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Domino dehydration/intermolecular (enantioselective) ketone-ene reactions catalysed by a simple solid in batch and in flow†

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The intermolecular carbonyl-ene reaction of ketones is still considered a challenge in organic chemistry, particularly with reusable solid catalysts, and implemented in a domino reaction. Herein, we show that the extremely cheap and non-toxic solid salt $MgCl_2$ catalyzes the reaction of trifluoromethyl pyruvates not only during the conventional carbonyl-ene reaction with various aromatic and alkyl alkenes (in very high yields, up to >99%) but also in a domino reaction with the corresponding alcohols (precursors to the alkenes) in similar good yields. The solid can be reused in both cases without any erosion of the catalytic activity and can be employed in an in-flow process to maximize the reaction throughput. Besides, the reaction can be performed under solventless reaction conditions. Addition of a catalytic amount of chiral binaphthyl hydrogen phosphate allows carrying out the reaction with a reasonable enantiomeric excess (up to >70%) and in flow, in a rare example of enantioselective solid-catalyzed domino carbonyl-ene reaction using a cheap, simple, readily available and physically mixed catalytic solid. The $MgCl_2$ -catalytic system is also active in the industrially relevant citronellal-to-isopulegol carbonyl-ene reaction. These results pave the way to design sustainable domino carbonyl-ene reactions with extremely cheap solid catalysts.

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1 Introduction

Use of reusable solid catalysts in relatively complex organic transformations is a key step towards the development of a sustainable organic synthesis.¹ However, these solid catalysts should ideally be readily available, non-toxic and as cheap as possible;² otherwise, researchers tend to employ much easier-to-prepare soluble catalysts, although the latter cannot be recovered at the end of the reaction. A representative example of the lack of simple solid catalysts in organic transformations is the carbonyl-ene reaction, which typically employs soluble catalysts, such as metal salts, complexes or organocatalysts (Fig. 1).³

The carbonyl-ene reaction is a fundamental reaction in organic chemistry, with industrial implementation in the multi-ton manufacturing of isopulegol to menthol,^{4a,b} the synthesis of drugs^{4c} or the production of pheromones,^{4d} to name a few.^{4e} This [3,3]-sigmatropic transformation proceeds with complete atom economy, but it is highly dependent on the nature of the carbonyl group since aldehydes react much faster than ketones.

While these reactive differences are not so relevant for intramolecular reactions, where the entropic gain by cyclic formation overcomes not only the reactivity resistance but also the

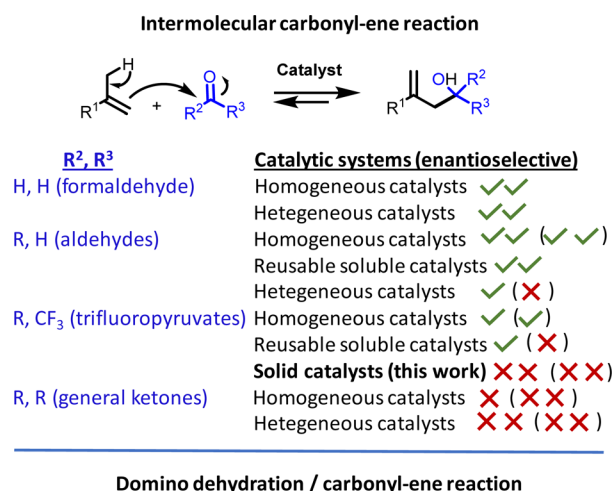


Fig. 1 Overall view of the catalytic maturity during the intermolecular carbonyl-ene reaction of the different reactive carbonyl groups and the envisioned domino reaction with ketones. ✓✓ well-resolved, ✓ several examples, X few examples, XX rare examples or none.

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potential reversible reaction and undesired alkene isomerization reactions, the latest undesired issues become dominant in the intermolecular carbonyl-ene reaction.⁵ Therefore, it is not surprising that aldehydes are, by far, the most studied starting materials for the intermolecular reaction and that various soluble catalysts have been reported in both racemic and enantioselective versions,^{3,6} including strategies such as ionic liquid solvents and selective precipitation to recover the catalyst (Fig. 1).⁷

Solid catalysts have been employed successfully for the intermolecular aldehyde-ene reaction, in particular for the coupling with formaldehyde, where simple solid catalysts such as zeolites are able to catalyze the transformation.⁸ However, for less reactive aldehydes, more complex solids are typically employed,^{4b,9} which often involve elaborated hybrid materials where a soluble catalyst has been immobilized by covalent anchoring on the solid surface or physically entrapped into a micro-structured structure,¹⁰ and in well-designed catalytic sites inserted into metal-organic frameworks.¹¹ These solid catalysts of course merit acknowledgement and pave new ways to perform sustainable aldehyde-ene reactions; however, their limited availability and high price hamper wide-ranging catalytic applications (Fig. 1).

The intermolecular ketone-ene reaction is much less developed than the aldehyde reaction, in all types of versions to be considered, *i.e.* racemic,¹² enantioselective,¹³ with reusable soluble catalysts^{7,14a,b} or solid-catalyzed,^{14c} with most of the examples reported for trifluoromethyl pyruvates. Racemic intermolecular trifluoromethyl pyruvate-ene reactions are catalysed by either Cu,^{12a} Ni^{12a} or Fe^{12b} salts, and enantioselective reactions have been reported for Cu,^{13a} Pt,^{13b} Pd,^{13b,c} Rh,^{13d} Ti^{13e} and Mg (solventless) chiral complexes,^{13f} and also with organocatalysts.^{13g-i} Regarding reusable soluble metal catalysts, the ionic liquid approach has been studied for Pd⁷ and In^{14a} complexes, and the selective precipitation approach, for Cu complexes.^{14b} However, trifluoromethyl pyruvate-ene reactions with solid catalysts are particularly devoid of examples in the literature: we just found a 20 years-old study on entrapped Cu complexes in zeolites.^{14c} Thus, any solid catalyst able to catalyze the intermolecular ketone-ene reaction, even for activated ketones such as trifluoromethyl pyruvates, would constitute a step forward in the field. Furthermore, if this solid is readily available, cheap and non-toxic, in other words really sustainable, the advance will be more relevant, since it is plausible that any other easier carbonyl-ene reaction, *i.e.* with aldehydes or intramolecular, will also be feasible with this solid catalyst. The enantioselective version with this type of cheap and available solid will only make sense, in our opinion, with a relatively simple and cheap chiral substance, after a physical mixture with the solid, since an otherwise elaborated complex material synthesis will avoid any wide access to researchers.

Domino reactions are desirable in organic synthesis to minimize the isolation of intermediates and maximize the throughput of the reaction, *i.e.* to intensify the chemical process.¹⁵ The domino reaction makes further sense if different reactions are catalysed by the same compound. The alkenes employed in the carbonyl-ene reaction come from the

corresponding cheaper alcohols, after dehydration, thus a domino reaction from the alcohol to the final carbonyl-ene product would be of interest. However, this domino reaction is not straightforward with ketones since the equivalent of H₂O generated during the dehydration reaction can degrade most of the metal catalysts employed so far for the carbonyl-ene reaction; indeed, we could not find in the literature any example of domino dehydration/intermolecular carbonyl-ene reaction with ketones, although other domino carbonyl-ene reactions have been reported.¹⁶ A simple solid catalyst for the intermolecular carbonyl-ene reaction of trifluoropyruvates, compatible with water, would open the door for this envisioned domino reaction.

MgCl₂ is one of the cheapest solids available, massively used in industrial catalysis as a support/modifier for the Ziegler-Natta catalyst.¹⁷ However, the catalytic behaviour of MgCl₂ in organic synthesis is yet to be exploited.¹⁸ Herein, we show that MgCl₂ catalyzes not only the intermolecular ketone-ene reaction of trifluoromethyl pyruvates in high yields, but also the domino dehydration/intermolecular (enantioselective) carbonyl-ene reaction with tertiary alcohols, and that the solid is fully reusable (up to ten uses for the ketone-ene reaction). MgCl₂ has apparently not been reported as a catalyst but as an additive in carbonyl-ene reactions.¹⁹ Besides, this process can be run in flow. The use of an amorphous solid catalyst such as MgCl₂ enables the suppression of the solvent, in contrast to some elaborated or micro-structured solid catalysts, where the diffusion of reactants and products plays a key role during the catalytic process.²⁰ Thus, our protocol here can be carried out solventless and with a 1/1 molar ratio of both reactants (the ketone with either the alcohol or the alkene), which maximizes the sustainable value of the process and also makes a substantial difference with many of the catalysts reported for the intermolecular carbonyl-ene reaction. In addition, the enantioselective version is achieved by mixing MgCl₂ with binaphthyl hydrogen phosphate,²¹ one of the cheapest chiral proton substances available, to be run in flow with decent enantioselective excess.

2 Experimental section

2.1 Materials

All reagents were obtained from commercial sources and used as received. Anhydrous MgCl₂ was obtained from Merck-Sigma. The list of synthesized compounds and their abbreviations (3–29) is given in the ESI†.

2.2 Instrumentals

See ESI† for details.

2.3 Catalytic tests

2.3.1 Reaction procedure for the MgCl₂-catalyzed racemic intermolecular ketone-ene reaction. In a 2 mL glass vial equipped with a magnetic stir bar, 0.25 mmol of the styrene derivative and 0.25 mmol of the corresponding pyruvate were introduced along with 0.0125 mmol of anhydrous solid MgCl₂,



and the mixture was magnetically stirred at room temperature for the required time. If the solvent was employed, 0.5 mL of solvent was added. The reaction was followed by either GC or TLC. At the end of the reaction, the crude was filtered for the removal of the catalyst and purified by column chromatography (if necessary) to afford the isolated products.

2.3.2 Reuses of MgCl₂ for the intermolecular ketone-ene reaction. After the completion of the first reaction, the crude mixture was separated from the catalyst *via* centrifugation, and the solid was washed a couple of times with *n*-hexane and dried under reduced pressure, to be directly used for the next reaction. The reaction yields were determined after analysis of the liquid phase by GC.

2.3.3 Reaction procedure for the MgCl₂/binaphthyl hydrogen phosphate-catalyzed enantioselective intermolecular ketone-ene reaction. In a 2 mL vial equipped with a magnetic stir bar, 0.0125 mmol of anhydrous MgCl₂ and 0.05 mmol of the corresponding chiral ligand were introduced, along with 0.5 mL of dichloromethane (DCM), and the mixture was stirred for 30 min. After that time, 0.25 mmol of the styrene derivative and 0.25 mmol of methyl 3,3,3-trifluoropyruvate **2** were introduced, and the mixture was magnetically stirred for the required time at room temperature. Reaction yields were determined by GC and the enantiomeric excess (ee) was determined by chiral HPLC.

2.3.4 Reaction in-flow for the intermolecular ketone-ene reaction. A fixed-bed tubular reaction, with a length of 21.5 cm and an inner diameter of 4 mm, was filled with 2 g of silicon carbide followed by a mixture of 2 g of silicon carbide and 111 mg of a mixture of anhydrous MgCl₂ and the chiral phosphoric acid **21** in an $\approx 5/2$ weight ratio, and finally, filled with another 2 g of silicon carbide. Then, 1.3 mL of α -methyl styrene **1** diluted in 9.7 mL of DCM and 1 mL of methyl 3,3,3-trifluoro pyruvate **2** diluted in 10 mL of DCM were introduced at once through a syringe pump with the chosen flow. Aliquots were periodically taken at the exit of the reactor and measured by GC to determine the yield of the reaction at different times, and chiral HPLC to determine the ee.

2.3.5 Synthesis of isopulegol **28 from citronellal **27**.** Citronellal **27** (0.25 mmol) in DCM (0.5 M) and anhydrous MgCl₂ (20 wt%, ≈ 10 mg) were placed in a 2 mL vial equipped with a magnetic stir bar, and the mixture was magnetically stirred at 40 °C overnight (the vial was sealed to avoid losses of DCM, the boiling point of which is 39.6 °C). After the reaction, the solid was separated and the mixture was analyzed by GC and purified by column chromatography to give product **28** in 52% isolated yield.

2.3.6 Reaction procedure for the MgCl₂-catalyzed racemic domino dehydration/intermolecular ketone-ene reaction. In a 2 mL glass vial equipped with a magnetic stir bar, 0.25 mmol of the alcohol derivative and 0.25 mmol of the corresponding pyruvate were introduced along with 0.0125 mmol of anhydrous solid MgCl₂, and the mixture was magnetically stirred in a pre-heated oil bath at 50 °C for the required time. If the solvent was employed, 0.5 mL of dichloroethane (DCE) was added. The reaction was followed by GC after taking aliquots periodically, diluting them in 1 mL of DCM, filtering through a 25 μ m

nylon™ filter and adding *N*-dodecane (11 μ L, 0.05 mmol) as an external standard.

2.3.7 Gram-scale domino reaction. In a 50 mL round-bottomed flask equipped with a magnetic stir bar, anhydrous solid MgCl₂ (285 mg, 3 mmol), 2-phenylpropan-2-ol **29** (4.2 g, 30 mmol) and methyl 3,3,3-trifluoropyruvate **2** (4.5 mL, 30 mmol) were sequentially weighted, and the mixture was magnetically stirred in a pre-heated oil bath at 50 °C for 18 h. After that time, the reaction was cooled and the solid catalyst was removed by decantation. The liquid phase was analysed by GC and NMR.

2.3.8 Leaching test. Two parallel reactions were set up in 2 mL glass vials equipped with a magnetic stir bar, as described above, but at 0.3 mmol scale and using DCE as the solvent (0.5 M). The reactions were followed by GC after taking 50 μ L aliquots periodically, diluting them in 1 mL of DCM, filtering through a 25 μ m nylon™ filter and adding *N*-dodecane (11 μ L, 0.05 mmol) as an external standard. After 40 min, one of the reactions was filtered in hot through a 25 μ m nylon™ filter, and the filtrates were placed in another 2 mL glass vial equipped with a magnetic stir bar at 50 °C. Both reactions were followed by GC as described above, for additional 3 h.

2.3.9 Reuses of MgCl₂ for the domino reaction. After completion of the first reaction, the crude mixture was separated from the catalyst *via* decantation, and the solid was directly used for the next reaction. The reaction yields were determined after analysing the liquid phase by GC.

2.3.10 Reaction in-flow for the domino reaction. The same procedure for in the ketone-ene reaction was followed, but using 2-phenylpropan-2-ol **29** instead of α -methyl styrene **1**.

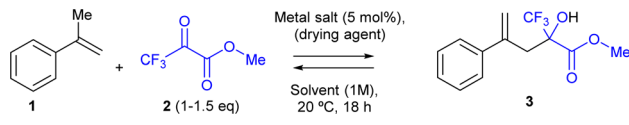
3 Results and discussion

3.1 Intermolecular carbonyl-ene reaction with trifluoromethyl pyruvates

3.1.1 Catalytic results with simple metal salts. First, we studied the intermolecular ketone-ene reaction with simple metal salts, in order to find a catalyst that will be compatible with the envisioned domino reaction. Table 1 shows the results for the benchmark intermolecular ketone-ene reaction between α -methyl styrene **1** and trifluoromethyl pyruvate **2**, catalyzed by different metal salts. We chose Cu and Fe simple salts (chlorides, acetates, *etc.*) in the first approach to study the reaction, since previous reports mainly used more expensive (and acidic) triflate-type salts.^{12b} The use of readily available CuCl₂·2H₂O led to a complete polymerization of the styrene reactant **1** in dichloromethane (DCM) as a solvent, despite using an excess (1.5 equiv.) of pyruvate **2** at room temperature (entry 1), which indicates that some pre-hydrated metal salts could not be compatible with the carbonyl-ene reaction. Thus, we repeated the reaction with anhydrous CuCl₂ and 4 Å molecular sieves (MS), and in contrast with the aqueous catalyst, a quantitative yield of the carbonyl-ene reaction product **3** was obtained after 18 h reaction time, after monitoring the reaction mixture by gas-chromatography coupled to mass spectrometry (GC-MS, entry 2). Cu(OTf)₂ was also tested, and the reaction also proceeded quantitatively (entry 3). These results indicate that it is not necessary to use highly strong acid metal salt catalysts but



Table 1 Catalytic results for the intermolecular ketone-ene reaction between α -methyl styrene **1** (0.25 mmol) and methyl pyruvate **2** (1–1.5 equiv.) with metal salts (5 mol%) in different solvents (1 M) at room temperature (20 °C) for 18 h



Entry	Metal catalyst (5 mol%)	2 (eq.)	Solvent	Drying agent ^a	3 ^b (%)
1 ^c	CuCl ₂ ·2H ₂ O	1.5	DCM	—	<1
2	CuCl ₂			4 Å MS	>99
3	Cu(OTf) ₂			—	>99
4	Cu(OAc) ₂			—	65
5	CuO			—	66
6	CuCl			—	87
7	FeCl ₂			—	91
8	CuCl ₂			—	>99
9	Cu(OTf) ₂			—	>99
10	—			4 Å MS	80
11	—			CH(OEt) ₃	47
12	—			—	55
13	—			MgSO ₄	80
14	MgCl₂			—	>99
15	MgO			—	67
16	MgCO ₃			—	30
17	CaCO ₃			—	38
18	MgCl ₂	1.0		—	>99
19			Toluene	—	86
20			Acetone	—	3
21			EtOAc	—	19
22			EtOH	—	<1
23			Et ₂ O	—	56
24			ACN	—	61
25			THF	—	<1
26			No solvent	—	>99

^a MS: molecular sieves. ^b GC yields, double-checked by ¹H-NMR, and referred to the starting material **1**. ^c Polymerization of **1**.

chloride salts are enough to achieve >99% yield of **3**, provided that water is not pre-coordinated to the metal catalyst.

Other Cu salts such as Cu(OAc)₂, CuO and CuCl gave intermediate yields of product **3** (65–87%, entries 4–6) after 18 h of reaction time, and the reactions did not progress further beyond an additional 5–10% after monitoring the reaction for 96 h (4 days). These results suggest that an intermediate acidity of the metal salt is positive to catalyze the reaction. The iron salt FeCl₂ gave 91% yield (entry 7) and the more active Cu salts also gave >99% yield of **3** without the 4 Å MS (entries 8 and 9). A blank experiment with 4 Å MS gave 80% yield of **3** (entry 10),^{22a} higher than the blank experiment with an organic drying agent (ethyl acetal, 47%, entry 11) or without any additive or catalyst (55%, entry 12). The use of another inorganic drying agent such as MgSO₄ gave 80% yield of **3** (entry 13), which not only confirms that the removal of water is beneficial for the reaction, but also suggests that water can be present during the reaction and that inorganic drying agents might also catalyse the reaction.^{22a} To check this, MgCl₂ was used as a catalyst without any

other drying agent, and product **3** was obtained >99% yield (entry 14). Other Mg²⁺ salts such as MgO and MgCO₃ were much less active for the reaction (30–67%, entries 15 and 16) as well as CaCO₃ (38%, entry 17). The fact that basic metal salts decrease the yield below the blank experiment (compare entries 16, 17 and 12) indicates that neutral to acid conditions are necessary for the carbonyl-ene reaction to proceed.

The reaction was repeated without any excess of pyruvate **2**, *i.e.* with equimolecular amounts of **1** and **2**, and >99% yield of **3** was still obtained (entry 18). The kinetic experiment shown in Fig. 2 clearly showcases the catalytic action of MgCl₂. At this point, the screening of different solvents was performed (entries 19–26). Toluene was the only solvent to give a high yield of **3** (86%, entry 19) with equimolecular amounts of **1** and **2**, while acetone, ethyl acetate (EtOAc), ethanol (EtOH), diethyl ether (Et₂O), acetonitrile (ACN) and tetrahydrofuran (THF) gave poorer results (>1–63%, entries 20–25). It seems that somewhat polar aprotic solvents are beneficial for the reaction.^{22b} Grati-fyingly, the solventless reaction gave >99% yield of product **3**. Notice that neither the reactants nor the solvents were thoroughly dried, indicating that the reaction conditions were compatible with water in the reaction medium, of interest for a possible domino dehydration/carbonyl-ene reaction. A kinetic experiment confirms the catalytic action of MgCl₂ under solventless reaction conditions (Fig. S1†). This result is satisfactory from both an economic and sustainable point of view, since the carbonyl-ene reaction proceeds quantitatively without any type of waste (nor solvent) and with an extremely cheap and easy-to-remove solid catalyst (see ahead), to give the final product **3** after simple filtration. It is worthy to comment here that these catalytic results with Mg(II) are drastically different from those previously reported with some soluble Mg(II) triflate salts,^{13f} since our study is focused on a simple, non-toxic, inexpensive and reusable solid catalyst. MgCl₂ acts here as

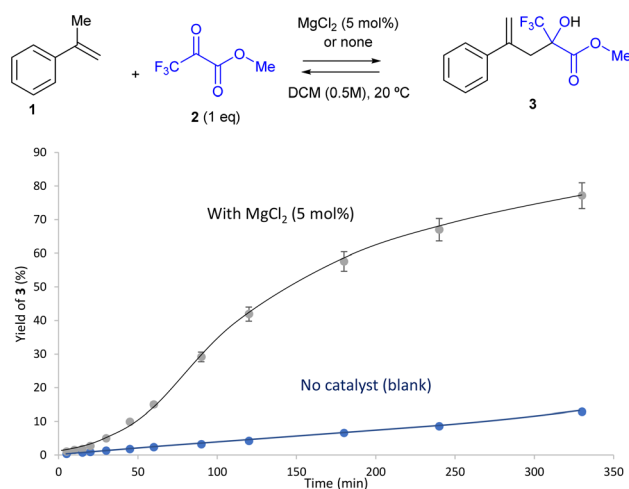


Fig. 2 Kinetic plot of the intermolecular ketone-ene reaction between α -methyl styrene **1** and methyl pyruvate **2** (1 equivalent) catalyzed by MgCl₂ (5 mol%, black line) or none (blue line) in a DCM (0.5 M) solvent at room temperature. Lines are a guide to the eye. GC yields. Error bars account for 5% uncertainty.



a general acid catalyst for the carbonyl-ene reaction, the mechanism of which is well known (see Fig. 1).

3.1.2 Scope of the reaction. The carbonyl-ene reaction of different alkenes and pyruvates, catalyzed by MgCl_2 , was carried out under optimized solventless reaction conditions, *i.e.* 5 mol% of MgCl_2 , room temperature and 18 h reaction time. The results are shown in Fig. 3. For the sake of comparison, the corresponding experiments with DCM as a solvent were also performed.

A variety of *para*-substituted α -methyl styrenes engage well with pyruvate **2** to give the carbonyl-ene methyl-, chloro-, trifluoro-, hydroxy- and methoxy-substituted products **4–8** in very good isolated yields (67–94%) under solventless reaction conditions. The *ortho*-substituted products **9–10** were also

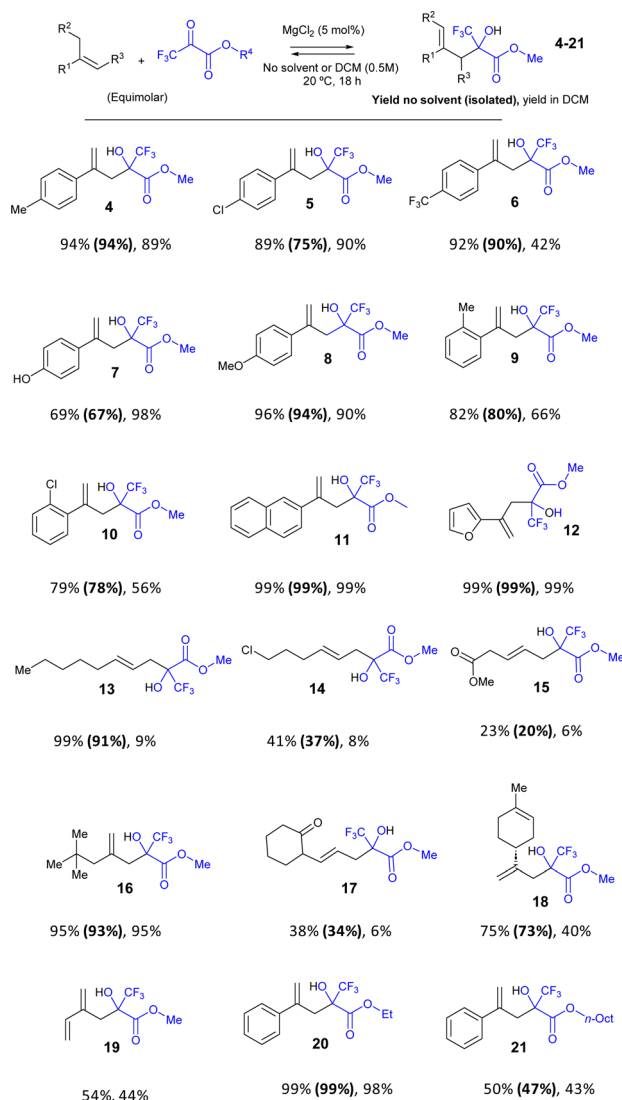


Fig. 3 Scope of the carbonyl-ene reaction of different alkenes and pyruvates catalyzed by MgCl_2 (5 mol%), at room temperature for 18 h, without any solvent or DCM (0.5 M). The results from left to right indicate: GC yield for the solventless reaction, isolated yield (between parentheses) and GC yield in DCM. Reactions were performed twice, showing very good reproducibility.

obtained in good isolated yields (78–80%). It is noteworthy that some of these products are obtained in significantly lower yields when DCM is used as a solvent (products **6**, **9** and **10**). On the contrary, only in one case (product **7**), the yield was higher in DCM, probably due to the lower solubility of the phenol group. Other aromatic rings such as naphthalene and furan are tolerated, to give products **11–12** in quantitative (99%) isolated yields.

A simple alkyl alkene also works satisfactorily in the reaction (product **13**, 91% isolated yield after 72 h reaction time), although the presence of a chloro-substitution significantly decreases the final yield (product **14**, 37% isolated yield) as well as with an ester substituted alkene (product **15**, 20% isolated yield) after 6 days. However, a *tert*-butyl-substituted alkyl alkene is obtained in very high yields (product **16**, 93% isolated yield). An unsaturated ketone is also reactive (product **17**, 34% isolated yield) and particularly remarkable is the reaction with the natural compound limonene, to give product **18** in 73% isolated yield. It is noticeable that a good tolerance to different functional groups is found during the reaction, and also that most of the alkyl alkenes showed lower yields in the DCM solution, in some cases <10% GC yield.

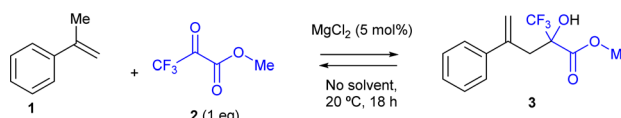
A diene such as isoprene also reacts to give product **19** in 54% yield; however, the Diels–Alder reaction competes under the present reaction conditions. Since both reactions are in equilibrium, the products of both reactions may interconvert during the course of the reaction. In order to assess this hypothesis, kinetic experiments were performed. The results (Fig. S2†) show that, indeed, the Diels–Alder product of isoprene with pyruvate **2** rapidly appears at the beginning of the reaction, to then slow and finally decrease, and give the carbonyl-ene product **19**. The formation of **19** is only possible by the action of MgCl_2 , since the reaction without catalyst gives the Diels–Alder product in >98% yield, at the same initial reaction rate than with MgCl_2 (Fig. S3†). In other words, MgCl_2 takes advantage of the equilibrium of the Diels–Alder reaction to drive the reactants to the carbonyl-ene product **19** under the present reaction conditions.

The pyruvate methyl ester can be changed, and ethyl and *n*-octyl pyruvates were also reactive with alkene **1**, to give products **20** and **21** in 99% and 47% isolated yields, respectively. These results, together, demonstrate the reasonable generality of the MgCl_2 -catalyzed pyruvate-ene reaction under solventless reaction conditions and employing equimolecular amounts of reactants, which results in the higher yields, to directly isolate the product after simple filtration.

3.1.3 Reuses of MgCl_2 . MgCl_2 is one the cheapest metal chlorides in the market, with an estimated price ten times lower than that of FeCl_2 (~3 € per kg). Therefore, its catalytic use in the carbonyl-ene reaction does not have any impact in the reaction material costs, neither to the process sustainability (MgCl_2 is non-toxic and easy-to-recover). With these data, in our opinion, a simple one catalytic use of MgCl_2 for the carbonyl-ene reaction justifies the sustainability of the process. Nevertheless, the reusability of MgCl_2 (5 mol%) was tested for the reaction between **1** and **2** under the optimized solventless reaction conditions. The results in Table 2 show that MgCl_2 can



Table 2 Reuses of MgCl₂ (5 mol%) for the intermolecular ketone-ene reaction between α -methyl styrene **1** and methyl pyruvate **2** (1 equivalent) without any solvent at room temperature for 18 h. GC yields



Use	1	2	3	4	5	6	7	8	9	10
Yield (%)	92	86	94	84	84	86	80	82	94	84

be reused up to 10 times without any significant erosion in the final yield of product **3**, after simple gravity filtration at the end of the reaction.

The used MgCl₂ catalyst was analyzed by powder X-ray diffraction (PXRD), Fourier transformed infrared (FT-IR) spectroscopy and X-ray photoelectron spectroscopy (XPS). The results show that the same diffractogram was obtained for the fresh and recovered MgCl₂ catalyst (Fig. S4†), and also a very similar FT-IR spectrum (Fig. S5†). Besides, the Mg 1s (Fig. S6†) and Cl 2p (Fig. S7†) XPS spectra of the fresh and recovered MgCl₂ coincide, indicating that any change in the oxidation state or bonding in the solid does not occur during the reaction. A filtration test shows that the reaction does not evolve further after removing the solid MgCl₂ catalyst, beyond the blank experiment (see Fig. 2). These results confirm the robustness of MgCl₂ during the intermolecular ketone-ene reaction between **1** and **2**.

3.1.4 Enantioselectivity with a chiral binaphthyl hydrogen phosphate ligand. Enantioselective intermolecular ketone-ene reactions have been achieved with chiral metal complexes, mainly with chelating chiral ligands (such as PyBox)^{7,13–16,23} but not with solid surfaces/chiral ligands. We envisioned here that solid MgCl₂ may adsorb particular chiral ligands on the surface and catalyze the ketone-ene reaction to some extent of chiral recognition. For that, the ligand should in principle have a high affinity for a relatively hard Lewis site such as Mg²⁺ and be non-chelating, since chelation is hampered on the solid surface. Thus, we choose chiral phosphate ligands in the first approach, which fulfil these two particularities. The catalytic results are shown in Fig. 4.

The addition of the simple (*R*)-(–)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate chiral phosphoric acid **21** (6 mol%) to the MgCl₂-catalysed reaction yielded the product (*S*)-**3** in 78% yield and induced an enantiomeric excess (ee) of 47%, according to high-pressure liquid chromatography (HPLC) in chiral columns after subtracting the blank experiment. Kinetic experiments show that the catalysis is caused by MgCl₂ and that the ligand only slows down the reaction (Fig. S8†). The much more hindered and acidic trifluorophosphoramidate naphthol (*R*) ligand **22** (ref. 24) gave product **3** in a similar yield (72%) but with just 6% ee. Different PyBox (*R,R*) ligands **23–26** also gave product **3** in 62–76% yields but without any ee. These results strongly support the coordination of the chiral ligand **21** with the MgCl₂

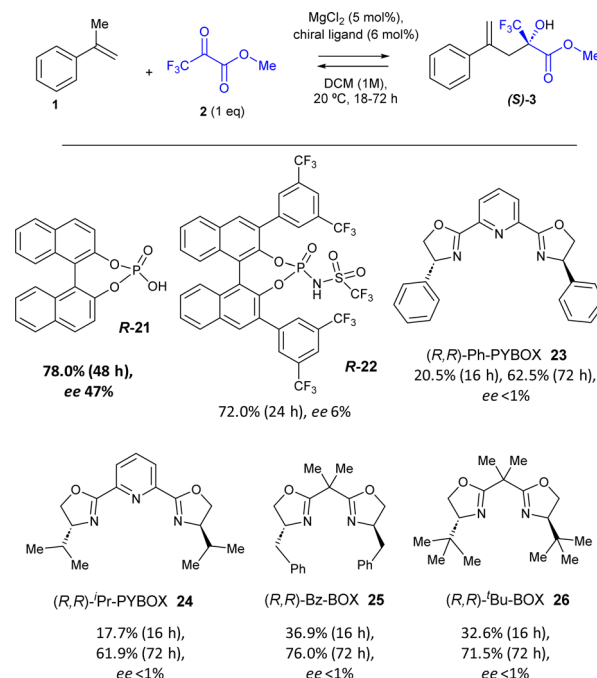



Fig. 4 Enantioselective catalytic results for the intermolecular ketone-ene reaction between α -methyl styrene **1** and methyl pyruvate **2** (1 equivalent) catalyzed by MgCl₂ (5 mol%) and the chiral (*R*) ligands **21–26** (6 mol%), in DCM (0.5 M) at room temperature. Yields calculated by GC and enantiomeric excess (ee) calculated by chiral HPLC resolution.

solid catalyst to induce enantioselectivity, and the poorer interaction of MgCl₂ with the rest of ligands **22–26**.

Table 3 shows the optimization of reaction conditions with the catalytic combination of MgCl₂/ligand **21**. The results show that the addition of 20 mol% of ligand **21** is beneficial for the ee

Table 3 Results of the enantioselective intermolecular ketone-ene reaction between α -methyl styrene **1** (0.25 mmol) and methyl pyruvate **2** (1 equiv.) with different catalytic amounts of MgCl₂ + ligand **21** (5 mol%), in either DCM (0.5 M) or solventless, at 0 or 20 °C, and for 24 or 72 h reaction time^a



Entry	MgCl ₂ + 21 (mol%)	Solvent	<i>T</i> (°C)	3 (%) [ee] (%)	
				24 h	72 h
1	5 + 20	DCM	20	65 [44]	85 [61]
2	—	—	—	89 [41]	94 [46]
3	50 + 20	DCM	20	92 [48]	>99 [57]
4	—	—	—	96 [29]	>99 [27]
5	—	DCM	0	77 [53]	N.D.
6	Reuse from entry 1	—	—	N.D.	85 [61]
7	Reuse from entry 6	—	—	N.D.	87 [72]
8	Reuse from entry 7	—	—	N.D.	90 [70]

^a GC yield and chiral HPLC ee. N.D.: not determined.



of the reaction, to give 85% yield and 61% ee after 72 h reaction time and subtraction of the blank (entry 1). If the reaction is run solventless, the yield increases up to 94% but the ee decreases to 46%, since the solubility of ligand **21** and its interaction with the solid metal salt diminishes (entry 2). Indeed, when a higher amount of MgCl_2 is added (50 mol%), the yields of **3** are nearly quantitative and the ee increases to 57% in DCM but not without any solvent (entries 3 and 4). A decrease in the reaction temperature to 0 °C slightly improves the ee after 24 h reaction time (53% in entry 5 vs. 48% in entry 3), but not that much to justify a low temperature set-up. These results demonstrate the possibility of achieving a significant enantioselectivity with the solid MgCl_2 in combination with the simple and commercially available ligand **21**. It is worthy to comment herein that better enantioselective results (up to 99%) can be found in the literature with optimized homogeneous catalysts and ligands;^{13f} however, they are often much expensive, toxic and unrecoverable (see ahead).

Table 3 also shows the reusability studies for the catalytic combination of MgCl_2 (5 mol%) and ligand **21** (20 mol%). The catalytic mixture was recovered after fully precipitating the ligand with *n*-hexane, filtering and drying. The recovered mixture of MgCl_2 and **21** was placed for a second run, to achieve 85% yield of **3** with 61% ee after 72 h at room temperature (entry 6). Two more uses of the catalytic solid mixture were carried out, with even higher yields and ee (up to 90% and 70%, respectively, entries 7 and 8). These results showcase the ability of a simple solid salt such as MgCl_2 to bring enantioselectivity throughout several reuses with the solid ligand **21**.

3.1.5 In-flow reaction. The good reusability of MgCl_2 in the batch reaction led us to explore a possible implementation of the solid MgCl_2 catalyst in an in-flow process. Continuous reactions are preferred in industry by its higher productivity, easy monitoring and better safety.²⁵ It is difficult to find in the literature in-flow reactions for the intramolecular carbonyl-ene reaction, particularly with ketones. Besides, we attempted the enantioselective reaction in this study, employing the combination of MgCl_2 + chiral ligand **21** as a catalyst in the fixed-bed tubular reactor. Thus, the reaction between **1** and **2** was repeated under the optimized solventless reaction conditions, but this time in a tubular reaction packaged with 111 mg of MgCl_2 and **21** (5 : 2 wt% ratio) embedded between 2 g of silicon carbide. Then, an equimolar mixture of **1** and **2** was passed through the solid catalyst using a syringe pump, contragravity wise to avoid excessive solid aggregation, and at a rate of 2 mL h^{-1} . The product mixture at the reactor exit was periodically analysed by GC-MS and chiral HPLC, and the results are shown in Fig. 5.

The in-flow reaction operates well for >6 h, with >90% yield of **3** on average during that time. Although the ees obtained are not high ($\approx 30\%$), they add value to the in-flow experiment, since they are also consistent with the corresponding in-batch reaction (see entry 4 in Table 3). These results pave the way to perform intermolecular carbonyl-ene reactions in continuous flows, catalysed by MgCl_2 .

3.1.6 Application to the synthesis of isopulegol (28). As commented in the introduction, isopulegol is a necessary

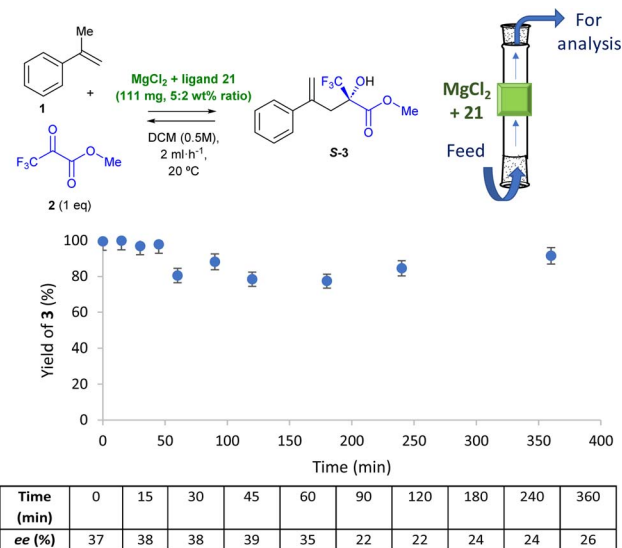


Fig. 5 In-flow reaction with MgCl_2 + chiral ligand **21** as a catalyst (111 mg in total, 5 : 2 wt% ratio) for the intermolecular ketone-ene reaction between α -methyl styrene **1** and methyl pyruvate **2** (1 equivalent) in DCM (0.5 M) at room temperature. The feed flow rate is 2 mL h^{-1} . GC yields and HPLC ees.

intermediate for the synthesis of menthol and it can be industrially produced by the intramolecular carbonyl-ene reaction of citronellal. Previous studies have shown that this natural compound can be obtained with nanoscopic metal fluorides,^{26,27} Au-supported MgF_2 ,²⁸ Zr-zeolites²⁹ or Beta-zeolites³⁰ as solid catalysts. Notice that MgF_2 has been used as a support and not as the active catalyst (Au in this case) and that a negligible activity was found for MgF_2 in that case.²⁸ Indeed, all these examples use supported metals as the active catalysts. Thus, in order to validate our methodology in an industrial reaction, we performed the reaction with MgCl_2 as a catalyst under our optimized reaction conditions for pyruvates. The results are shown in Fig. 6.

MgCl_2 catalyzes well the carbonyl-ene reaction of citronellal **27** into isopulegol **28** (neo-isopulegol is the only isolated isomer, and the one with the higher conversion) with almost full diastereoselectivity,³¹ starting from a racemic mixture of **27**. It is true that higher amounts of MgCl_2 (20 wt%) and a slightly higher reaction temperature (40 °C) were required, but the desired compound could be isolated in a reasonable isolated yield of 52% as the major diastereoisomer. Two different conformers were detected in GC in a 25% ratio for each of them. These results showcase the feasibility of the MgCl_2 -catalysed protocol in industrially interesting processes.

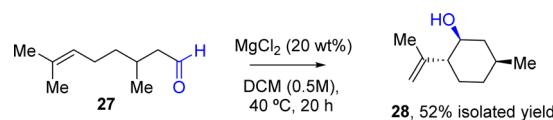


Fig. 6 Results of the intramolecular carbonyl-ene reaction of citronellal **27** (0.25 mmol) with MgCl_2 as a catalyst (20 wt%) in DCM (0.5 M) at 40 °C. Isolated yield.

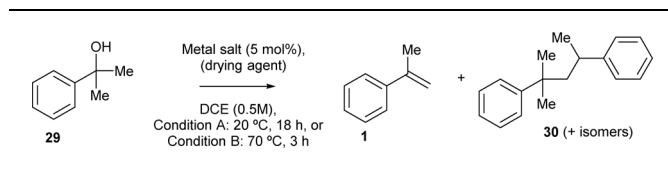


3.2 Domino dehydration/intermolecular carbonyl-ene reaction

3.2.1 Dehydration reaction of 2-phenylpropan-2-ol (29). α -Methyl styrene **1** was synthesized³² by the dehydration of phenylpropan-2-ol **29** which, in turn, is easily prepared from cumene and O₂.³³ Thus, it would be of interest to directly synthesise the carbonyl-ene reaction product **3** from alcohol **29** rather than from alkene **1**, not only because of the higher availability, stability and lower price of the former but also because, in contrast to the carbonyl-ene reaction,^{5b} the dehydration reaction is irreversible, thus smoothly generating small amounts of (now) intermediate **1**, which does not turn back to alcohol **29** but should rapidly progress to the desired product **3** in the presence of the corresponding trifluoromethyl pyruvate **2**. However, as mentioned in the Introduction, this domino reaction is not straightforward with ketones, since the equivalent of H₂O generated during the dehydration reaction can degrade most of the metal catalysts employed thus far for the carbonyl-ene reaction.

The dehydration reaction was, first, independently studied with some of the most active catalysts for the ketone-ene reaction (Table 1). The results are shown in Table 4, for two different reaction temperatures and reaction times (20 °C and 18 h, and 75 °C and 3 h, named conditions A and B, respectively). It can be

Table 4 Catalytic results of the dehydration reaction of 2-phenylpropan-2-ol **29** (0.2 mmol) to form α -methyl styrene **1** with different metal salts (5 mol%) in dichloroethane (DCE) as a solvent (0.5 M), either at room temperature (20 °C) for 18 h (condition A) or at 70 °C for 3 h (condition B)^a



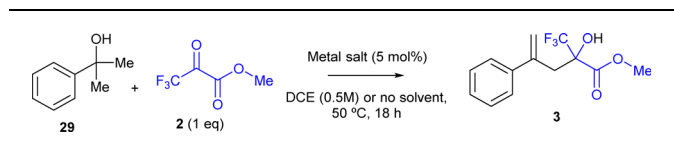
Entry	Metal catalyst (5 mol%)	Condition	1 ^b (%)	30 ^b (%)	Ratio 1/30
1	—	A	<1	<1	—
2	—	B	5	<1	5.0
3	CuCl ₂	A	<1	<1	—
4	—	B	40	4	10.0
5	Cu(OTf) ₂	A	8	2	4.0
6	—	B	52	20	2.6
7	Cu(OAc) ₂	A	<1	<1	—
8	—	B	<1	<1	—
9	CuCl	A	<1	<1	—
10	—	B	<1	<1	—
11	FeCl ₂	A	19	3	6.3
12	—	B	<1	>99	0.01
13	4 Å MS	A	2	<1	2
14	—	B	15	<1	15
15	MgO	A	<1	<1	—
16	—	B	<1	<1	—
17	MgCl ₂	A	<1	<1	—
18	—	B	24	<1	24

^a MS: molecular sieves. ^b GC yields, mass balances are complete with unreacted starting material **29**.

seen that all the catalysts were inactive at room temperature (20 °C) except FeCl₂ (entry 11), which however generates significant amounts of by-products **30**. This mixture of by-products (the structure for the head-to-tail product is shown, but the other potential dimers are also formed) comes from either the dimerization of alkene **1** or the coupling of the carbocation intermediate of alcohol **29**, which may be expected with strong Lewis acids, as those typically required for the carbonyl-ene reaction of reluctant carbonyl group such as ketones.¹² Indeed, when heating at 70 °C, the complete conversion to by-products **30** was realized with FeCl₂ (entry 12). In contrast, Cu salts with enough Lewis acidity were able to catalyse the desired dehydration reaction to form product **1** after heating (entries 4 and 6), although unavoidably generating some by-products **30**. Gratifyingly, 4 Å MS (entry 14) and, particularly, MgCl₂ (entry 18), only gave product **1** without any by-products **30**. The high selectivity of MgCl₂ towards **1** is explained by an intermediate Lewis acidity, circumventing the formation of **30** while reasonably giving the desired product **1**. The relatively low yield of the former (24%) should not be a problem since, in the domino reaction, **1** (as an intermediate) will rapidly react with pyruvate **2** to the desired carbonyl-ene reaction product **3**, while still at low concentrations. Besides, the non-reversible nature of the dehydration reaction will shift the equilibrium towards the domino reaction; indeed, an independent experiment shows the lack of reactivity of **1** with H₂O under the optimized reaction conditions (Fig. S9†).

3.2.2 Domino reaction of 2-phenylpropan-2-ol (29) with trifluoromethyl pyruvate (2). Table 5 shows the results for the domino dehydration/intermolecular carbonyl-ene reaction of alcohol **29** with trifluoromethyl pyruvate **2** catalysed by MgCl₂ (5 mol%). The reaction temperature was set at 50 °C and the reaction time at 18 h, in order to have intermediate reaction conditions between the dehydration (Table 4) and the intermolecular carbonyl-ene reaction (Table 1). For the sake of comparison, CuCl₂ was also tested as a catalyst.

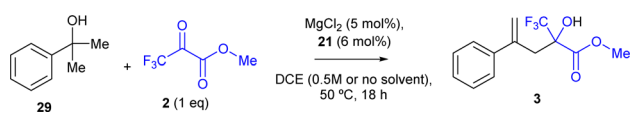
Table 5 Catalytic results for the domino dehydration/intermolecular carbonyl-ene reaction of alcohol **29** with methyl pyruvate **2** (1 equiv.) catalysed by MgCl₂ (5 mol%) in either dichloroethane (DCE) as a solvent (0.5 M) or without any solvent, at 50 °C for 18 h



Entry	Metal catalyst	Solvent	1 ^a (%)	30 ^a (%)	3 ^a (%)	Select. to 3 (%)
1	—	DCE	3	4	7	50
2	MgCl ₂	DCE	10	14	60	71
3	CuCl ₂	DCE	<1	84	15	15
4 ^b	MgCl ₂	None	3 (<1)	12 (9)	85 (91)	85 (91)

^a GC yields, mass balances are complete with unreacted starting material **29**. ^b GC, weight and ¹H NMR yield for an experiment on a 9 g scale (30 mmol of **29** and 45 mmol of **2**).

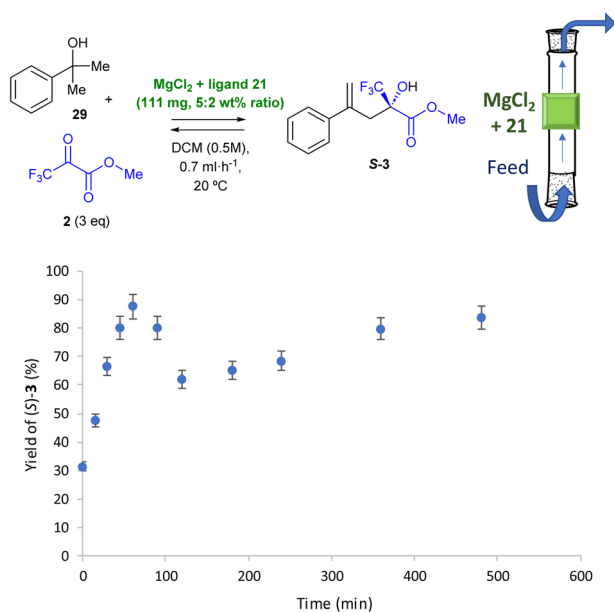


Table 7 Results of the domino reaction catalysed by a mixture of MgCl_2 + chiral ligand **21**, either in DCM (0.5 M) or without any solvent, at room temperature


Entry	Pyruvate 2 (eq.)	Solvent	1 ^a (%)	30 ^a (%)	3 ^b [ee] (%)
1	1	DCE	12	5	54
2	3		92	7	44
3	5		95	5	44
4	1	None	8	92	55
5	3		74	26	46
6	5		79	21	37

^a GC yields. ^b HPLC ees.

both reagents **29** and **2** led mostly to the formation of product **30** either in the absence or presence of DCE as a solvent (entries 1 and 4). However, increasing the amount of pyruvate to 3 equivalents led to a severe decrease in the undesired by-product formation (entries 2 and 5), even though this amount is not negligible in the case of the solventless reaction. As a result, and due to any small difference in performance between the reaction using 3 or 5 equivalents of **2** (entries 3 and 6), the use of 3 equivalents of **2** was selected for the application of the reaction conditions for the in-flow reaction.

**Fig. 8** In-flow reaction with MgCl_2 + chiral ligand **21** as a catalyst (111 mg in total, 5 : 2 wt% ratio) for the domino reaction, in DCE (0.5 M) at room temperature. The feed flow rate is 0.7 mL h^{-1} . GC yields and chiral GC ees. Error bars account for a 5% uncertainty.

The same conditions as in the ene-reaction were tested for the in-flow domino dehydration/intermolecular carbonyl-ene reaction, as shown in Fig. 8. Although conversions towards the desired ene-product **3** did not exceed 20% at a flow rate of 2 mL h^{-1} (Fig. S12[†]), a slight decrease in the flow rate to 1.5 mL h^{-1} led to good conversions with moderate enantiomeric excesses during the first hour of the flow reaction (Fig. S13[†]). The conversion decreased drastically after that time. Consequently, flow was further decreased to 0.7 mL h^{-1} , leading to the best results, as shown in Fig. 8.

The in-flow reaction operates well for >6 h; after stabilization of the reactive system during the first 30 min, the yields range from 70 to 90%. Furthermore, a 44% ee is achieved after 30 min reaction, which is consistent with the enantioselectivity obtained in the batch experiment and demonstrates that the in-flow chiral version of the domino dehydration/intermolecular carbonyl-ene reaction can be achieved with moderate ees during the first hour, similarly to the intermolecular carbonyl-ene.

4 Conclusions

The intermolecular ketone-ene reaction of trifluoromethyl pyruvates with alkenes and the corresponding domino dehydration/ketone-ene reaction with tertiary alcohols are catalysed by the simple salt MgCl_2 in high yields (up to >99%) under solventless, mild reaction conditions. The solid salt can be reused in batch or implemented in flow, to give very good yields (>80%) in both cases of the ketone-ene product after extensive use (up to 10 uses in batch and 6 h reaction time in flow for the ketone-ene reaction). The use of the simple and commercially available chiral phosphoric acid ligand **21** allows performing the enantioselective version of the reaction, in very high yields (>85%) and with significant enantiomeric excess (up to 70%) when the solid mixture is reused in batch (the in-flow enantiomeric excess is $\approx 30\%$). The industrial synthesis of isopulegol from citronellal is also viable with MgCl_2 as a solid catalyst. This study brings the extremely inexpensive and non-toxic solid MgCl_2 as an efficient reusable catalyst for carbonyl-ene reactions, preferable in tandem with the previous dehydration reaction of the corresponding tertiary alcohols.

Data availability

The data supporting this article have been included as part of the ESI.[†]

Author contributions

M. E. performed the experimental work and analysis, including all product characterization, and interpreted the results. A. L.-P. conceived the idea, interpreted the results and supervised the project. Both authors wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.



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References

- (a) Y. Peng and M. Beller, Geminal-atom catalysts: Advanced single-atom catalysis for cross-coupling reactions, *Chem Catal.*, 2023, 3(11), 100814; (b) R. J. Lewis and G. J. Hutchings, Selective oxidation using in situ-generated hydrogen peroxide, *Acc. Chem. Res.*, 2024, 57(1), 106–119.
- (a) J. R. Cabrero-Antonino, A. Leyva-Pérez and A. Corma, Beyond Acid Strength in Zeolites: Soft Framework Counteranions for Stabilization of Carbocations on Zeolites and Its Implication in Organic Synthesis, *Angew. Chem., Int. Ed.*, 2015, 54(19), 5658–5661; (b) X. Frogneux, F. Borondics, S. Lefrançois, F. D'Accriscio, C. Sanchez and S. Carencó, Surprisingly high sensitivity of copper nanoparticles toward coordinating ligands: consequences for the hydride reduction of benzaldehyde, *Catal. Sci. Technol.*, 2018, 8(19), 5073–5080; (c) L. R. Smith, P. J. Smith, K. S. Mugford, M. Douthwaite, N. F. Dummer, D. J. Willock, M. Howard, D. W. Knight, S. H. Taylor and G. J. Hutchings, New insights for the valorisation of glycerol over MgO catalysts in the gas-phase, *Catal. Sci. Technol.*, 2019, 9(6), 1464–1475; (d) F. Garnes-Portolés, R. Greco, J. Oliver-Meseguer, J. Castellanos-Soriano, M. C. Jiménez, M. López-Haro, J. C. Hernández-Garrido, M. Boronat, R. Pérez-Ruiz and A. Leyva-Pérez, Regioirregular and catalytic Mizoroki-Heck reactions, *Nat. Catal.*, 2021, 4, 293–303; (e) V. A. Ghadge, R. Krishnan, D. R. Naikwadi, P. B. Shinde and A. V. Biradar, Natural eumelanin-based porous N-doped carbon as an active biocatalyst for base- and initiator-free aerobic oxidation of olefins and alkyl aromatic hydrocarbons, *Green Chem.*, 2023, 25(7), 2863–2871; (f) P. Minguez-Verdejo, J. C. Hernández-Garrido, A. Vidal-Moya, J. Oliver-Meseguer and A. Leyva-Pérez, Zeolites catalyze the halogen exchange reaction of alkyl halides, *Catal. Sci. Technol.*, 2023, 13(8), 2308–2316; (g) L. A. Gomez, C. Q. Bavluka, T. E. Zhang, D. E. Resasco and S. P. Crossley, Revealing the mechanistic details for the selective deoxygenation of carboxylic acids over dynamic MoO₃ catalysts, *ACS Catal.*, 2023, 13, 8455–8466; (h) A. S. Singh, H. G. Kachgunde, R. Krishnan, D. R. Naikwadi and A. V. Biradar, Bifunctional heterogeneous catalyst: A sustainable route for cyclic acetals synthesis through tandem hydroformylation-acetalization reaction, *Mol. Catal.*, 2024, 555, 113859.
- M. L. Clarke and M. B. France, The carbonyl ene reaction, *Tetrahedron*, 2008, 64(38), 9003–9031.
- (a) E. D. Anderson, J. J. Ernat, M. P. Nguyen, A. C. Palma and R. S. Mohan, Environment friendly organic synthesis using bismuth compounds. An efficient method for carbonyl-ene reactions catalyzed by bismuth triflate, *Tetrahedron Lett.*, 2005, 46(45), 7747–7750; (b) S. Imachi, K. Owada and M. Onaka, Intramolecular carbonyl-ene reaction of citronellal to isopulegol over ZnBr₂-loading mesoporous silica catalysts, *J. Mol. Catal. A: Chem.*, 2007, 272(1–2), 174–181; (c) S. Baeurle, M. Berger, S. Jaroch, K. Krolikiewicz, D. Nguyen, H. Rehwinkel, H. Schaecke, N. Schmees and W. Skuballa, Alkylidene tetrahydronaphthalene derivatives, method for their production and their use as anti-inflammatory agents, *World Intellectual Property Organization*, 2006; (d) M. Terada and K. Mikami, Periselective and enantioselective carbonyl-ene reaction of isoprene with fluoroalkyl glyoxylate catalysed by modified binaphthol-titanium complex: asymmetric catalytic synthesis of enantiomerically pure ipsdienol, *J. Chem. Soc., Chem. Commun.*, 1995, 23, 2391–2392; (e) L. E. Overman and D. Lesuisse, The synthesis of indolizidines by intramolecular ene cyclizations. Preparation of (*E*)-alkylidene analogs of pumiliotoxin A, *Tetrahedron Lett.*, 1985, 26(35), 4167–4170.
- (a) M. L. Clarke, C. E. S. Jones and M. B. France, The first organocatalytic carbonyl-ene reaction: isomerization-free C–C bond formations catalysed by H-bonding thio-ureas, *Beilstein J. Org. Chem.*, 2007, 3, 24; (b) P. Tremel, C. Iacobucci, L. Massi, S. Olivero, J.-F. Gal and E. Duñach, Catalytic intramolecular carbonyl-ene reaction with ketones: evidence for a retro-ene process, *New J. Chem.*, 2015, 39(9), 7453–7458.
- (a) F. Alonso, M. Rodríguez-Fernández, D. Sánchez and M. Yus, Synthesis of perhydrofuro[2,3-*b*]furans from isopentenyl alcohol through carbonyl-ene and Wacker-type reactions, *Eur. J. Org. Chem.*, 2011, 32, 6459–6469; (b) A. Crespo-Peña, D. Monge, E. Martín-Zamora, E. Alvarez, R. Fernández and J. M. Lassaletta, Asymmetric formal carbonyl-ene reactions of formaldehyde tert-butyl hydrazone with α -keto esters: dual activation by bis-urea catalysts, *J. Am. Chem. Soc.*, 2012, 134(31), 12912–12915; (c) X. Xu, X. Wang, Y. Liu and M. P. Doyle, Enantioselective carbonyl-ene reactions catalyzed by chiral cationic dirhodium(II,III) carboxamidates, *J. Org. Chem.*, 2014, 79(24), 12185–12190; (d) L. Liu, M. Leutzsch, Y. Zheng, M. W. Alachraf, W. Thiel and B. List, Confined acid-catalyzed asymmetric carbonyl-ene cyclization, *J. Am. Chem. Soc.*, 2015, 137(41), 13268–13271; (e) H. A. Rodríguez, D. A. Cruz, J. I. Padrón and I. Fernández, Lewis Acid-catalyzed carbonyl-ene reaction: Interplay between aromaticity, synchronicity, and Pauli repulsion, *J. Org. Chem.*, 2023, 88(15), 11102–11110.
- R. G. Gore, T.-K.-T. Truong, M. Pour, L. Myles, S. J. Connon and N. Gathergood, Tandem ionic liquid antimicrobial toxicity and asymmetric catalysis study: carbonyl-ene



- reactions with trifluoropyruvate, *Green Chem.*, 2013, **15**(10), 2727–2739.
- 8 (a) J. Tateiwa, A. Kimura, M. Takasuka and S. Uemura, Metal cation-exchanged montmorillonite(M^{n+} -Mont)-catalysed carbonyl-ene reactions, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2169–2174; (b) T. Okachi and M. Onaka, Formaldehyde encapsulated in zeolite: A long-lived, highly activated one-carbon electrophile to carbonyl-ene reactions, *J. Am. Chem. Soc.*, 2004, **126**(8), 2306–2307; (c) A. Corma and M. Renz, Sn-Beta zeolite as diastereoselective water-resistant heterogeneous Lewis-acid catalyst for carbon-carbon bond formation in the intramolecular carbonyl-ene reaction, *Chem. Commun.*, 2004, **5**, 550–551; (d) A. Corma and M. Renz, Water-resistant Lewis-acid sites: carbonyl-ene reactions catalyzed by tin-containing hydrophobic molecular sieves, *ARKIVOC*, 2007, **8**, 40–48; (e) S. Wannakao, P. Khongpracha and J. Limtrakul, Density functional theory study of the carbonyl-ene reaction of encapsulated formaldehyde in Cu(I), Ag(I), and Au(I) exchanged FAU zeolites, *J. Phys. Chem. A*, 2011, **115**(45), 12486–12492; (f) H. Fu, S. Xie, A. Fu and T. Ye, Theoretical study of the carbonyl-ene reaction between formaldehyde and propylene on the MgY zeolite, *Comput. Theor. Chem.*, 2012, **982**(15), 51–57; (g) S. Yoshimura, D. Kiriya and T. Kurata, Carbonyl-ene reaction of styrene derivatives catalyzed by H-Beta zeolite in water, *J. Jpn. Pet. Inst.*, 2014, **57**(2), 84–87; (h) T. Maihom, M. Probst and J. Limtrakul, Computational study of the carbonyl-ene reaction between formaldehyde and propylene encapsulated in coordinatively unsaturated metal-organic frameworks $M_3(\text{btc})_2$ ($M = \text{Fe, Co, Ni, Cu and Zn}$), *Phys. Chem. Chem. Phys.*, 2019, **21**(5), 2783–2789.
- 9 (a) R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi and M. Pitillo, Poly(ethylene glycol)-supported bisoxazolines as ligands for catalytic enantioselective synthesis, *J. Org. Chem.*, 2001, **66**(9), 3160–3166; (b) S. Kobayashi, R. Akiyama and H. Kitagawa, Polymer-supported glyoxylate and alpha-imino acetates. Versatile reagents for the synthesis of alpha-hydroxycarboxylic acid and alpha-amino acid libraries, *J. Comb. Chem.*, 2001, **3**(2), 196–204; (c) J. H. Koh, A. O. Larsen, P. S. White and M. R. Gagné, Disparate roles of chiral ligands and molecularly imprinted cavities in asymmetric catalysis and chiral poisoning, *Organometallics*, 2002, **21**(1), 7–9; (d) Y. M. A. Yamada, M. Ichinohe, H. Takahashi and S. Ikegami, Assembled catalysts of titanium and non-cross-linked chiral copolymers for and enantioselective carbonyl-ene reaction, *Tetrahedron Lett.*, 2002, **43**(18), 3431–3434; (e) S. Takizawa, H. Somei, D. Jayaprakash and H. Sasai, Metal-bridged polymers as insoluble multicomponent asymmetric catalysts with high enantiocontrol: An approach for the immobilization of catalysts without using any support, *Angew. Chem., Int. Ed.*, 2003, **42**(46), 5711–5714; (f) H. Guo, X. Wang and K. Ding, Assembled enantioselective catalysts for carbonyl-ene reactions, *Tetrahedron Lett.*, 2004, **45**(9), 2009–2012; (g) Y. Huang, Synthesis of new polymer-supported C_2 -symmetric chiral bis(oxazoline)s and their applications in asymmetric reactions, *Chem. J. Internet*, 2004, **6**(11), 79; (h) A. Mandoli, S. Orlandi, D. Pini and P. Salvadori, Insoluble polystyrene-bound bis(oxazoline): Batch and continuous-flow heterogeneous enantioselective glyoxylate-ene reaction, *Tetrahedron: Asymmetry*, 2004, **15**(20), 3233–3244; (i) F. Ono, S. Kanemasa and J. Tanaka, Reusable nano-sized chiral bisoxazoline catalysts, *Tetrahedron Lett.*, 2005, **46**(44), 7623–7626; (j) K. Ding, Z. Wang, X. Wang, Y. Liang and X. Wang, Self-supported chiral catalysts for heterogeneous enantioselective reactions, *Chem.-Eur. J.*, 2006, **12**(10), 5188–5197.
- 10 X. Wang, X. Wang, H. Guo, Z. Wang and K. Ding, Self-supported heterogeneous titanium catalysts for enantioselective carbonyl-ene and sulfoxination reactions, *Chem.-Eur. J.*, 2005, **11**(14), 4078–4088.
- 11 (a) L. Mitchell, B. Gonzalez-Santiago, J. P. S. Mowat, M. E. Gunn, P. Williamson, N. Acerbi, M. L. Clarke and P. A. Wright, Remarkable Lewis acid catalytic performance of the scandium trimesate metal organic framework MIL-100(Sc) for C-C and C=N bond-forming reactions, *Catal. Sci. Technol.*, 2013, **3**(3), 606–617; (b) L. Mitchell, P. Williamson, B. Ehrlichová, A. E. Anderson, V. R. Seymour, S. E. Ashbrook, N. Acerbi, L. M. Daniels, R. L. Walton, M. L. Clarke and P. A. Wright, Mixed-metal MIL(Sc, m) ($M = \text{Al, Cr, Fe}$) for Lewis acid catalysis and tandem C-C bond formation and alcohol oxidation, *Chem.-Eur. J.*, 2014, **20**(51), 17185–17197; (c) J. Han, M. S. Lee, P. K. Thallapally, M. Kim and N. Jeong, Identification of reaction sites on metal-organic framework-based asymmetric catalysts for carbonyl-ene reactions, *ACS Catal.*, 2019, **9**(5), 3969–3977; (d) R. R. R. Prasad, S. E. Seidner, D. B. Cordes, M. M. Lozinska, D. M. Dawson, M. J. Thompson, T. Düren, K. K. Chakarova, M. Y. Mihaylov, K. I. Hadjiivanov, F. Hoffmann, A. m. Z. Slawin, S. E. Ashbrook, M. L. Clarke and P. A. Wright, STA-27, a porous Lewis acidic scandium MOF with an unexpected topology type prepared with 2,3,5,6-tetrakis(4-carboxyphenyl)pyrazine, *J. Mater. Chem. A*, 2019, **7**(10), 5685–5701.
- 12 (a) B. Xiang, T.-F. Xu, L. Wu, R.-R. Liu, J.-R. Gao and Y.-X. Jia, Lewis Acid Catalyzed Friedel-Crafts alkylation of alkenes with trifluoropyruvates, *J. Org. Chem.*, 2016, **81**(9), 3929–3935; (b) D. Meng and T. Ollevier, $\text{Fe}(\text{BF}_4)_2$ -catalyzed inter- and intramolecular carbonyl-ene reaction of trifluoropyruvate, *Synlett*, 2018, **29**(5), 640–644.
- 13 (a) D. A. Evans, S. W. Tregay, C. S. Burgey, N. A. Paras and T. Vojtkovsky, C_2 -symmetric Copper(II) complexes as chiral Lewis acids. Catalytic enantioselective carbonyl-ene reactions with glyoxylate and pyruvate esters, *J. Am. Chem. Soc.*, 2000, **122**(33), 7936–7943; (b) S. Doherty, J. G. Knight and H. Mehdi-Zodeh, Asymmetric carbonyl-ene and Friedel-Crafts reactions catalysed by Lewis acid platinum group metal complexes of the enantiopure atropisomeric biaryl-like diphosphine (*S*)- Me_2 -CATPHOS: A comparison with BINAP, *Tetrahedron: Asymmetry*, 2012, **23**(3–4), 209–216; (c) L. Jiang, B. Hu, X. Xie and Z. Zhang, Asymmetric carbonyl-ene reaction of trifluoropyruvate catalyzed by



- Pd(II)–SunPhos complex, *Tetrahedron*, 2017, 73(49), 6901–6905; (d) T. Wang, X.-Q. Hao, J.-J. Huang, J.-L. Niu, J.-F. Gong and M.-P. Song, Chiral bis(imidazolyl)phenyl NCN pincer rhodium(III) catalysts for enantioselective allylation of aldehydes and carbonyl–ene reaction of trifluoropyruvates, *J. Org. Chem.*, 2013, 78(17), 8712–8721; (e) Y. Yuan, X. Zhang and K. Ding, Quasi solvent-free enantioselective carbonyl–ene reaction with extremely low catalyst loading, *Angew. Chem., Int. Ed.*, 2003, 42(44), 5478–5480; (f) K. Zheng, Y. Yang, J. Zhao, C. Yin, L. Lin, X. Liu and X. Feng, The magnesium(II)–catalyzed asymmetric ketone–ene reaction under solvent-free conditions: Stereocontrolled access to enantioenriched trifluoromethyl-substituted compounds, *Chem.–Eur. J.*, 2010, 16, 9969–9972; (g) J. Lv, Q. Zhang, X. Zhong and S. Luo, Asymmetric latent carbocation catalysis with chiral trityl phosphate, *J. Am. Chem. Soc.*, 2015, 137(49), 15576–15583; (h) Y.-B. Shen, S.-S. Li, Y.-M. Sun, L. Yu, Z.-H. Hao, Q. Liu and J. Xiao, Organocatalytic C(sp³)–H functionalization of 5-methyl-2,3-dihydrofuran derivatives with trifluoropyruvates via a sequential *exo*-tautomerization/carbonyl–ene process, *J. Org. Chem.*, 2019, 84(5), 2779–2785; (i) H. Ishihara, J. Huang, T. Mochizuki, M. Hatano and K. Ishihara, Enantio- and diastereoselective carbonyl–ene cyclization–acetalization tandem reaction catalyzed by tris(pentafluorophenyl) borane-assisted chiral phosphoric acids, *ACS Catal.*, 2021, 11(10), 6121–6127.
- 14 (a) J. F. Zhao, B.-H. Tan, M.-K. Zhu, T.-B. W. Tjan and T.-P. Loh, Enantioselective carbonyl–ene reactions of trifluoropyruvate in ionic liquid via a recyclable indium(III)–pybox complex, *Adv. Synth. Catal.*, 2010, 352(11–12), 2085–2088; (b) D. Didier and E. Schulz, Recycling chiral copper bis(oxazoline) complexes in an original multireaction procedure, *ChemCatChem*, 2011, 3(12), 1880–1884; (c) N. A. Caplan, F. E. Hancock, P. C. B. Page and G. J. Hutchings, Heterogeneous enantioselective catalyzed carbonyl- and imini-ene reactions using copper bis(oxazoline) zeolite Y, *Angew. Chem., Int. Ed.*, 2004, 43(13), 1685–1688.
- 15 A. Leyva-Pérez, P. García-García and A. Corma, Multisite organic–inorganic hybrid catalysts for the direct sustainable synthesis of GABAergic drugs, *Angew. Chem., Int. Ed.*, 2014, 53, 8687–8690.
- 16 (a) K. Mikami and H. Ohmura, One-pot synthesis of tropinone by tandem (domino) ene-type reactions of acetone silyl enol ethers, *Chem. Commun.*, 2002, 22, 2626–2627; (b) S. Kaden and M. Hiersemann, The first catalytic asymmetric domino Claisen rearrangement/intramolecular carbonyl ene reaction, *Synlett*, 2002, 12, 1999–2002; (c) B. T. Parr and H. M. L. Davies, Stereoselective synthesis of highly substituted cyclohexanes by a rhodium–carbene initiated domino sequence, *Org. Lett.*, 2015, 17(4), 794–797.
- 17 (a) N. Kashiwa, The discovery and progress of MgCl₂–supported TiCl₄ catalysts, *J. Polym. Sci., Part A: Polym. Chem.*, 2004, 42(1), 1–8; (b) T. B. Mikenas, V. A. Zakharov, V. E. Nikitin, L. G. Echevskaia and M. A. Matsko, New generation of supported Ziegler-type catalysts for polyethylene production, *Russ. J. Appl. Chem.*, 2010, 83, 2210–2219.
- 18 D. Yang, L. Wang, D. Li and R. Wang, Magnesium catalysis in asymmetric synthesis, *Chem*, 2019, 5(5), 1108–1166.
- 19 C. Nadeau, F. Gosselin, P. D. O'Shea, I. W. Davies and R. P. Volante, A concise synthesis of (*S*)- γ -fluoroleucine ethyl ester, *Synlett*, 2006, 2, 291–295.
- 20 (a) R. Greco, E. Tiburcio, B. Palomar-De Lucas, J. Ferrando-Soria, D. Armentano, E. Pardo and A. Leyva-Pérez, Click amidations, esterifications and one-pot reactions catalyzed by Cu salts and multimetal-organic frameworks (M-MOFs), *Mol. Catal.*, 2022, 522, 112228; (b) E. Tiburcio, Y. Zheng, C. Bilanin, J. C. Hernández-Garrido, A. Vidal-Moya, J. Oliver-Meseguer, N. Martín, M. Mon, J. Ferrando-Soria, D. Armentano, A. Leyva-Pérez and E. Pardo, MOF-triggered synthesis of subnanometer Ag₂⁰ clusters and Fe³⁺ single atoms: heterogenization led to efficient and synergetic one-pot catalytic reactions, *J. Am. Chem. Soc.*, 2023, 145(18), 10342–10354.
- 21 Z. Mao, F. Mo and X. Lin, Diastereo- and enantioselective assembly of spirooxindole tetrahydroquinoline skeletons through asymmetric binary acid catalyzed hydride transfer–cyclization, *Synlett*, 2015, 27(04), 546–550.
- 22 (a) T. Okachi, K. Fujimoto and M. Onaka, Practical carbonyl–ene reactions of α -methylstyrenes with paraformaldehyde promoted by a combined system of boron trifluoride and molecular sieves 4A, *Org. Lett.*, 2002, 4(10), 1667–1669; (b) C. Reichardt and T. Welto, *Solvents and Solvent Effects in Organic Chemistry*, Wiley, 2010, 692 pages, online ISBN:9783527632220.
- 23 J. F. Zhao, T.-B. W. Tjan, B.-H. Tan and T.-P. Loh, Highly enantioselective ketone–ene reactions of trifluoropyruvate: Significant counterion effect of the In(III)–pybox complex, *Org. Lett.*, 2009, 11(24), 5714–5716.
- 24 M. Rueping, T. Theissmann, A. Kuenkel and R. M. Koenigs, Highly enantioselective organocatalytic carbonyl–ene reaction with strongly acidic, chiral Brønsted acids as efficient catalysts, *Angew. Chem., Int. Ed.*, 2008, 47(36), 6798–6801.
- 25 (a) F. Garnes-Portolés, C. López-Cruz, J. Sánchez-Quesada, E. Espinós-Ferri and A. Leyva-Pérez, Solid-catalyzed synthesis of isomers-free terpinen-4-ol, *Mol. Catal.*, 2022, 533, 112785; (b) A. Martínez-Castelló, M. Tejada-Serrano, A. Nowacka, J. Oliver-Meseguer and A. Leyva-Pérez, Solid-catalyzed esterification reaction of long-chain acids and alcohols in fixed-bed reactors at pilot plant scale, *Chem. Eng. Process.*, 2022, 178, 109038; (c) P. Mínguez-Verdejo, J. P. Cerón-Carrasco, J. Oliver-Meseguer and A. Leyva-Pérez, a formal exchange reaction between ketones and vinyl ethers with solid catalysts, *Synthesis*, 2024, 56(3), 455–461.
- 26 Y. Guo, P. Gaczyński, K.-D. Becker and E. Kemnitz, Sol-gel synthesis and characterisation of nanoscopic FeF₃–MgF₂ heterogeneous catalysts with bi-acidic properties, *ChemCatChem*, 2013, 5(8), 2223–2232.
- 27 S. M. Coman, P. Patil, S. Wuttke and E. Kemnitz, Cyclisation of citronellal over heterogeneous inorganic fluorides–highly



- chemo- and diastereoselective catalysts for (\pm)-isopulegol, *Chem. Commun.*, 2009, **4**, 460–462.
- 28 A. Negoi, S. Wuttket, E. Kemnitz, D. Macovei, V. I. Parvulescu, C. M. Teodorescu and S. M. Coman, One-pot synthesis of menthol catalyzed by a highly diastereoselective Au/MgF₂ catalyst, *Angew. Chem., Int. Ed.*, 2010, **49**, 8134–8138.
- 29 Z. Yongzhong, N. Yuntong, S. Jaenickem and G. K. Chuah, Cyclisation of citronellal over zirconium zeolite Beta—a highly diastereoselective catalyst to (\pm)-isopulegol, *J. Catal.*, 2005, **229**(2), 404–413.
- 30 (a) A. Corma and M. Renz, Sn-Beta zeolite as diastereoselective water-resistant heterogeneous Lewis-acid catalyst for carbon-carbon bond formation in the intramolecular carbonyl-ene reaction, *Chem. Commun.*, 2004, **5**, 550–551; (b) A. Corma, F. X. Llabres i Xamena, C. Prestipino, M. Renz and S. Valencia, Water resistant, catalytically active Nb and Ta isolated Lewis acid sites, homogeneously distributed by direct synthesis in a beta zeolite, *J. Phys. Chem. C*, 2009, **113**(26), 11306–11315.
- 31 H. Itoh, H. Maeda, S. Yamada, Y. Hori, T. Mino and M. Sakamoto, Highly selective aluminium-catalysed intramolecular Prins reaction for *L*-menthol synthesis, *RSC Adv.*, 2014, **4**(106), 61619–61623.
- 32 A. Petronilho, A. Vivancos and M. Albrecht, Ether formation through reductive coupling of ketones or aldehydes catalyzed by a mesoionic carbene iridium complex, *Catal. Sci. Technol.*, 2017, **7**(23), 5766–5774.
- 33 (a) T. Kojima, K. Nakayama, K. Ikemura, T. Ogura and S. Fukuzumi, Formation of a ruthenium(IV)-oxo complex by electron-transfer oxidation of a coordinatively saturated ruthenium(II) complex and detection of oxygen-rebound intermediates in C–H bond oxygenation, *J. Am. Chem. Soc.*, 2011, **133**(30), 11692–11700; (b) B. Wang, Y.-M. Lee, M. Clémancey, M. S. Seo, R. Sarangi, J.-M. Latour and W. Nam, Mononuclear nonheme high-spin iron(III)-acylperoxo complexes in olefin epoxidation and alkane hydroxylation reactions, *J. Am. Chem. Soc.*, 2016, **138**(7), 2426–2436; (c) A. Malekafzali, K. Malinowska and F. W. Patureau, The cumene/O₂ system: a very simple tool for the radical chain oxidation of some functional groups, *New J. Chem.*, 2017, **41**(15), 6981–6985.

