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# Catalytic formation of C(sp<sup>3</sup>)–F bonds *via* decarboxylative fluorination with mechanochemically-prepared Ag<sub>2</sub>O/TiO<sub>2</sub> heterogeneous catalysts†

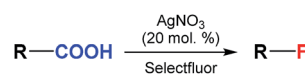
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Mechanochemically-prepared, Ag<sub>2</sub>O-containing solid materials, are shown to be efficient heterogeneous catalysts for the synthesis of C(sp<sup>3</sup>)–F bonds *via* decarboxylative fluorination. Five catalytic cycles without loss of intrinsic activity could be performed with the optimal catalyst, composed of 1 wt% Ag<sub>2</sub>O supported on TiO<sub>2</sub> (P25), despite the challenging conditions. The catalyst is easily prepared from the corresponding oxides in 20 minutes by simple mechanical mixing methods. In addition to ease of separation and re-use, the turnover numbers obtained over the solid catalyst are over one order of magnitude higher than those obtained with the state-of-the-art homogeneous catalyst, AgNO<sub>3</sub>, under otherwise identical conditions. To the best of our knowledge, this represents the first true heterogeneous catalyst for the selective formation of C(sp<sup>3</sup>)–F bonds with electrophilic fluorine donors, representing a major breakthrough in the field of catalytic fluorination.

## Introduction

Fluorinated compounds are widely employed in several industrial fields as agrochemicals, pharmaceuticals and materials.<sup>1</sup> Furthermore, <sup>18</sup>F compounds are widely used as tracers for Positron Emission Tomography.<sup>2</sup> Unfortunately, the synthesis of fluorinated molecules is very difficult and whilst several breakthroughs<sup>3</sup> have been achieved, the synthesis of C(sp<sup>3</sup>)–F bonds *via* catalytic fluorination remains an immense challenge. Whilst several recent studies have demonstrated that transition metals such as iron, copper, silver and palladium react with electrophilic fluorinating reagents such as F-TEDA (Selectfluor®), NFSI or DAST,<sup>1a</sup> to yield new C(sp<sup>3</sup>)–F and C(sp<sup>2</sup>)–F bonds,<sup>4</sup> several of these methods require stoichiometric (*i.e.* 100 mol%) metal loadings (*i.e.* metal use is non-catalytic, hence TON < 1). Moreover, heterogeneous catalysis – preferred for several process intensification reasons – has not yet been achieved, likely due to the extremely challenging conditions, which can easily induce restructuring, leaching and hence, deactivation, of solid catalysts.

The decarboxylative fluorination of aliphatic carboxylic acids, catalysed by homogeneous AgNO<sub>3</sub>, represents a powerful way to selectively synthesise new C(sp<sup>3</sup>)–F bonds from readily available substrates under mild reaction conditions (Scheme



**Scheme 1** Decarboxylative fluorination of aliphatic carboxylic acids to yield new C(sp<sup>3</sup>)–F bonds.

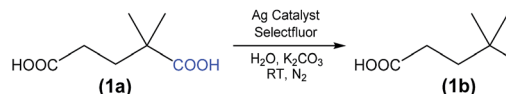
1).<sup>5</sup> However, despite the potential of this process, an active and reusable heterogeneous catalyst has not yet been developed, and catalyst activity remains extremely low, with typical turnover numbers being below 5 even after extended periods *i.e.* <24 h. Accordingly, the development of a highly active, stable and truly heterogeneous catalyst for this process is the focus of this study.

## Results and discussion

Amongst a range of metal oxide-supported, Ag-containing catalysts, we first identified 1 wt% Ag/TiO<sub>2</sub>, prepared by sol immobilisation<sup>6</sup> (henceforth denoted 1AgTiO<sub>2</sub>(SI)), as being a suitable catalyst for decarboxylative fluorination. The performance of the material after various heat treatment procedures was first evaluated for the decarboxylative fluorination of 2,2-dimethylglutaric acid (DMGA, (**1a**)), a useful model substrate possessing both a primary and a tertiary carboxylic group (Scheme 2). Under conditions optimized from homogeneous AgNO<sub>3</sub> (20 mol% Ag, 1.0 equivalent K<sub>2</sub>CO<sub>3</sub>, 25 °C) higher levels of activity were observed with the heterogeneous catalyst following calcination at 350 °C (Fig. 1, left). The only product

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Scheme 2 Decarboxylative fluorination of **1a** to yield **1b** with Selectfluor® as fluorine donor.

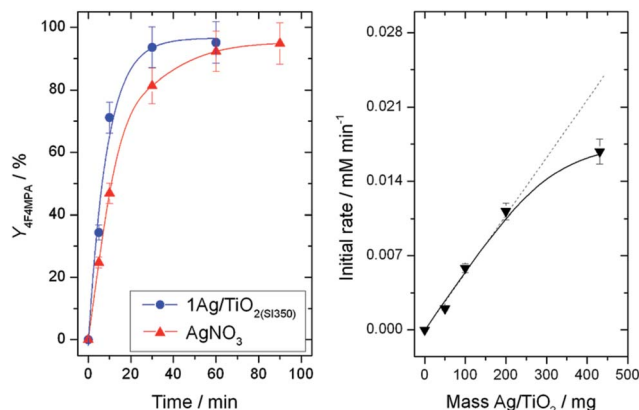


Fig. 1 (Left) Yield of **1b** with time over (blue/circles) 1Ag/TiO<sub>2</sub>(Si<sub>350</sub>) and (red/triangles) AgNO<sub>3</sub>. Reaction conditions: 0.2 mmol of **1a**, 0.4 mmol of Selectfluor®, 0.04 mmol of Ag, 4 mL H<sub>2</sub>O, 0.2 mmol K<sub>2</sub>CO<sub>3</sub>, N<sub>2</sub> atmosphere, 25 °C. (Right) Initial rate with different amounts of 1Ag/TiO<sub>2</sub>(Si<sub>350</sub>). Reaction conditions otherwise identical to left.

observed over the timescale of the reaction by NMR and HPLC was 4-fluoro-4-methylpentanoic acid (4F4MPA (**1b**), selectivity > 95%) confirming the higher reactivity of the tertiary carboxylic group in accordance with previous studies.<sup>5</sup>

Whilst the system exhibited good kinetic behaviour between 0–200 mg loading of 1Ag/TiO<sub>2</sub>(Si<sub>350</sub>) (Fig. 1, right) the rate deviated from linear above this loading, demonstrating transport limitations to be present at the highest catalyst loading. Accordingly, all further studies were performed with 100 mg of 1Ag/TiO<sub>2</sub>(Si<sub>350</sub>) (4.64 mol% Ag), which represents the best compromise between intrinsic activity and overall performance. To further optimise reaction conditions, the impact of the loading of base (in a range 0–2 equivalents) on the catalytic performance of 1Ag/TiO<sub>2</sub>(Si<sub>350</sub>) was investigated (ESI Fig. S1†). An optimal base loading of 1.16 equivalents (K<sub>2</sub>CO<sub>3</sub>/DMGA ratio of 1.16) was identified. Interestingly substantially lower activity was found in the absence of K<sub>2</sub>CO<sub>3</sub>.

The system under study represents a formidable challenge from a catalyst stability perspective, given that various amounts of carboxylic groups, fluorine sources and also HF (as possible reaction by-product)<sup>7</sup> are present to some extent. Each of these species are known to cause extensive reorganisation, leaching and hence, permanent deactivation, of solid catalysts.<sup>8</sup> To rule out any homogeneous contribution to the reaction rate, a hot filtration experiment at the optimal base loading was performed (Fig. 2, left).<sup>8d</sup> The removal of the solid catalyst from the reaction mixture clearly terminated the catalytic reaction, demonstrating catalysis to be truly heterogeneous, and confirming that potential traces of Ag in solution did not contribute to the reaction rate. Full termination of the reaction also implies Ag to

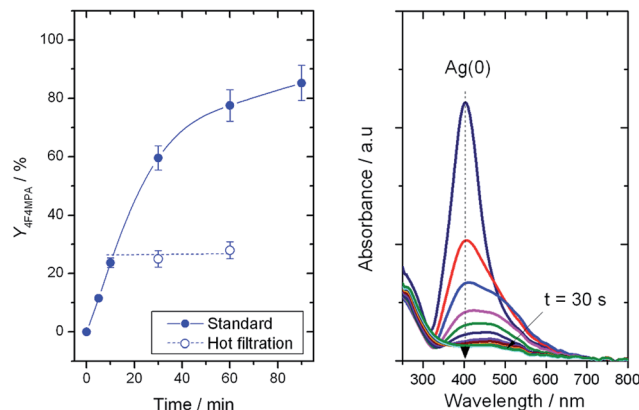


Fig. 2 (Left) Solid line: yield of **1b** with time without filtering the catalyst. Dashed line, catalytic activity of the supernatant solution following filtration of the catalyst at 10 min. Reaction conditions identical to Fig. 1, left, albeit with 0.23 mmol of K<sub>2</sub>CO<sub>3</sub> and 100 mg of 1Ag/TiO<sub>2</sub>(Si<sub>350</sub>). (Right) UV-Vis spectra of colloidal Ag(0) after addition of Selectfluor® and K<sub>2</sub>CO<sub>3</sub>.

be a true catalyst, and not solely a reaction initiator in the same manner as Cu(I) as observed by Pitts *et al.*<sup>7</sup> TiO<sub>2</sub>-supported Ag is, therefore, the first truly heterogeneous catalysts for the formation of C(sp<sup>3</sup>)–F bonds with electrophilic fluorine donors.

According to previous studies, decarboxylative fluorination requires cationic Ag species for efficient catalysis to be observed.<sup>5</sup> However, sol immobilisation catalysts are known to contain a heterogeneous distribution of cationic and metallic species following heat treatment.<sup>8,9</sup> Thus, to understand the catalytic roles of Ag(0) and Ag(I), we investigated the interaction between Selectfluor® and Ag. Accordingly, a colloidal solution of Ag(0) was placed into a UV-Vis cuvette, and the Plasmon resonance<sup>10</sup> of Ag(0) at 400 nm monitored *in situ* following addition of Selectfluor® and K<sub>2</sub>CO<sub>3</sub> (Fig. 2, right). This treatment resulted in the disappearance of the Plasmon peak in <30 s. Clearly, any residual Ag(0) species in the solid catalysts

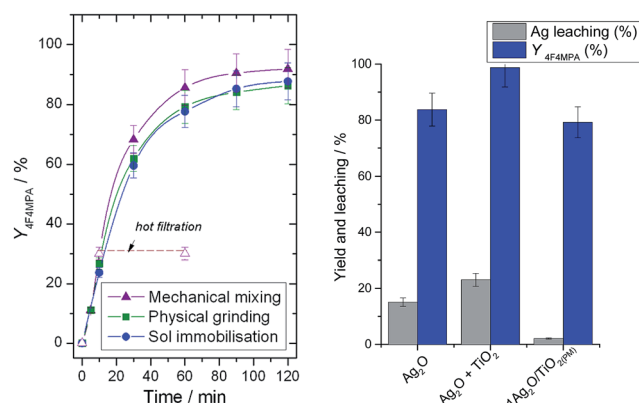


Fig. 3 (Left) Yield of **1b** against time for 1Ag<sub>2</sub>O/TiO<sub>2</sub>(PM) (green squares), 1Ag/TiO<sub>2</sub>(Si<sub>350</sub>) (blue circles) and 1Ag<sub>2</sub>O/TiO<sub>2</sub>(MM) (purple triangles). Reaction conditions as Fig. 2, left. (Right) Ag leaching (grey bars) at 10 min and yield of **1b** (blue bars) at 60 min over neat Ag<sub>2</sub>O, not supported Ag<sub>2</sub>O + TiO<sub>2</sub>, and 1Ag<sub>2</sub>O/TiO<sub>2</sub>(PM).



are immediately oxidised to Ag(I) upon interaction with Selectfluor®, and cationic Ag is responsible for catalytic performance.

Given the requirement for cationic Ag active sites, the preparation of materials directly containing Ag(I), and not Ag(0), was targeted. Mechanochemistry, whereby mechanical energy is employed to facilitate chemical processes, has recently received considerable attention as a sustainable and scalable method of catalyst synthesis.<sup>11</sup> In addition, it allows metal oxides such as Ag<sub>2</sub>O to be directly employed as solid precursors of the desired active phase.<sup>11c</sup> We first investigated the mechanochemical synthesis of Ag<sub>2</sub>O/TiO<sub>2</sub> catalysts by simple physical grinding (denoted 1Ag<sub>2</sub>O/TiO<sub>2</sub>(PM)). Physically grinding mixtures of Ag<sub>2</sub>O and TiO<sub>2</sub> in a pestle and mortar for 20 min led to a catalyst demonstrating almost identical behaviour to heat-treated 1Ag/TiO<sub>2</sub>(SI350), despite the rapidity of the method and the complete absence of high temperature heat treatments (Fig. 3, left). Notably, in the absence of the TiO<sub>2</sub> support *i.e.* when Ag<sub>2</sub>O is ground alone, and in the absence of the grinding stage *i.e.* when Ag<sub>2</sub>O and TiO<sub>2</sub> were placed into the reaction mixture together without prior physical contact, high levels of leaching occurred (Fig. 3, right). Moreover, homogeneous contributions to the reaction rate were observed (ESI Fig. S2†). Clearly, obtaining strong interaction between Ag<sub>2</sub>O and TiO<sub>2</sub> is essential. We note that homogeneous catalytic activity with Ag<sub>2</sub>O has previously been reported by the Ritter group.<sup>12</sup>

In view of this, and to allow a greater control of the preparation conditions, thus improving the reproducibility of the preparation method (ESI, Fig. S3†), the optimal catalyst composition was re-made by mechanochemical mixing in a high frequency milling machine. Mixing Ag<sub>2</sub>O and TiO<sub>2</sub> for 20 minutes at 15 Hz led to the formation of a catalyst that was both more active and more stable than the sol immobilisation and physical grinding analogues (the catalyst is denoted 1Ag<sub>2</sub>O/TiO<sub>2</sub>(MM)). For 1Ag<sub>2</sub>O/TiO<sub>2</sub>(MM), catalysis was also totally heterogeneous (Fig. 3 (left)), and fully reproducible and stable over long periods of time (Fig. 4). Preparing an effective and reproducible catalyst directly from Ag<sub>2</sub>O so rapidly, without the

presence of solvents or other additives, and in readily available experimental apparatus, presents several synthetic advantages over other catalyst preparation methodologies, such as sol immobilisation (Scheme 3).

To further optimize the preparation of 1Ag<sub>2</sub>O/TiO<sub>2</sub>(MM), a series of different milling frequencies, in a range 3–30 Hz, was explored (Fig. 5). Interestingly, increasing the milling frequency results in a decrease in catalytic activity, with **1b** yield values decreasing from 95% to around 10% over the frequency series. Nevertheless, while metal leaching values below the instrument detectability limits were detected by MP-AES analysis for 1Ag<sub>2</sub>O/TiO<sub>2</sub>(MM) milled at higher frequencies (15 Hz, 22.5 and 30 Hz), leaching values of 6% and 5% were found for the two lowest frequencies (3 Hz and 7.5 Hz, respectively). This demonstrates that although low frequencies result in active materials, they do not provide sufficient energy to result in strong metal-support interactions nor synthesise a truly heterogeneous catalysts. Accordingly, all further studies utilised 1Ag<sub>2</sub>O/TiO<sub>2</sub>(MM) milled at 15 Hz.

To fully understand the effect of the different frequencies on the Ag speciation and the resultant performances of the catalysts, detailed characterization of the mechanochemically-prepared catalysts with Powder X-ray Diffraction (pXRD), Temperature Programmed Reduction (TPR) and X-ray Photoelectron Spectroscopy (XPS) was performed. XRD analysis (Fig. 6, left) reveals that upon increasing the frequency from 3 to 30 Hz, the reflection at 32.7°, corresponding to Ag<sub>2</sub>O, decreases in intensity, and a new reflection at 32.2°, characteristic of AgO, appears. As reported in literature, AgO is known to be a mixture of Ag(III) and Ag(I) oxides,<sup>13</sup> and will therefore be denoted as Ag<sub>2</sub>O<sub>2</sub> herein. In agreement with the trend seen in the XRD patterns, the presence of multiple Ag species in the higher frequency materials was also observed by TPR (Fig. 6, right). The TPR profile of 1Ag<sub>2</sub>O/TiO<sub>2</sub>(MM) prepared at 3 Hz clearly shows only one intense reduction step at 240 °C, at temperatures higher than that found for unsupported Ag<sub>2</sub>O (196 °C). We attribute this reduction peak to Ag<sub>2</sub>O interacting with the support material. Upon increasing the milling frequency from 3 Hz to 22.5 Hz, the reduction step at 240 °C gradually decreases, whilst a new reduction feature appears around 160–170 °C. This new feature perfectly overlaps with the reduction temperature measured for unsupported Ag<sub>2</sub>O<sub>2</sub>. The presence of two features in these samples indicates the presence of two

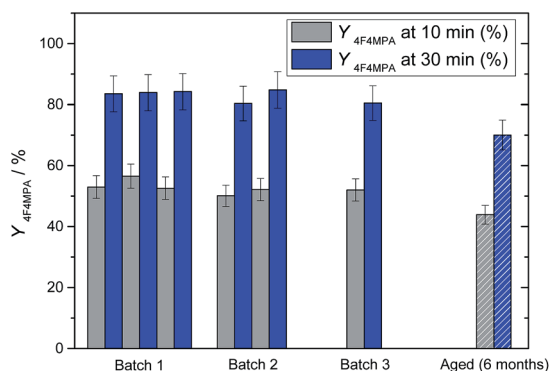
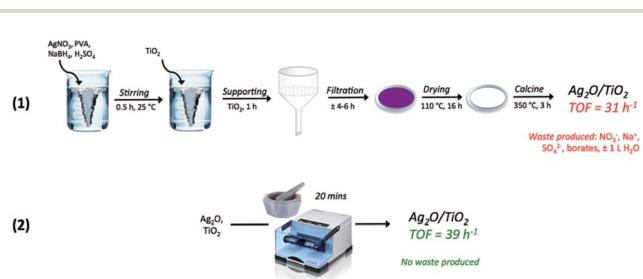


Fig. 4 Activity and reproducibility of three different batches of 1Ag<sub>2</sub>O/TiO<sub>2</sub>(MM). Grey bars are percentage yield of **1b** at 10 min, blue bars conversion at 30 min. White and blue/grey bars correspond to the activity of 1Ag<sub>2</sub>O/TiO<sub>2</sub>(MM) aged for 6 months. Reaction conditions as Fig. 2, right, 30 °C.



Scheme 3 Graphical representation of classical “wet” preparation methodologies *e.g.* sol immobilisation (1), and physical methods *e.g.* mechanochemical mixing (2).



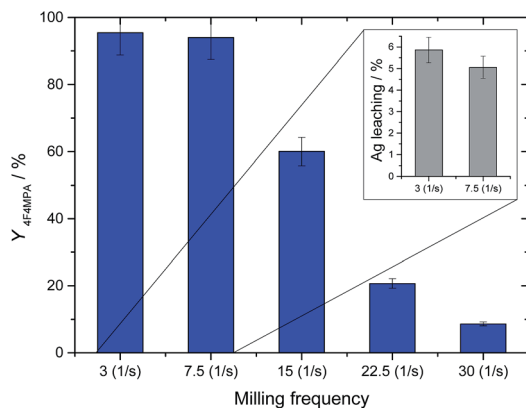


Fig. 5 Yield of **1b** (blue bars) at 30 min with 1%  $\text{Ag}_2\text{O}/\text{TiO}_2$  milled at various frequencies. Inset on the top right: Ag leaching values at 10 min for 1%  $\text{Ag}_2\text{O}/\text{TiO}_2$  milled at 3 Hz and 7.5 Hz. Reaction conditions as Fig. 2, right, room temperature.

distinct Ag species in these materials. At the highest frequency, only  $\text{Ag}_2\text{O}_2$  was observed, indicating full transformation of  $\text{Ag}_2\text{O}$  to  $\text{Ag}_2\text{O}_2$ . Although several of the Ag signals overlap, XPS analysis also revealed the presence of multiple  $\text{AgO}_x$  species in the optimal material prepared at 15 Hz (Fig. 7, left). Deconvolution of the broad asymmetrical peak observed for  $1\text{Ag}_2\text{O}/\text{TiO}_2(\text{MM})$  into two different components; firstly, a signal at 368.0 eV, perfectly overlapping with the signal obtained for  $\text{Ag}_2\text{O}$ ; secondly, a signal at lower binding energy (367 eV), assigned in the literature to  $\text{Ag}(\text{III})$ .<sup>14</sup>

Clearly, increasing the energy of the mechanochemical preparation by increasing the milling frequency results in a transformation of  $\text{Ag}_2\text{O}$  to  $\text{Ag}_2\text{O}_2$ , with a distribution of both oxides being observed at the optimal frequency (15 Hz).

An increase in  $\text{Ag}_2\text{O}_2$  formation at higher frequencies appears to correlate with decreased catalytic performance (*vide supra*). To verify that the loss in activity observed upon increasing the milling frequency from 3–15 Hz correlates to the partial conversion of  $\text{Ag}_2\text{O}$  into  $\text{Ag}_2\text{O}_2$ ,  $1\text{Ag}_2\text{O}_2/\text{TiO}_2(\text{MM})$  was prepared by milling  $\text{Ag}_2\text{O}_2$  with  $\text{TiO}_2$  at 15 Hz. As expected, substantially decreased performance was observed (Fig. 7). Powder X-ray Diffraction (pXRD) analysis of  $1\text{Ag}_2\text{O}_2/\text{TiO}_2(\text{MM})$  demonstrates that only  $\text{Ag}_2\text{O}_2$  is present in this material (ESI Fig. S4†).

The loss of activity observed for  $1\text{Ag}_2\text{O}_2/\text{TiO}_2(\text{MM})$  agrees well with the reaction mechanisms hypothesised in previous works.<sup>5</sup> According to these studies, the key reaction step involves the oxidation of a  $\text{Ag}(\text{I})\text{-COOR}$  species by Selectfluor®. It is likely that  $\text{Ag}(\text{III})$  (present as approximately 50% of the Ag content in  $\text{Ag}_2\text{O}_2$ ) cannot be further oxidized, thus stopping the reaction cycle and acting as a “trap”. According to this, it would be expected that catalysts milled at the highest frequencies (22.5 and 30 Hz) should still display some levels of catalytic performance, given that  $\text{Ag}_2\text{O}_2$  contains approximately 50%  $\text{Ag}(\text{I})$ . We hypothesise that the greater than expected decrease in activity for these materials may be due to decreased crystallinity of the support, as evidenced by XRD and BET measurements (ESI Fig. S5 and Table S1†).

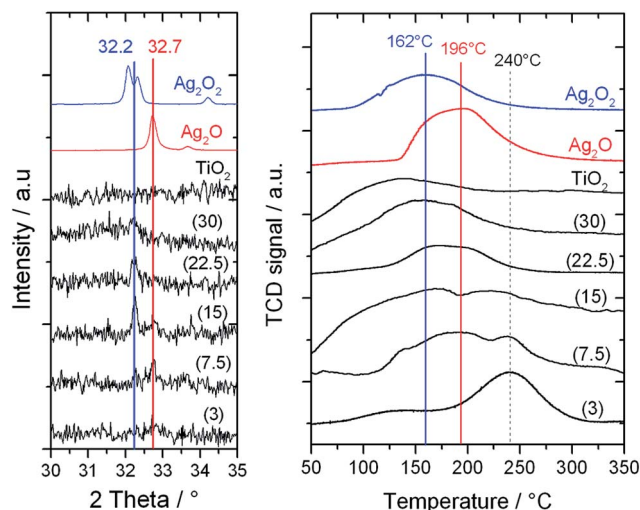


Fig. 6 (Left) XRD patterns of  $1\text{Ag}_2\text{O}/\text{TiO}_2(\text{MM})$  prepared at different milling frequencies (3–30 Hz). (Right) TPR profiles of  $1\text{Ag}_2\text{O}/\text{TiO}_2(\text{MM})$  prepared at different milling frequencies (3–30 Hz).

The general applicability of the heterogeneous catalytic system in terms of  $\text{C}(\text{sp}^3)\text{-F}$  bond formation was also investigated with  $1\text{Ag}_2\text{O}/\text{TiO}_2(\text{MM})$  milled at 15 Hz as catalyst. These studies demonstrated the catalytic system to be versatile and able to convert even difficult primary carboxylic groups such as succinic acid (**3a**, Table 1 entry 3). In all cases, catalytic numbers of turnovers were observed within a short period of time ( $\leq 1$  h). A strong influence of  $\text{K}_2\text{CO}_3$  loading on both the activity and stability of the  $1\text{Ag}_2\text{O}/\text{TiO}_2(\text{MM})$  was also observed with these substrates, such as pivalic acid (**2a**, Table 1 entry 2) and 2,2-dimethyl-valeric acid (**4a**, Table 1 entry 4). In both cases, a two-fold increase in the TON values, 18.6 and 6.47 respectively, was observed when only 0.58 equivalents of  $\text{K}_2\text{CO}_3$  were used (Table 1, entries 2 and 4). Optimizing the base : carboxylic acid ratio for each individual substrate is critical for obtaining the highest levels of catalytic performance. Substrates not soluble in neat water, such as 2,2-dimethyl-3-phenylpropionic acid (**5a**), were

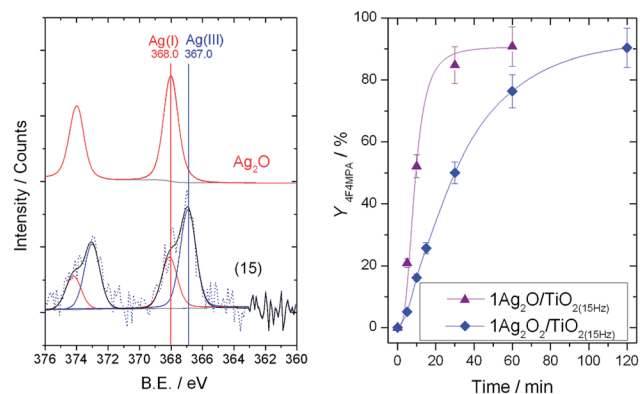


Fig. 7 (Left) XPS analysis of commercial  $\text{Ag}_2\text{O}$  and  $1\text{Ag}_2\text{O}/\text{TiO}_2(\text{MM})$  prepared at 15 Hz. (Right) Yield of **1b** against time over  $1\text{Ag}_2\text{O}/\text{TiO}_2(\text{MM})$  (purple triangles), and  $1\text{Ag}_2\text{O}_2/\text{TiO}_2(\text{MM})$  (blue rhomboids) both prepared at 15 Hz. Reaction conditions as Fig. 2, right, 30 °C.





**Table 1** Yields calculated with  $^{19}\text{F}$  NMR using  $\alpha,\alpha,\alpha$ -trifluorotoluene and HPLC analysis against authentic standards. Values in parentheses correspond to total TON including reuses. Reaction conditions: 0.2 mmol substrate, 0.4 mmol Selectfluor®, 100 mg  $1\text{Ag}_2\text{O}/\text{TiO}_2(\text{MM})$ , 4 mL  $\text{H}_2\text{O}$ , 0.23 mmol  $\text{K}_2\text{CO}_3$ ,  $\text{N}_2$ , 30 °C, 0.5 h

Entry	Product	TON <sup>a</sup>
1		<b>1b</b> 17.8 (34.2 after 2 cycles)
2		<b>2b</b> 9.6 <sup>b</sup> , 18.6 <sup>c</sup>
3		<b>3b</b> 4.0 <sup>d</sup>
4		<b>4b</b> 3.25 <sup>b</sup> , 6.47 <sup>b,c</sup> (14.6 after 5 cycles) <sup>b</sup>
5		<b>5b</b> 3.21 <sup>c,e</sup>

<sup>a</sup> TON calculated as “mol (product)/mol (Ag)” for entries 1 and 3–5, and as “mol (2a converted)/mol(Ag)” for entry 2. <sup>b</sup> Reaction time 1 h. <sup>c</sup> 0.115 mmol  $\text{K}_2\text{CO}_3$ . <sup>d</sup> 200 mg  $1\text{Ag}_2\text{O}/\text{TiO}_2(\text{MM})$ , 50 °C, 2 mL  $\text{H}_2\text{O}$ . <sup>e</sup> 200 mg  $1\text{Ag}_2\text{O}/\text{TiO}_2(\text{MM})$ ,  $\text{H}_2\text{O}/\text{acetone}$  (2 mL/2 mL), 60 °C.

also efficiently converted into the corresponding  $\text{C}(\text{sp}^3)\text{-F}$  fluorinated compounds (**5b**, Table 1 entry 5). In this case, a water:acetone mixture (1 : 1) was employed as solvent, and TONs comparable or better to the ones obtained using  $\text{AgNO}_3$  were observed.<sup>5</sup>

A major advantage of a heterogeneous catalyst over a homogeneous analogue is the ease in which it can be recovered and reused. Accordingly, we first explored the reusability of  $1\text{Ag}_2\text{O}/\text{TiO}_2(\text{MM})$  with **4a** as substrate. To ensure that true kinetic comparisons were made, the activity of the catalyst in multiple cycles was examined at low conversion, so that the intrinsic activity and reusability of the catalyst was correctly examined.<sup>8b,d</sup> As can be seen (Fig. 8, left),  $1\text{Ag}_2\text{O}/\text{TiO}_2(\text{MM})$  exhibited good

levels of reusability, even without any intermediate treatments being performed. Substrates containing additional functional groups, such as **1a**, presented a greater challenge. Indeed, in the absence of secondary treatments, a large drop in the catalytic activity of  $1\text{Ag}_2\text{O}/\text{TiO}_2(\text{MM})$  was observed during the second cycle for **1a** decarboxylative fluorination (ESI Fig. S6†). However, even in these cases, the initial level of performance could be fully restored by suspending the catalyst in an aqueous  $\text{K}_2\text{CO}_3$  solution for 60 min between successive cycles (Fig. 8, right). We hypothesize that removal of residual carboxylic species by  $\text{K}_2\text{CO}_3$  is responsible for improved recyclability, as such species are well established poisons of metal-based catalysts.<sup>8a</sup> It is therefore clear that the heterogeneous catalyst possesses promising stability characteristics for intensified operation. For **4a** and **1a**, TONs over one order of magnitude higher than previously reported were obtained after 5 and 2 cycles, respectively.

## Conclusions

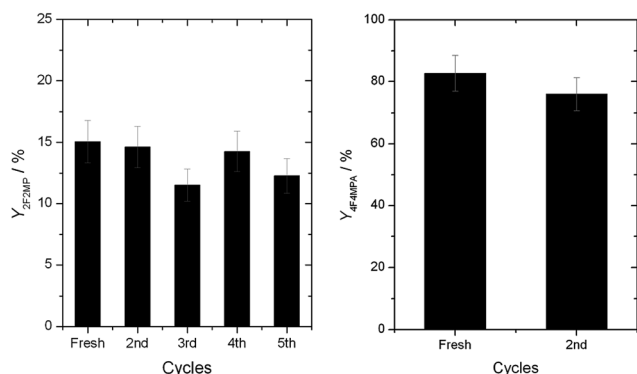
Mechanochemically-prepared 1 wt%  $\text{Ag}_2\text{O}/\text{TiO}_2$  is found to be an efficient and reusable heterogeneous catalyst for the decarboxylative fluorination of various carboxylic acids in aqueous media at 25 °C. The mechanochemical mixture presents higher levels of catalytic activity than the state-of-the-art homogeneous catalyst, and is also easily recovered and reused over five successive catalytic cycles. Good general applicability of the catalytic system is also observed, with a variety of primary and tertiary carboxylic acid groups being selectively converted to the desired  $\text{C}(\text{sp}^3)\text{-F}$  products. Spectroscopic characterisation of the mechanochemically-prepared materials indicates that phase transformations between  $\text{Ag}_2\text{O}$  and  $\text{Ag}_2\text{O}_2$  can occur, and that the optimal milling frequency in terms of activity and stability is 15 Hz.

## Acknowledgements

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**Fig. 8** (Left) Reusability of  $1\text{Ag}_2\text{O}/\text{TiO}_2(\text{MM})$  at 30 °C with **4a** as substrate. No intermediate treatments were performed. (Right) Reusability of  $1\text{Ag}_2\text{O}/\text{TiO}_2(\text{MM})$  at 30 °C with **1a** as substrate. The catalyst was washed in an aqueous  $\text{K}_2\text{CO}_3$  solution (0.06 M) for 1 h between cycles. Reaction conditions otherwise as Fig. 2, left.



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