$ (10)	240	—[d]
16	Toluene	$FeCl_3$ (10)	240	15

[a] Reactions performed under air, at RT using 0.2 mmol of **1a** (250 mM). [b] The ratio is in molar ratio. [c] Conversion measured by HPLC. [d] Null conversion after 24 h. [e] 70% conversion after 24 h.

We envisaged that the high concentration of catalytic species within metallic LADESs containing Zn, Fe, Mn or Cu could offset a lower reactivity. Isomerization of 1,1-diphenyl-2-propyn-1-ol (**1a**) into 3,3-diphenylpropenal (**1b**) was selected as a model reaction. The mild and bench-type reaction conditions involved RT, under air, and 250 mM as substrate loading. Preliminary screening revealed that only those DESs having metallic salt as the HBA actively catalyzed the rearrangement (Table 1, entries 5,6). The mixtures $FeCl_3{\cdot}6H_2O$/Gly (3 : 1 mol mol^{-1}) and $FeCl_3{\cdot}6H_2O$/MEG (2 : 1 mol mol^{-1}) emerged as optimal as they converted **1a** into **1b** in 10 min only (Table 1, entries 6 and 7). When alternatively using $ZnCl_2$/Gly (2 : 1 mol mol^{-1}), the conversion reached 70% after 24 h only (Table 1, entry 5). In all the other cases tested, even longer reaction times (up to 24 h) did not lead to any measurable conversion. A possible explanation might reside in the fact that $FeCl_3$ is the strongest Lewis acid of the series,[13] being on the same ground of reactivity of $InCl_3$, which is a traditional catalyst for MS rearrangements.[9] Quite interestingly, the null conversion displayed by the counterpart choline chloride (ChCl)-based DES, namely ChCl/$FeCl_3$ (1 : 2 mol mol^{-1}) (Table 1, entry 2), revealed the critical role played by $FeCl_3$ as an HBA to ensure a successful outcome. How important is the synergistic use of the two DES components and, thus, the peculiar three-dimensional structure of the so-formed DES? To answer this question, a solution of **1a** in Gly was treated with 10 mol% of $FeCl_3{\cdot}6H_2O$. After 24 h at RT, HPLC analysis revealed the presence of exclusively the starting material and by-products (Table 1, entry 10). Even upon increasing the concentration of $FeCl_3{\cdot}6H_2O$ up to 40 mol%, a very low conversion was detected (Table 1, entry 11). To gain more insights into the influence of the nature of the solvent, the reaction was run into three prototypical eutectic mixtures, namely ChCl/Gly (1 : 2 mol mol^{-1}), ChCl/MEG (1 : 2 mol mol^{-1}) and ChCl/H_2O (1 : 2 mol mol^{-1}) using 10 mol% of $FeCl_3{\cdot}6H_2O$, as well as in toluene and water. The reaction profile in toluene revealed low conversion and the formation of some unidentified products (Table 1, entry 16), whereas in the three DESs and water only the starting material was recovered (Table 1, entries 12–15). We conclude that the reaction is not or poorly affected by iron-based catalysts as such. This is in agreement with the few reports on Fe-catalyzed MS isomerizations.[14] At the same time, the poor solubility of $FeCl_3$ in those eutectic mixtures at RT, as well as of **1a** in water, poses critical pitfalls to approaching a manufacturing setting. The results compiled in Table 1 indicate the importance of the nanostructure of the DES on the reactivity of $FeCl_3{\cdot}6H_2O$/Gly (3 : 1 mol mol^{-1}), which enhanced the catalytic activity of iron species and displayed high-solubilization power.

By capitalizing on these results, we then evaluated the scope of the reaction by treating several propargylic carbinols with $FeCl_3{\cdot}6H_2O$/Gly at RT and under air (Table 2). Aryl-containing propargylic alcohols **2a–7a** bearing either electron-donating or electron-withdrawing groups (Table 2, entries 2–7) underwent a smooth MS rearrangement, thereby providing unsaturated aldehydes **2b–7b** in 85–92% yields. On the other hand, aliphatic alcohols **8a–10a**, bearing a C–H bond at the β-position, required

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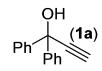
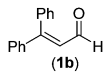
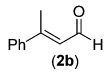
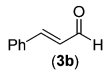
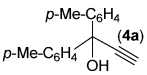
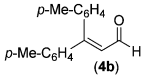
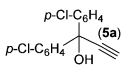
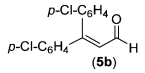
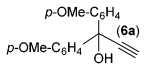
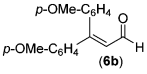
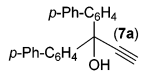
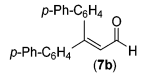
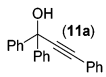
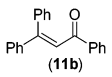
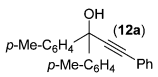
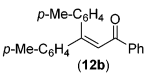
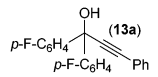
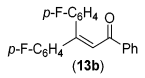
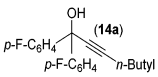
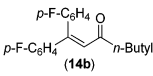
Table 2 $FeCl_3·6H_2O$/Gly (3 : 1 mol mol^{-1})-catalyzed isomerization of propargylic alcohols under air and mild reaction conditions[a]

Entry	Substrate	T (°C)	Time (min)	Product	c[c] (%)	Yield[d] (%)
1[b]	 (1a)	RT	10	 (1b)	>99	85
2	(2a)	RT	10	 (2b)	>99	86[e]
3	(3a)	RT	10	 (3b)	>99	85
4	 (4a)	RT	10	 (4b)	>99	90
5	 (5a)	RT	10	 (5b)	>99	85
6	 (6a)	RT	10	 (6b)	>99	92
7	 (7a)	40	60	 (7b)	>99	88
8	(8a)	40	480	(8b)	>99	45[f]
9	(9a)	40	480	(9b)	>99	60[f]
10	(10a)	40	480	(10b)	>99	65[f]
11	 (11a)	RT	30	 (11b)	>99	92
12	 (12a)	RT	30	 (12b)	>99	90
13	 (13a)	RT	30	 (13b)	>99	75
14	 (14a)	RT	30	 (14b)	>99	92

[a] Reactions performed under air, using 0.2 mmol of alcohol (250 mM). [b] Reaction performed at 1.0 M of **1a**. [c] Measured by HPLC. [d] Isolated yield after filtration through silica gel. [e] *E*/Z ratio was 86 : 14. [f] The yield was affected by the volatility of the products.

a slight heating to 40 °C and at 8 h to be fully converted to α,β-unsaturated methyl ketones **8b–10b** as a result of Rupe rearrangement (Table 2, entries 8–10).[8] Typically, Rupe-type rearrangements demand more drastic conditions than the MS counterparts.[9,10] Finally, internal propargylic alcohols **11a–14a** were also isomerized to the corresponding enones **11b–14b** (75–92% yields) at RT within 30 min reaction time (Table 2, entries 11–14). Once the substrate scope was assessed, we turned our attention to the greenness and applicability of the process. We first tried to set out a better volumetric productivity. Pleasingly, by increasing the substrate (**1a**) loading from 250 mM to 1 M, we achieved a similar

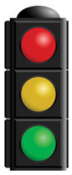


Fig. 1 Work-up and recycling procedures for the MS rearrangement in $FeCl_3·6H_2O$/Gly (3 : 1 mol mol^{-1}) using different solvents.

performance within 10 min reaction time (Table 2, entry 1). A one-gram-scale isomerization of **1a** (250 mM) proved to be equally feasible, with **1b** being isolated in a slightly higher yield (88%). On the other hand, the intrinsic concentration of $FeCl_3$ makes the recyclability of the DES mandatory to attain a sustainable and catalytically-sound process. Thus, we devised two possible reaction workups enabling the isolation of products. The first one consisted of an extraction step using an organic solvent. As depicted in Fig. 1, the tested solvents were classified into three groups: (*i*) miscible with DES, (*ii*) immiscible with DES but ineffective in the extraction, and (*iii*) immiscible with DES and effective in the extraction. The first group comprising environmentally friendly candidates such as cyclopentyl methyl ether (CPME), 2-methyl tetrahydrofuran (2-Me-THF) or dimethyl isosorbide (DMI), was discarded for obvious reasons. As for the second group, *n*-hexane and cyclohexane led to two phases, but the target products could be poorly extracted. Finally, some successful candidates were identified, namely toluene, CH_2Cl_2, $CHCl_3$ and cyrene, which remained immiscible with DES. These solvents extracted the product efficiently leaving the iron in the lower DES phase. In terms of sustainability, cyrene, which is a bio-based solvent obtained from cellulose,[15] is highly recommended compared to chlorinated derivatives. By using cyrene, the recyclability of the catalytic system was assessed in the isomerization of **1a** under the conditions described in Table 2 (see the ESI†). As a result, 10 consecutive runs were successfully accomplished, each with 10 min reaction time (*c* >99%). Going further, the second workup involved the challenge of avoiding any organic solvent. Indeed, inspection of the crude reaction mixture revealed that the MS rearrangement of internal propargylic alcohols like **11a** allowed the precipitation of a solid. The reaction mixture was then diluted with water and the solid was filtered off, thus providing pure **11b**, whereas the DES was easily reconstituted from the filtrate by evaporation of water. Following this procedure, the DES could be reused for 10 consecutive cycles without using VOCs in any step (*c* >99%, see the ESI†).

Finally, we investigated the utility of $FeCl_3·6H_2O$/Gly to promote some synthetic transformations involving catalytic $FeCl_3$ in organic solvents (Scheme 2, see the ESI† for details). First, the hydration of phenylacetylene (**15**) to afford acetophenone (**16**) was essayed at 300 mM in $FeCl_3·6H_2O$/Gly. The process showed complete conversion after 18 h at 45 °C in the absence of any co-catalyst/co-solvent,[16] and the catalytic system was recycled up to 4 runs (*c* >95%). It is worth mentioning that such reactions, when run in 1,4-dioxane and at 80 °C in the presence of 10% mol of $FeCl_3$, required up to

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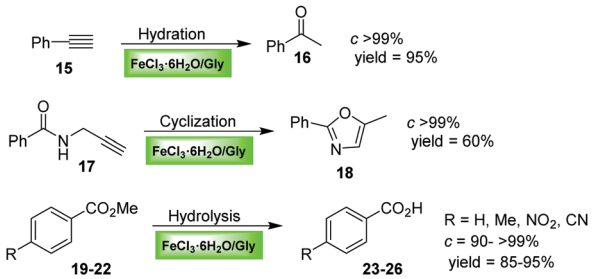

Scheme 2 Reactions catalyzed by DES $FeCl_3{\cdot}6H_2O$/Gly (3 : 1 mol mol^{-1}).

20 h to reach 96% of conversion, whereas in water led to a negligible yield.[17] Some years ago, an efficient synthesis of 2-oxazolines and 2-oxazoles was reported to take place *via* a selective cyclization of propargyl amides catalyzed by ZnI_2 or $FeCl_3$ in chlorinated solvents.[18] As a proof of concept, *N*-prop-2-ynylbenzamide (**17**, 200 mM) could be quantitatively converted into 5-methyl-2-phenyloxazole (**18**) at 40 °C within 4 h in $FeCl_3{\cdot}6H_2O$/Gly, and the catalytic system was recycled up to 5 runs ($c > 99\%$). Finally, we ascertained that the hydrolysis of several methyl benzoate esters (**19–22**) could smoothly be accomplished within 14 h at 70 °C (90–>99% conversion) in $FeCl_3{\cdot}6H_2O$/Gly to afford the corresponding acids (**23–26**) in 85–95% yields (ESI†), whereas the traditional $FeCl_3$-promoted (1.5 equiv. of $FeCl_3$) ester cleavage of **19** took up to 24 h at 115 °C in a sealed tube when using trichloroethylene as the solvent.[19] The Fe-based DES was stable at 70 °C, and thus it could be efficiently recycled for 5 runs (see the ESI†).

In conclusion, we report that MS isomerization of propargylic carbinols takes place in an Fe-based DES acting both as a solvent and a Lewis acid catalyst. The whole process was accomplished under very mild and bench-type reaction conditions, which is a recalcitrant challenge in this synthetic transformation, thereby breaking new grounds for further applications involving sensitive substrates. Besides streamlining the MS isomerization, the present work highlights the fascinating properties of the neoteric mixture $FeCl_3{\cdot}6H_2O$/Gly as a tool to expand the synthetic usefulness of iron catalysis in sustainable reaction media.

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Conflicts of interest

There are no conflicts to declare.

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